# Interventions for cutaneous disease in systemic lupus erythematosus (Review)

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<td>of acne</td>
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Interventions for cutaneous disease in systemic lupus erythematosus

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Editorial group: Cochrane Skin Group.


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ABSTRACT

Background

Lupus erythematosus is an autoimmune disease with significant morbidity and mortality. Cutaneous disease in systemic lupus erythematosus (SLE) is common. Many interventions are used to treat SLE with varying efficacy, risks, and benefits.

Objectives

To assess the effects of interventions for cutaneous disease in SLE.

Search methods

We searched the following databases up to June 2019: the Cochrane Skin Specialised Register, CENTRAL, MEDLINE, Embase, Wiley Interscience Online Library, and Biblioteca Virtual em Saude (Virtual Health Library). We updated our search in September 2020, but these results have not yet been fully incorporated.

Selection criteria

We included randomised controlled trials (RCTs) of interventions for cutaneous disease in SLE compared with placebo, another intervention, no treatment, or different doses of the same intervention. We did not evaluate trials of cutaneous lupus in people without a diagnosis of SLE.

Data collection and analysis

We used standard methodological procedures expected by Cochrane. Primary outcomes were complete and partial clinical response. Secondary outcomes included reduction (or change) in number of clinical flares; and severe and minor adverse events. We used GRADE to assess the quality of evidence.

Main results

Sixty-one RCTs, involving 11,232 participants, reported 43 different interventions. Trials predominantly included women from outpatient clinics; the mean age range of participants was 20 to 40 years. Twenty-five studies reported baseline severity, and 22 studies included participants with moderate to severe cutaneous lupus erythematosus (CLE); duration of CLE was not well reported. Studies were conducted mainly in multi-centre settings. Most often treatment duration was 12 months. Risk of bias was highest for the domain of reporting bias, followed by performance/detection bias. We identified too few studies for meta-analysis for most comparisons. We limited this abstract to main comparisons (all administered orally) and outcomes. We did not identify clinical trials of other commonly used treatments, such as topical corticosteroids, that reported complete or partial clinical response or numbers of clinical flares.
Complete clinical response

Studies comparing oral hydroxychloroquine against placebo did not report complete clinical response.

Chloroquine may increase complete clinical response at 12 months' follow-up compared with placebo (absence of skin lesions) (risk ratio (RR) 1.57, 95% confidence interval (CI) 0.95 to 2.61; 1 study, 24 participants; low-quality evidence).

There may be little to no difference between methotrexate and chloroquine in complete clinical response (skin rash resolution) at 6 months' follow-up (RR 1.13, 95% CI 0.84 to 1.50; 1 study, 25 participants; low-quality evidence).

Methotrexate may be superior to placebo with regard to complete clinical response (absence of malar/discoid rash) at 6 months' follow-up (RR 3.57, 95% CI 1.63 to 7.84; 1 study, 41 participants; low-quality evidence).

At 12 months' follow-up, there may be little to no difference between azathioprine and ciclosporin in complete clinical response (malar rash resolution) (RR 0.83, 95% CI 0.46 to 1.52; 1 study, 89 participants; low-quality evidence).

Partial clinical response

Partial clinical response was reported for only one key comparison: hydroxychloroquine may increase partial clinical response at 12 months compared to placebo, but the 95% CI indicates that hydroxychloroquine may make no difference or may decrease response (RR 7.00, 95% CI 0.41 to 120.16; 20 pregnant participants, 1 trial; low-quality evidence).

Clinical flares

Clinical flares were reported for only two key comparisons: hydroxychloroquine is probably superior to placebo at 6 months' follow-up for reducing clinical flares (RR 0.49, 95% CI 0.28 to 0.89; 1 study, 47 participants; moderate-quality evidence). At 12 months' follow-up, there may be no difference between methotrexate and placebo, but the 95% CI indicates there may be more or fewer flares with methotrexate (RR 0.77, 95% CI 0.32 to 1.83; 1 study, 86 participants; moderate-quality evidence).

Adverse events

Data for adverse events were limited and were inconsistently reported, but hydroxychloroquine, chloroquine, and methotrexate have well-documented adverse effects including gastrointestinal symptoms, liver problems, and retinopathy for hydroxychloroquine and chloroquine and teratogenicity during pregnancy for methotrexate.

Authors' conclusions

Evidence supports the commonly-used treatment hydroxychloroquine, and there is also evidence supporting chloroquine and methotrexate for treating cutaneous disease in SLE. Evidence is limited due to the small number of studies reporting key outcomes. Evidence for most key outcomes was low or moderate quality, meaning findings should be interpreted with caution. Head-to-head intervention trials designed to detect differences in efficacy between treatments for specific CLE subtypes are needed. Thirteen further trials are awaiting classification and have not yet been incorporated in this review; they may alter the review conclusions.

PLAIN LANGUAGE SUMMARY

What are the benefits and risks of different treatments for skin disease in people with systemic lupus erythematosus (an autoimmune disease that affects the whole body)

Why is this question important?

Systemic lupus erythematosus (SLE; also known as 'lupus') is a disease in which the body's immune (defence) system mistakenly attacks healthy tissue in many parts of the body. It affects 7.5 million people worldwide. Around 70% of affected people develop skin problems such as rash on the nose or cheeks. Often, SLE also causes pain in joints and muscles and extreme tiredness. Symptoms can improve temporarily, or they can worsen suddenly (flare). In severe cases, SLE can cause life-threatening damage to the heart, lungs, brain, or kidneys.

There is no cure for SLE. However, there are treatments designed to improve symptoms. In particular, there are a range of options for treating skin problems.

• Medicines that can be taken by mouth (orally), applied as creams, or given as injections.

• Therapies to help people cope with their skin problems, such as talking therapies.

• Other approaches, including herbal medicine, light therapy, or make-up.

To find out which treatments work best for people with SLE, and to compare adverse (unwanted) effects, we reviewed the evidence from research studies.
How did we identify and evaluate the evidence?

We searched the medical literature for studies that compared any treatment for skin disease in SLE against:

- a placebo (dummy) treatment;
- no treatment;
- another treatment; or
- a different dose of the same treatment.

We compared the results and summarised the evidence from all the studies. Finally, we rated our confidence in the evidence based on factors such as study methods and sizes and the consistency of findings across studies.

What did we find?

We found 61 studies that included 11,232 people (mostly women) and investigated 43 different treatments. Most treatments lasted one year, and people were followed for up to 48 months.

Here we report the main findings of our review on the effects of five different oral medicines: hydroxychloroquine, chloroquine, methotrexate, ciclosporin, and azathioprine.

**Disappearance of skin problems**

We do not know if hydroxychloroquine is better or worse than placebo at making skin problems disappear because no studies reported information about this.

The evidence suggests that:

- chloroquine may be better at making skin problems disappear after 12 months than placebo (1 study, 24 people);
- when we compare methotrexate and chloroquine, there may be little to no difference in how often they make skin rashes disappear after six months (1 study, 25 people);
- methotrexate may be better for making skin rashes disappear after six months than placebo (1 study, 41 people); and
- there may be little to no difference in how often skin problems disappear after 12 months between ciclosporin and azathioprine (1 study, 25 people).

**Partial disappearance of skin problems (at least 50% improvement in the skin condition)**

It is unclear if hydroxychloroquine is better or worse than placebo at making skin problems disappear at least partially after 12 months. This is because the evidence is too imprecise (1 study, 20 pregnant women).

No other studies have examined how treatments affect the partial disappearance of skin problems.

**Flares**

The evidence suggests that after six months, fewer flares probably occur with hydroxychloroquine than with placebo (1 study, 47 people).

It is unclear if flares are more, or less, likely to occur after 12 months with methotrexate compared to placebo (1 study, 86 people).

No other studies have reported information on how treatments affect flares.

**Adverse events**

Evidence is often imprecise, and whether treatments lead to more or fewer adverse events than placebo or other treatments is not clear.

We found limited data for adverse events, and reports were discrepant, but hydroxychloroquine, chloroquine, and methotrexate have well-known adverse effects including stomach and liver problems. Hydroxychloroquine and chloroquine can cause eye problems, and methotrexate can cause serious harm to a developing baby if taken during pregnancy.

**Other outcomes**

We do not know how treatments affect other aspects of disease severity or quality of life. This is because studies did not report information on this.
What does this mean?

When compared against a placebo, studies in people with SLE show that:

• fewer flares probably occur with hydroxychloroquine; and
• methotrexate and chloroquine may be better at making skin problems disappear.

Information about adverse effects is limited.

How up-to-date is this review?

The evidence in this Cochrane Review is current to June 2019.
### SUMMARY OF FINDINGS

#### Summary of findings 1. Oral methotrexate versus placebo for cutaneous disease in systemic lupus erythematosus

**Oral methotrexate versus placebo for cutaneous disease in systemic lupus erythematosus**

**Patient or population:** patients with cutaneous disease in systemic lupus erythematosus  
**Settings:** academic and research institutions  
**Intervention:** oral methotrexate  
**Comparator:** placebo

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Illustrative comparative risks* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No. of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
</table>
| **Primary outcome: complete clinical response** (malar/discoid rash) Follow-up: 6 months  | Study population<sup>a</sup>  
238 per 1000  
(388 to 1000)  
Moderate<sup>a</sup>  
238 per 1000  
(388 to 1000)  | RR 3.57 (1.63 to 7.84)  
41 (1 study)  
⊕⊕⊝ ⊝ ⊝
 | More participants in the methotrexate group had complete clinical response (absence of malar or discoid rash) at the time of outcome assessment at 6 months | |
| **Primary outcome: partial clinical response** Follow-up: 12 months  | Study population<sup>a</sup>  
222 per 1000  
(71 to 407)  
Moderate<sup>a</sup>  
222 per 1000  
171 per 1000  
(71 to 407)  | Not estimable  
0 (0)  
See comment | This outcome was not reported in any of the studies | |
| **Secondary outcome: clinical flare** Follow-up: 12 months  | Study population<sup>a</sup>  
222 per 1000  
171 per 1000  
(71 to 407)  
Moderate<sup>a</sup>  
222 per 1000  
171 per 1000  | RR 0.77 (0.32 to 1.83)  
86 (1 study)  
⊕⊕⊕⊕ moderate<sup>c</sup>
 | More participants in the placebo group experienced a severe clinical flare requiring withdrawal from the study compared with the methotrexate group | |

---

<sup>a</sup>See comment

<sup>b</sup>low

<sup>c</sup>moderate
### Secondary outcome: CLASI

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<th>Not estimable</th>
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<th>This outcome was not reported by any of the studies</th>
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### Secondary outcome: Dermatology quality of life measure

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<th>This outcome was not reported by any of the studies</th>
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### Adverse events: severe

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<th>See comment</th>
<th>RR 12.05 (0.69 to 211.36)</th>
<th>86 (1 study)</th>
<th>⊗⊗⊗⊕ moderate</th>
<th>There were more severe side effects in the methotrexate group compared with the placebo group at 12 months; however, confidence intervals were wide, as there were zero events in the placebo group (hence we were unable to calculate the absolute event rate)</th>
</tr>
</thead>
</table>

Follow-up: 12 months

### Adverse events: minor

<table>
<thead>
<tr>
<th>Study population</th>
<th>RR 0.68 (0.39 to 1.17)</th>
<th>86 (1 study)</th>
<th>⊗⊗⊗⊕ moderate</th>
<th>Fewer participants in the methotrexate group had mild &quot;adverse mucocutaneous events&quot; than in the placebo group at 12 months but with a wide confidence interval including 1</th>
</tr>
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</table>

Follow-up: 12 months

<table>
<thead>
<tr>
<th>467 per 1000</th>
<th>317 per 1000 (182 to 546)</th>
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<tbody>
<tr>
<td>Moderate</td>
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<table>
<thead>
<tr>
<th>467 per 1000</th>
<th>318 per 1000 (182 to 546)</th>
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</table>

*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: confidence interval; RR: risk ratio.

GRADE Working Group grades of evidence.

**High quality:** further research is very unlikely to change our confidence in the estimate of effect.

**Moderate quality:** further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

**Low quality:** further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

**Very low quality:** we are very uncertain about the estimate.

---

a Assumed risk/control group risk estimates come from control group risk (median).
b Downgraded by two levels due to (1) study design limitations - unclear risk of bias (sequence generation not stated, allocation method not detailed, intent to treat analysis not stated and could not be confirmed by examination of published data) and (2) imprecision (small study).
c Downgraded by one level due to imprecision (small study).
d Downgraded by one level due to study design limitations - unclear risk of bias (randomisation method not stated, allocation method not detailed, intent-to-treat analysis not stated and could not be confirmed by examination of published data).
### Summary of findings 2. Oral hydroxychloroquine versus placebo for cutaneous disease in systemic lupus erythematosus

**Oral hydroxychloroquine versus placebo for cutaneous disease in systemic lupus erythematosus**

**Patient or population:** patients with cutaneous disease in systemic lupus erythematosus  
**Settings:** academic and research institutions  
**Intervention:** oral hydroxychloroquine  
**Comparator:** placebo

<table>
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<th>Relative effect (95% CI)</th>
<th>No. of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Placebo</td>
<td>Oral hydroxychloroquine</td>
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<tr>
<td><strong>Primary outcome:</strong> complete clinical response</td>
<td>See comment</td>
<td>See comment</td>
<td>Not estimable</td>
<td>0 (0)</td>
<td>See comment</td>
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<tr>
<td><strong>Primary outcome:</strong> partial clinical response</td>
<td>See comment</td>
<td>See comment</td>
<td><strong>RR 7.00</strong> (0.41 to 120.16)</td>
<td><strong>20</strong> (1 study)</td>
<td>⊗⊗⊗⊝ lowb</td>
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<tr>
<td>Follow-up: 12 months</td>
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<tr>
<td><strong>Secondary outcome:</strong> clinical flare</td>
<td><strong>Study population</strong></td>
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<tr>
<td>Follow-up: 6 months</td>
<td>727 per 1000</td>
<td>364 per 1000 (204 to 647)</td>
<td><strong>RR 0.49</strong> (0.28 to 0.89)</td>
<td>47 (1 study)</td>
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<tr>
<td>Moderate</td>
<td>727 per 1000</td>
<td>363 per 1000 (204 to 647)</td>
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<td><strong>Secondary outcome:</strong> CLASI</td>
<td>See comment</td>
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### Secondary outcome: Dermatology Quality of Life measure

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<th>See comment</th>
<th>See comment</th>
<th>Not estimable</th>
<th>0 (0)</th>
<th>See comment</th>
<th>This outcome was not reported by any of the studies</th>
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### Adverse events: severe

| Follow-up: 12 months | See comment | See comment | RR 3.90 (0.19 to 78.46) | 71 (1 study) | ⬤⬤⬤⬤ moderate<sup>d</sup> | More participants in the hydroxychloroquine group had severe side effects attributed to the medication than in the placebo group at 12 months. There were zero events in the placebo group; hence we were unable to calculate the absolute events rate |

### Adverse events: minor

| Follow-up: 6 months | Study population<sup>a</sup> | See comment | RR 1.32 (0.24 to 7.19) | 47 (1 study) | ⬤⬤⬤⬤ moderate<sup>c</sup> | There were more mild side effects in the hydroxychloroquine group than in the placebo group at 6 months |

| | 91 per 1000 | 120 per 1000 (22 to 654) | 91 per 1000 | 120 per 1000 (22 to 654) |

*The basis for the assumed risk (e.g., the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: confidence interval; RR: risk ratio.

**GRADE Working Group grades of evidence.**

- **High quality:** further research is very unlikely to change our confidence in the estimate of effect.
- **Moderate quality:** further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- **Low quality:** further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- **Very low quality:** we are very uncertain about the estimate.

- <sup>a</sup>Assumed risk/control group risk estimates come from control group risk (median).
- <sup>b</sup>Downgraded by two levels due to risk of bias (unclear methods of sequence generation and allocation concealment) and imprecision (one small study).
- <sup>c</sup>Downgraded by one level due to imprecision (one small study).
- <sup>d</sup>Downgraded by one level due to risk of bias (unclear method of allocation concealment).

### Summary of findings 3. Oral dehydroepiandrosterone versus placebo for cutaneous disease in systemic lupus erythematosus

**Oral dehydroepiandrosterone versus placebo for cutaneous disease in systemic lupus erythematosus**

- **Patient or population:** patients with cutaneous disease in systemic lupus erythematosus
- **Settings:** research and academic institutions
<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Illustrative comparative risks* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No. of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>Corresponding risk</td>
<td>Assumed risk</td>
<td>Relative effect (95% CI)</td>
<td>Quality of the evidence (GRADE)</td>
<td>Comments</td>
</tr>
<tr>
<td>Oral dehydroepiandrosterone</td>
<td>RR 1.11 (1.00 to 1.22)</td>
<td>381</td>
<td>☉☉☉☉ moderate</td>
<td>More participants in the DHEA group experienced absence of oral stomatitis at 12 months compared with the placebo group</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study population^a</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up: 12 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>Oral dehydroepiandrosterone</td>
<td>RR 1.11 (1.00 to 1.22)</td>
<td>381</td>
<td>☉☉☉☉ moderate</td>
<td></td>
</tr>
<tr>
<td>771 per 1000</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>856 per 1000 (771 to 940)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Moderate^a</td>
<td></td>
<td>RR 1.11 (1.00 to 1.22)</td>
<td>381</td>
<td>☉☉☉☉ moderate</td>
<td></td>
</tr>
<tr>
<td>771 per 1000</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>856 per 1000 (771 to 941)</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Primary outcome: complete clinical response</th>
<th>Study population^a</th>
<th>No. of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up: 12 months</td>
<td>See comment</td>
<td>0 (0)</td>
<td></td>
<td>This outcome was not reported by any of the studies</td>
</tr>
<tr>
<td>Partial clinical response</td>
<td>See comment</td>
<td>Not estimable</td>
<td>See comment</td>
<td>This outcome was not reported by any of the studies</td>
</tr>
<tr>
<td>Clinical flare</td>
<td>See comment</td>
<td>Not estimable</td>
<td>See comment</td>
<td>This outcome was not reported by any of the studies</td>
</tr>
<tr>
<td>CLASI</td>
<td>See comment</td>
<td>Not estimable</td>
<td>See comment</td>
<td>This outcome was not reported by any of the studies</td>
</tr>
<tr>
<td>Dermatology Quality of Life measure</td>
<td>See comment</td>
<td>Not estimable</td>
<td>See comment</td>
<td>This outcome was not reported by any of the studies</td>
</tr>
<tr>
<td>Adverse events: severe</td>
<td>Study population^a</td>
<td>RR 0.09 (0.01 to 1.66)</td>
<td>381</td>
<td>☉☉☉☉ moderate</td>
</tr>
<tr>
<td>Follow-up: 12 months</td>
<td>See comment</td>
<td>Not estimable</td>
<td>See comment</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>See comment</td>
<td>Not estimable</td>
<td>See comment</td>
<td></td>
</tr>
<tr>
<td>26 per 1000</td>
<td>RR 0.09 (0.01 to 1.66)</td>
<td>381</td>
<td>☉☉☉☉ moderate</td>
<td></td>
</tr>
<tr>
<td>2 per 1000 (0 to 43)</td>
<td></td>
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</tr>
</tbody>
</table>
Participants taking DHEA were more likely to have hirsutism at 12 months. A meta-analysis of adverse events included increased acne (RR 2.98, 95% CI 1.16 to 7.62; n = 409, 2 RCTs, low-quality evidence, I² = 32%) and hirsutism (RR 2.38, 95% CI 0.11 to 50.74; n = 409, 2 RCTs, low-quality evidence; I² = 90%).

*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: confidence interval; RR: risk ratio.

GRADE Working Group grades of evidence.
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

Assumed risk/control group risk estimates come from control group risk (median).

Downgraded one level due to study design issues (unclear if assessors were blinded and allocation concealment was somewhat unclear).

Summary of findings 4. Oral chloroquine versus placebo for cutaneous disease in systemic lupus erythematosus

**Outcomes**

<table>
<thead>
<tr>
<th>Illustrative comparative risks* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No. of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>26 per 1000</td>
<td>RR 10.50 (3.26 to 33.75)</td>
<td>381 (1 study)</td>
<td>⊕⊕⊕☉ moderate</td>
<td></td>
</tr>
<tr>
<td>2 per 1000</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(0 to 43)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>164 per 1000</td>
<td>RR 10.50 (3.26 to 33.75)</td>
<td>381 (1 study)</td>
<td>⊕⊕⊕☉ moderate</td>
<td></td>
</tr>
<tr>
<td>(51 to 527)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>168 per 1000</td>
<td>RR 10.50 (3.26 to 33.75)</td>
<td>381 (1 study)</td>
<td>⊕⊕⊕☉ moderate</td>
<td></td>
</tr>
<tr>
<td>(52 to 540)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study population</td>
<td>Assumed risk</td>
<td>Corresponding risk</td>
<td>Relative effect</td>
<td>Commentary</td>
</tr>
<tr>
<td>------------------</td>
<td>-------------</td>
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<td>------------</td>
</tr>
<tr>
<td><strong>Primary outcome: complete clinical response</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow-up: 12 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>583 per 1000 (554 to 1000)</td>
<td>915 per 1000 (554 to 1000)</td>
<td>RR 1.57 (0.95 to 2.61)</td>
<td>24 (1 study)</td>
</tr>
<tr>
<td>Oral chloroquine</td>
<td>More participants taking chloroquine had complete clinical response (absence of skin lesions) at 12 months compared with placebo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Primary outcome: partial clinical response</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>See comment</td>
<td>See comment</td>
<td>Not estimable</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>Secondary outcome: clinical flare</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>See comment</td>
<td>See comment</td>
<td>Not estimable</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>Secondary outcome: CLASI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>See comment</td>
<td>See comment</td>
<td>Not estimable</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>Secondary outcome: Dermatology Quality of Life measure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>See comment</td>
<td>See comment</td>
<td>Not estimable</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>Adverse events: severe</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow-up: 12 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>83 per 1000 (1 to 621)</td>
<td>28 per 1000 (1 to 621)</td>
<td>RR 0.33 (0.01 to 7.45)</td>
<td>24 (1 study)</td>
</tr>
<tr>
<td>Oral chloroquine</td>
<td>There were fewer severe events in the chloroquine group compared with the placebo group; however confidence intervals were wide</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Adverse events: minor</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>See comment</td>
<td>See comment</td>
<td>Not estimable</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).*
<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Illustrative comparative risks* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No. of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcome:</strong> complete clinical response</td>
<td><strong>Assumed risk</strong></td>
<td><strong>Corresponding risk</strong></td>
<td><strong>Relative effect</strong></td>
<td><strong>No. of participants</strong></td>
<td><strong>Quality of the evidence</strong></td>
</tr>
<tr>
<td>Study population</td>
<td>Assumed risk</td>
<td>Corresponding risk</td>
<td>RR 0.83 (0.46 to 1.52)</td>
<td>89 (1 study)</td>
<td>⊕⊕⊝⊝ low</td>
</tr>
<tr>
<td>Follow-up: 12 months</td>
<td>357 per 1000</td>
<td>296 per 1000 (164 to 543)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>357 per 1000</td>
<td>296 per 1000 (164 to 543)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Primary outcome:</strong> partial clinical response</td>
<td>See comment</td>
<td>See comment</td>
<td>Not estimable</td>
<td>0 (0)</td>
<td>See comment</td>
</tr>
</tbody>
</table>

CI: confidence interval; RR: risk ratio.

GRADE Working Group grades of evidence.

**High quality:** further research is very unlikely to change our confidence in the estimate of effect.

**Moderate quality:** further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

**Low quality:** further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

**Very low quality:** we are very uncertain about the estimate.

*a*Assumed risk/control risk estimate comes from control group risk (median).

*b*Downgraded two levels due to risk of bias (unclear sequence generation and allocation concealment) and imprecision (one small study).

Summary of findings 5. Oral ciclosporin versus oral azathioprine for cutaneous disease in systemic lupus erythematosus

**Oral ciclosporin versus oral azathioprine for cutaneous disease in systemic lupus erythematosus**

**Patient or population:** patients with cutaneous disease in systemic lupus erythematosus

**Settings:** academic and research institutions

**Intervention:** oral ciclosporin

**Comparator:** oral azathioprine
<table>
<thead>
<tr>
<th>Secondary outcome: clinical flare</th>
<th>See comment</th>
<th>See comment</th>
<th>Not estimable</th>
<th>0 (0)</th>
<th>See comment</th>
<th>This outcome was not reported in any of the studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary outcome: CLASI</td>
<td>See comment</td>
<td>See comment</td>
<td>Not estimable</td>
<td>0 (0)</td>
<td>See comment</td>
<td>This outcome was not reported in any of the studies</td>
</tr>
<tr>
<td>Secondary outcome: Dermatology Quality of Life measure</td>
<td>See comment</td>
<td>See comment</td>
<td>Not estimable</td>
<td>0 (0)</td>
<td>See comment</td>
<td>This outcome was not reported in any of the studies</td>
</tr>
<tr>
<td>Adverse events: severe</td>
<td>Study population&lt;sup&gt;a&lt;/sup&gt;</td>
<td>RR 0.89 (0.48 to 1.65)</td>
<td>89 (1 study)</td>
<td>⧼&lt;sup&gt;⊕⊕⊕⊕&lt;/sup&gt; low&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Cicloporin resulted in fewer severe side effects than azathioprine at 12 months; however there was insufficient evidence of a distinct difference</td>
<td></td>
</tr>
<tr>
<td>Follow-up: 12 months</td>
<td>333 per 1000</td>
<td>297 per 1000 (160 to 550)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Moderate&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>333 per 1000</td>
<td>296 per 1000 (160 to 549)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse events: minor (hirsutism)</td>
<td>Study population&lt;sup&gt;a&lt;/sup&gt;</td>
<td>RR 9.83 (1.32 to 72.95)</td>
<td>89 (1 study)</td>
<td>⧼&lt;sup&gt;⊕⊕⊕⊕&lt;/sup&gt; low&lt;sup&gt;b&lt;/sup&gt;</td>
<td>There was strong evidence of more cases of hirsutism for ciclosporin at 12 months compared with azathioprine</td>
<td></td>
</tr>
<tr>
<td>Follow-up: 12 months</td>
<td>24 per 1000</td>
<td>234 per 1000 (31 to 1000)</td>
<td></td>
<td></td>
<td></td>
<td>The difference between groups for other adverse events at 12 months was less clear (gum hypertrophy, alopecia, herpes zoster, non-lupus rash, acne, herpes simplex)</td>
</tr>
<tr>
<td></td>
<td>Moderate&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>24 per 1000</td>
<td>236 per 1000 (32 to 1000)</td>
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</tr>
</tbody>
</table>

*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: confidence interval; RR: risk ratio.

GRADE Working Group grades of evidence.

**High quality:** further research is very unlikely to change our confidence in the estimate of effect.

**Moderate quality:** further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

**Low quality:** further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

**Very low quality:** we are very uncertain about the estimate.

<sup>a</sup>Assumed risk/control risk estimate come from control group risk (median).

<sup>b</sup>Downgraded by two levels due to risk of bias (very serious study design limitations from unblinded study).
## Summary of findings 6. Oral methotrexate versus oral chloroquine for cutaneous disease in systemic lupus erythematosus

### Oral methotrexate versus oral chloroquine for cutaneous disease in systemic lupus erythematosus

**Patient or population:** patients with cutaneous disease in systemic lupus erythematosus  
**Settings:** academic and research institutions  
**Intervention:** oral methotrexate vs oral chloroquine

### Outcomes

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Illustrative comparative risks* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No. of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcome: complete clinical response</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Both methotrexate (100% complete clinical response) and chloroquine (84% complete clinical response) were efficacious for skin rash resolution at 6 months</td>
</tr>
<tr>
<td>Follow-up: 6 months</td>
<td>Study population&lt;sup&gt;a&lt;/sup&gt;</td>
<td>RR 1.13 (0.84 to 1.50)</td>
<td>25 (1 study)</td>
<td>⊕⊕⊝ low&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>842 per 1000</td>
<td>952 per 1000</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(707 to 1000)</td>
<td>(707 to 1000)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Moderate&lt;sup&gt;a&lt;/sup&gt;</td>
<td>842 per 1000</td>
<td>951 per 1000</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(707 to 1000)</td>
<td>(707 to 1000)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Primary outcome: partial clinical response</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>This outcome was not reported in any of the studies</td>
</tr>
<tr>
<td>Follow-up: 6 months</td>
<td>See comment</td>
<td>See comment</td>
<td>Not estimable (0)</td>
<td>See comment</td>
<td></td>
</tr>
<tr>
<td><strong>Secondary outcome: clinical flare</strong></td>
<td></td>
<td></td>
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<td>This outcome was not reported in any of the studies</td>
</tr>
<tr>
<td>Follow-up: 6 months</td>
<td>See comment</td>
<td>See comment</td>
<td>Not estimable (0)</td>
<td>See comment</td>
<td></td>
</tr>
<tr>
<td><strong>Secondary outcome: Dermatology Quality of Life measure</strong></td>
<td></td>
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<td>This outcome was not reported in any of the studies</td>
</tr>
<tr>
<td>Follow-up: 6 months</td>
<td>See comment</td>
<td>See comment</td>
<td>Not estimable (0)</td>
<td>See comment</td>
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<tr>
<td><strong>Secondary outcome: CLASI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>This outcome was not reported in any of the studies</td>
</tr>
<tr>
<td>Follow-up: 6 months</td>
<td>See comment</td>
<td>See comment</td>
<td>Not estimable (0)</td>
<td>See comment</td>
<td></td>
</tr>
<tr>
<td>Adverse events: severe</td>
<td>Study population</td>
<td>RR 1.73 (0.27 to 11.07)</td>
<td>41 (1 study)</td>
<td>low</td>
<td></td>
</tr>
<tr>
<td>------------------------</td>
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</tr>
<tr>
<td>Follow-up: 6 months</td>
<td>77 per 1000</td>
<td>133 per 1000 (21 to 852)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>133 per 1000 (21 to 852)</td>
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<td></td>
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<td>RR 3.90 (1.45 to 10.51)</td>
<td>41 (1 study)</td>
<td>low</td>
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</tr>
<tr>
<td></td>
<td>154 per 1000</td>
<td>601 per 1000 (223 to 1000)</td>
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<tr>
<td></td>
<td>Moderate</td>
<td>600 per 1000 (223 to 1000)</td>
<td></td>
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</tr>
</tbody>
</table>

*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: confidence interval; RR: risk ratio.

GRADE Working Group grades of evidence.

High quality: further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: we are very uncertain about the estimate.

Assumed risk/control risk estimate comes from control group risk (median).

Downgraded two levels due to risk of bias (unblinded study) and imprecision (one small study).
BACKGROUND

A glossary that defines commonly used terms is available in Table 1.

Description of the condition

Lupus erythematosus is an autoimmune disease with significant morbidity and mortality. It affects multiple organ systems including brain, heart, kidneys, lungs, joints, liver, blood, eyes, and skin (Wallace 2007). Many clinical variants are grouped under the name ‘lupus erythematosus’ (Yazdany 2019).

Clinical variants of lupus erythematous

Some of the clinical variants of lupus erythematous include the following.

- Systemic lupus erythematous (SLE).
- Cutaneous lupus erythematous (CLE) (including subacute cutaneous lupus erythematous (SCLE) and discoid lupus erythematous (DLE)).
- Child-onset lupus erythematous.
- Neonatal lupus erythematous.
- Drug-induced lupus erythematous (DILE).

Systemic lupus erythematous (SLE)

Briefly, systemic lupus erythematous (SLE) is defined as the condition that is diagnosed when certain standard criteria (Feldman 2019), as established by the American College of Rheumatology (ACR) (Cohen 1971; Hochberg 1997; Tan 1982), or by the Systemic Lupus International Collaborating Clinics (SLICC) (Petri 2012), are met.

Cutaneous lupus erythematous (CLE)

Cutaneous lupus erythematous (CLE) is characterised by skin symptoms that fall under the spectrum of lupus erythematous conditions. CLE may occur with or without systemic involvement.

Child-onset lupus erythematous

Children may also be affected by SLE, so called "child-onset lupus" (Livingston 2011). Because there are some clinical differences between child-onset and typical adult-onset SLE, it has been divided into a separate subcategory.

Neonatal lupus erythematous

Infants born to women with lupus can also be affected by lupus, so called ‘neonatal lupus’. Neonatal lupus occurs when maternal anti-Sjögren’s syndrome-related antigen A, also called anti-Ro (SSA/Ro), or anti-Sjögren’s syndrome-related antigen B, also called anti-La (SSB/La), antibodies pass via the placenta and trigger the neonatal lupus syndrome characterised by congenital heart block, photosensitivity rash, cytopenia, and liver abnormalities (Miliaresis 2019).

Drug-induced lupus erythematous (DILE)

Medications can trigger a drug reaction that is similar to SLE, called ‘drug-induced lupus erythematous’ (DILE). DILE has characteristics that distinguish it from classical (also known as idiopathic) SLE. For example, DILE develops in parallel with drug exposure and stops once treatment is complete (Richardson 2019; Yazdany 2019).

Focus of this review

In this systematic review, we focused on SLE and, most specifically, on the subset of patients who meet ACR (or other) criteria for SLE and have at least one skin symptom. Said another way, we include patients who have been diagnosed with CLE and at the same time meet full ACR criteria for SLE, as well as patients with child-onset lupus meeting ACR (or other) criteria AND who have at least one skin symptom.

We excluded patients with subacute cutaneous lupus (SCLE) without a diagnosis of SLE (given that another Cochrane Review was planned to cover this topic), DILE, or neonatal lupus erythematous. We also excluded patients with DLE without a diagnosis of SLE because this was already the topic of another Cochrane Review (Jessop 2005; Jessop 2017).

Epidemiology of SLE

Based on averaging the incidence and mortality data from multiple centres and multiplying them by the world population, it was estimated that there were approximately 282,000 new cases of SLE and 340,000 deaths worldwide in 2008 (Hannoun 2008a). Incidence may be increasing over time in certain populations (Wallace 2007). For example, Uramoto noted that the incidence of SLE tripled over a period of four decades in the USA (Uramoto 1999). Other populations (Southern Sweden) had a stable incidence over this time (Stahl-Hallegren 2000). A recent detailed systematic review of SLE epidemiological studies showed wide geographic variation in reported incidence and prevalence and noted a trend of increasing prevalence over time, with the trend for incidence less clear (Rees 2017). Prevalence ranged from a low of zero cases in an 847-person sample in North Australia to a high of 241 per 100,000 in North America (Rees 2017). If worldwide SLE prevalence is estimated at approximately 100 cases per 100,000 population and is multiplied by the world population of 7.5 billion reported in July 2019 (US Census Bureau 2019), this translates to approximately 7.5 million SLE cases worldwide.

SLE incidence and prevalence are age related, and peak incidence and prevalence differ for each sex (Rees 2017). SLE affects women more than men, at a ratio of 9 to 1 (Jarukitsopa 2015; Wecklerle 2011). SLE is diagnosed most often in women in the first to fourth decades (Margery-Muir 2017), the so called ‘child-bearing years’ (Feldman 2019). In men, diagnosis is most common after age 59 (Jarukitsopa 2015). Most recent studies have confirmed that females have higher incidence and prevalence regardless of age or ethnic origin (Rees 2017). Gender differences in the clinical presentation of this disease have been reported (Yacoub Wasef 2004). Rees 2017 noted differences based on ethnicity, reporting that for either gender, prevalence of SLE was highest among those of black ethnicity, with white ethnic groups reporting the lowest prevalence, and Asian and Hispanic groups an intermediate prevalence.

Etiology of SLE

The cause of SLE is not yet completely understood (Wallace 2007). Environmental and genetic factors interact in the onset and progression of SLE (Wallace 2007). Epidemiological studies indicate that smoking, ultraviolet radiation, and certain medications are risk factors (Wallace 2007).
Some of the medications more commonly implicated in drug-induced lupus erythematosus are procainamide, hydralazine, isoniazid, quinidine, methyldopa, chlorpromazine, minocycline, anti-tumour necrosis factor agents (infliximab, etanercept, adalimumab, certolizumab pegol), terbinafine, non-steroidal anti-inflammatory drugs (NSAIDs), fluorouracil agents, and pantoprazole (Dalle Vedove 2012; Merola 2012).

**Classification/Diagnosis of SLE**

The diagnosis of SLE is typically made when the classification criteria of the ACR, first established in 1971 (Cohen 1971), revised in 1982 (Tan 1982), and again in 1997 (Hochberg 1997) are met. A more recent SLE classification system is the Systemic Lupus Collaborating Clinics Criteria (SLICC), which was developed in 2012. Details about these SLE classification systems are compared in detail in Feldman 2019.

**Skin disease in SLE (adult onset)**

Of the estimated seven and one-half million people with SLE in the world, 70% are believed to have at least one skin symptom at some point in their disease (Tebbe 1997). In an international survey of lupus treatment centres, the prevalence of mucocutaneous findings ranged from 30% to 60% among participants with SLE (Vitalli 1996); the malar rash was most frequent (40%), followed by alopecia (24.1%), and oral ulcers (18.6%).

In most studies of SLE, skin is second only to joints as the most affected organ system (Vitalli 1996). Skin symptoms are the second most common reason why people with SLE initially seek medical care (Cervera 1993; Jonsson 1988).

Depending on the ACR criteria used, a person can be diagnosed with SLE based on skin disease alone (Albrecht 2004). For example, four of the 11 ACR criteria from 1982 were related to the skin: malar rash (classic butterfly rash across cheeks), discoid rash, photosensitivity (excessive sensitivity to sunlight), and mouth ulcers (Tan 1982).

**Quality of life in adults with skin disease in SLE**

Cutaneous disease in SLE, which can be temporary or may lead to permanent scarring, causes less mortality than internal organ involvement but can be distressing to those with the condition, and may result in significant psychosocial disabilities (Tebbe 1997).

Studies have shown that cutaneous SLE can have a profoundly negative effect on quality of life, especially on mental health (Klein 2011). Compared to other common skin conditions, patients with cutaneous lupus have worse quality of life and similar or worse mental health status scores than people with hypertension, type 2 diabetes mellitus, recent myocardial infarction, or congestive heart failure (Klein 2011). Young females who have severe, generalised disease are said to have a poorer quality of life; distribution of lesions is also a factor for quality of life (Klein 2011).

**Skin disease in SLE (child-onset)**

Child-onset lupus is SLE that occurs after the neonatal period and before adulthood. In this review, we included child-onset lupus. Child-onset lupus is associated with higher odds of malar rash (odds ratio (OR) 1.9) or ulcers/mucocutaneous involvement (OR 1.4) (Livingston 2011). There was no difference between adults and children in the odds of discoid rash, photosensitivity, or alopecia (Livingston 2011). Raynaud’s was more common among adults than children (OR 0.4 to 0.7) (Livingston 2011).

**Categories of CLE**

Cutaneous lupus erythematosus (CLE) is most basically defined as skin findings in patients with lupus erythematosus.

CLE can be divided into three basic categories.

- CLE with systemic involvement (meeting ACR/SLICC criteria).
- CLE with some systemic involvement (not meeting full ACR/SLICC criteria).
- CLE with no systemic involvement (single-organ involvement confined to skin).

Over the years, various authors have proposed similar classifications (Halmi 1993; Watanabe 1995). The distinction between these three basic categories is important from clinical and prognostic standpoints. Patients with CLE and systemic involvement are treated by practitioners of primary care, rheumatology, and dermatology, and they often require more extensive diagnostic workups; more complex, extensive, and risky treatments; and more frequent follow-up; they may have a worse prognosis. Patients with CLE and minimal/mild systemic involvement that does not yet meet full criteria for SLE are followed by a team comprising primary care, rheumatology, and dermatology specialists, and they are monitored at intervals for signs of progression to a full diagnosis of SLE. CLE patients with no signs of systemic involvement are typically followed by primary care and dermatology practitioners. These ‘CLE only’ patients should be monitored for signs of progression to SLE because in an estimated 20% of people with CLE, disease eventually evolves over years to meet the full ACR criteria for SLE (Tebbe 1997).

**Epidemiology of CLE**

In the past, CLE or lupus-associated skin disease was estimated to be two to three times more common than SLE (Tebbe 1997). Reasons cited for the difference are that not all people with CLE meet full ACR criteria for the diagnosis of SLE (Tan 1982). However, data from Tebbe 1997 may also have been subject to bias because they were derived from a dermatology population. More recent data suggest more equal numbers of CLE and SLE (Durosaro 2009), particularly in women (Jarukitsopa 2015). However, CLE was three times more common than SLE among men (Jarukitsopa 2015).

**Diagnosis/Classification of CLE**

The classification of CLE has a long history in dermatology and rheumatology, with many proposed systems. The Kuhn 2005 review describes this history in detail.

In brief, one of the most commonly used classification systems for CLE is the Gilliam and Sontheimer classification (Gilliam 1981; Gilliam 1982), which categorises cutaneous signs in lupus erythematosus by their histopathological characteristics into the two main categories of (1) lupus-specific and 2) lupus-non-specific disease.

Lupus-specific CLE lesions were noted in Gilliam 1981 to have the same specific histology under the microscope, namely, inflammation at the dermoepidermal junction, also known as an
interface dermatitis, whereas lupus-non-specific lesions had non-specific histological findings.

Other classification systems are discussed in detail in Kuhn 2005 these include the Düsseldorf Classification of Cutaneous Lupus Erythematosus 2003 (Kuhn 2003), as well as the European Academy of Dermatology and Venereology (EADV) classification (Beutner 1993).

The Düsseldorf classification of CLE 2003 has the classical three categories of (1) acute, (2) subacute, and (3) chronic CLE, as proposed by Gilliam 1981, plus two additional categories of CLE disease: (4) intermittent cutaneous lupus erythematosus (ICLE), and (5) bullous lesions in lupus erythematosus erythematosus (BLE) (Kuhn 2005).

Study authors also present many versions of modified Gilliam classifications (Chong 2019).

Skin disease in CLE: lupus-specific subsets

Lupus-specific skin symptoms are further defined as skin symptoms found exclusively in people with lupus erythematosus and not seen in those with other diseases. They are subcategorised into three groups based on the length of time that skin symptoms are typically present: acute, subacute, and chronic (Gilliam 1981).

**Acute CLE**

Acute CLE is defined as four main types (Chong 2019).

- Bilateral malar rashes (butterfly rash, localised to the face area).
- Morbilliform rashes (generalised on the body).
- Toxic epidermal necrosis-like.
- Bullous LE.

**Subacute CLE**

Subacute cutaneous lupus erythematosus (SCLE) also has four main types (Chong 2019).

- Annular (round or polycyclic inflamed skin lesions occurring on areas exposed to the sun).
- Papulosquamous/psoriasiform.
- Vesiculobullous annular.
- Toxic epidermal necrosis-like.

Subacute cutaneous lupus erythematosus is associated with characteristic antibodies in the blood against components of the cell nucleus, called ribonuclear protein and ‘Ro’ and ‘La’ antibodies (Wallace 2007). Approximately one-half of those with SCLE meet full ACR criteria for SLE (Callen 2007). We excluded SCLE patients without a diagnosis of SLE from this review because a separate Cochrane Review was planned on this topic.

**Chronic CLE**

Chronic CLE (CCLE) has different forms (Chong 2019). One of the most common forms of CCLE is the classical discoid lupus erythematosus (DLE), characterised by discoid or coin-shaped erythematous plaques that can be localised or generalised. Other forms of CCLE include hypertrophic/verruccous DLE, lupus panniculitis/lupus profundus, mucosal DLE, tumid LE, chilblain LE, and LE-lichen planus overlap (Chong 2019).

About 90% of people with DLE and other forms of CCLE never go on to meet full ACR criteria for SLE through the course of their disease (Gilliam 1981), so CCLE/DLE is often considered solely as a skin disease and is the topic of a separate Cochrane Review (Jessop 2005; Jessop 2017).

Skin disease in CLE: lupus-non-specific subsets

Lupus-non-specific skin symptoms are defined in Gilliam 1981 as skin symptoms occurring in people who have been diagnosed with SLE by ACR (Cohen 1971; Hochberg 1997; Tan 1982), or SLICC criteria (Petri 2012), but that are not exclusive to SLE (i.e. also found in other autoimmune conditions). Some of the most common lupus-non-specific skin symptoms are photosensitivity (excessive sensitivity to sunlight), mouth ulcers, alopecia (hair loss), Raynaud’s phenomenon (spasm of blood vessels in fingers and toes), and vasculitis (inflammation of blood vessels), and these same signs/symptoms have served as official ACR (Cohen 1971; Hochberg 1997; Tan 1982), or SLICC (Petri 2012), classification criteria over the years. Other lupus-non-specific skin symptoms include antiphospholipid antibody-associated rashes (livedo reticularis, superficial thrombophlebitis, cutaneous ulcers, purpura/eczematoses, subungual splinter haemorrhages, digital gangrene), cryoglobulin-associated rashes (purpura/eczymosis, haemorrhagic skin necrosis, cutaneous ulcers), other cutaneous vascular reactions (urticaria, periungual telangiectasia, erythromelalgia/palmar erythema), papulonodular mucinosis, calcinosis cutis, nail changes, anetoderma, and interstitial granulomatous dermatitis/palisaded neutrophilic granulomatous dermatitis (Chong 2019).

CLE and disease prognosis

Different skin symptoms correspond to different levels of overall SLE disease severity. For example, acute lupus-specific skin symptoms are associated with higher SLE activity when compared with chronic lupus-specific skin symptoms (Parodi 2000; Zeccevic 2001). On the other hand, lupus-non-specific skin symptoms are associated with higher SLE disease severity than lupus-specific skin symptoms (Parodi 2000; Zeccevic 2001). It has also been noted that active lesions are more bothersome than scarring for most patients (Verma 2014).

Description of the intervention

A wide variety of interventions are available for cutaneous disease in SLE, including pharmacological agents and complementary and alternative therapies, as well as other interventions.

Pharmacological agents include topical and systemic medications (Lee 2003). Topical medications are divided into the main categories of beta-2-adrenergic receptor agonists, calcineurin inhibitors, corticosteroids, and Janus kinase (JAK) inhibitors. Systemic medications are divided into the following broad categories: antibiotics, antimalarials, biologic therapies, calcineurin inhibitors, calcium channel blockers, chemotherapy, corticosteroids, hormones, immunomodulatory agents, JAK inhibitors, leukotriene synthesis inhibitors, monoclonal antibodies, and supplements.

Systemic agents may be delivered in a topical (via absorption), oral, injectable, intravenous, intramuscular, or subcutaneous manner, or in combinations thereof.
Other categories of interventions include behavioural interventions, camouflage makeup, and light (photo) therapy.

Complementary and alternative medicine treatments include naturopathic medicine, cognitive-behavioural therapy (CBT), Traditional Chinese Medicine (TCM), and other healing traditions from around the world.

A summary of treatment options mentioned in this review, along with their interventional categories, mechanisms of action, and references to relevant RCTs for cutaneous disease in SEL, is provided in Table 2.

Current treatment options for cutaneous disease in SLE

Topical pharmacological therapies

Beta-2-adrenergic receptor agonists

Levosalbutamol cream (R-salmbutamol 0.05% cream) has been studied for cutaneous SEL (Jemeck 2009).

Calcineurin inhibitors

The main types of topical calcineurin inhibitors used for cutaneous disease in SEL are tacrolimus ointment - Kuhn 2011; Pothinamthong 2012; Tzong 2007 - and pimecrolimus cream (Barikbin 2009; Sticherling 2007).

Corticosteroids

In clinical practice, many different types of topical steroids of varying potency are used for cutaneous disease in SEL. The corticosteroid may be selected on the basis of one or more factors including location of disease on the body, severity of lesions, efficacy, side effects, availability, and cost. Some examples of topical steroids that have been featured in studies over the years include clobetasol propionate (Tzong 2007), fluocinolone ointment (Bjornberg 1963), diflucortolone valerate (Handa 1985), hydrocortisone acetate (Handa 1985), and betamethasone 17-valerate (Barikbin 2009).

JAK inhibitors

Topical 6% R932333 ointment (also known as R333), a JAK inhibitor, was studied in cutaneous disease in SEL (Duliege 2016).

Systemic pharmacological medications

Antibiotics (oral)

An antibiotic that has been used in cutaneous disease in SEL is clofazimine (Bezerra 2005).

Antimalarials (oral)


Biologic therapies (intravenous)

Biologic therapies that have been used in SEL include abatacept - Merrill 2010b - and atacicept (Pen-Rossi 2009).

Blisibimod, also known as A-623 or AMG-623, is a selective antagonist of B cell-activating factor (BAFF) used in cutaneous disease in SEL (Furie 2015b).

A novel recombinant, soluble, human FcγRIIB receptor used in SEL is SM101 (Tillmanns 2014).

Calcineurin inhibitors (oral)

Oral calcineurin inhibitors used in SEL include ciclosporin (Dammacco 2000; Griffiths 2010).

Calcium channel blockers (oral)

Calcium channel blockers such as nicardipine - Rupp 1987 - and nifedipine - Kahan 1985 - are used for Raynaud's phenomenon or disease manifestations of cutaneous disease in SEL.

Cereblon inhibitor (oral)

A cereblon inhibitor that is used in cutaneous disease in SEL is CC-220, also known as iberdomide hydrochloride, or IBER (Werth 2017a).

Chemotherapy (intravenous and oral)

Chemotherapy agents used include intravenous bortezomib - Ishii 2015 - and oral lenalidomide (Okon 2014).

Corticosteroids (oral or intravenous)

Corticosteroids used include oral prednisone - Tseng 2006 - and intravenous 6-methylprednisolone - Dammacco 2000 - given in pulsed, continuous, or tapered dosing.

Hormones (oral, repository injection, or gel)

Hormonal therapy used in cutaneous disease in SEL includes corticotropin repository injection or gel - Furie 2015a; Furie 2016a - and oral dihydroepiandrosterone - Dammacco 2000 - known as prasterone (Petri 2004; Van Vollenhoven 1995).

Immunomodulatory agents (oral and intravenous)

Immunosuppressant agents used in cutaneous disease in SEL include azathioprine (Griffiths 2010; Ord-Ros 2017), cyclophosphamide (Andrade-Ortega 2009; Petri 2010), dapsone (Yahya 2013), methotrexate (Carneiro 1998; Fortin 2005; Islam 2012), and mycophenolate sodium (Ord-Ros 2017; Yahya 2013).

Thalidomide is also used in SEL around the world (Vitali 1996).

JAK inhibitors (oral)

An oral JAK inhibitor that is used in cutaneous disease of SEL is baricitinib (Wallace 2018).

Leukotriene synthesis inhibitors (oral)

A leukotriene synthesis inhibitor that has been used is zileuton (Hackshaw 1995).

Monoclonal antibodies (intravenous and subcutaneous)

Many different types of monoclonal antibodies are being used as treatments for cutaneous diseases in SEL, including anifrolumab (Furie 2015c), belimumab (Furie 2011; Navarra 2011; Stohl 2017; Wallace 2009), BIIB059 (Furie 2016a), epratuzumab (Clowse 2015; Wallace 2013; Wallace 2014), subcutaneous lutilizumab pegol (Merrill 2018), rituximab (Andrade-Ortega 2009; Merrill 2010a), sitafirumab (Khamashia 2016; Merrill 2011; Petri 2013), sirukumab (Szepeitowski 2013), tabalumab (LY-2127399) (Merrill 2016), and ustekinumab (Van Vollenhoven 2018).
Retinoid (oral)
A retinoid used in cutaneous disease in SLE is acitretin (Ruzicka 1992).

Supplements (oral)
Nutritional supplements that have been used for cutaneous disease in SLE include cholecalciferol (vitamin D) (Lima 2016), copper (Duffy 2004), and fish oil (Duffy 2004; Walton 1991; Westberg 1990; Wright 2008).

Other Interventions

 Behavioural interventions
Given that smoking and ultraviolet light exposure (UVB and UVA-2) are risk factors for development of SLE, behaviour modifications such as smoking cessation (Callen 2005), sun avoidance with the use of sunscreen (high sun protection factor (SPF) with UVA protection) (Kuhn 2011a; Stege 2000), and protective clothing are used to treat cutaneous disease in SLE.

Camouflage
Camouflage makeup therapy is used in cutaneous SLE (Lanna 2019).

Light (photo) therapy
Ultraviolet
UVA-1 phototherapy (limited to 340 to 400 NM) delivered dermally and at low levels has been used to treat SLE (McGrath 1996; Polderman 2001).

Laser (visible spectrum)
A pulsed dye laser with wavelength of 595 NM has been used to treat cutaneous SLE (NCT00523588).

Complementary and alternative medicine treatments for SLE
It is estimated that 50% of people with SLE have used complementary and alternative medicine treatments for symptoms (Greco 2013).

Complementary and alternative therapies that have been studied and reviewed for SLE include supplements vitamin C, vitamin E, N-acetylcycteine (NAC), and tumeric (Greco 2013); green tea extract (Shamekhi 2017); acupuncture; and mind-body therapy including cognitive-behavioural therapy (CBT), interpersonal therapy, meditation, and other behavioural treatments (Greco 2013). However, unfortunately, far fewer of these therapies have been studied in any detail for specifically cutaneous disease in SLE. Yarnell 2008 reviewed some herbal medications used for SLE (some of which are also used for DLE) such as Urtica dioica (nettles), Nelumbo nucifera (lotus), phytoestrogens such as coumestrol, and Linum usitatissimum (flax seeds) for lupus nephritis.

Traditional Chinese Medicine (TCM) treatments for SLE
Traditional Chinese Medicine (TCM) treatments are also available for SLE (Li 2012). Some of the more commonly used TCM treatments for SLE have been reviewed in detail by Zhong 2013: Radix astragali (dried root of Astragalus membranaceus (Fisch.) Bunge, and Astragalus mongholicus Bunge (Fabaceae)), Wolfberry (Goji) fruit (Lycium barbarum or Lycium chinense), Radix polygoni multiformi (root tuber of Polygonum multiflorum Thumb.), Ganoderma lucidum (medicinal mushroom), and Glycyrrhiza uralensis. Qing Hao is a TCM with antimalarial properties (Dharmananda 2020); it has been used in SLE (ChiCTR-12002402). Heng 2016 conducted a systematic review of TCM integrated with western medication for lupus nephritis and identified six RCTs.

The following forms of TCM were studied in cutaneous disease in SLE or CLE: Zi Sen Qing oral herbal formula (Zhong 2013), and oral ginsenosides from Radix ginseng (dried root of Panax ginseng C.A. Meyer (Araliaceae)) (You 2010), Dharmananda 2020 reviewed some forms of TCM used in SLE including some of the variations used to treat cutaneous manifestations. Yarnell 2008 reviewed TCM used for SLE (some of which may also be used for DLE) such as the immunosuppressant Tripterygium wilfordii (lei gong teng, thunder god vine), the antimalarials Artemisia annua and Artemisia apicaceae (sweet Annie, qing hao), and the immunomodulators Trametes versicolor (cloud mushroom, yun zhi), Cordyceps sinensis (cordingceps, dong chong xiao cao), Ganoderma lucidum (reishi, ling zhi), and Centella asiatica (gotu kola).

Clinical approach to cutaneous disease in SLE
The treatment chosen depends on the severity, type, extent, and empirical clinical responsiveness of skin symptoms, as well as the severity of non-skin symptoms (Lee 2003).

For mild or localised cutaneous disease in SLE, standard treatments include topical or injectable corticosteroids and oral antimalarials (hydroxychloroquine, chloroquine, and quinacrine) (Callen 2002; Callen 2004; Callen 2005). If these standard treatments are not effective, other topical immunomodulators such as calcineurin inhibitors (tacrolimus or pimecrolimus) may be tried (Callen 2005; Callen 2006). For cutaneous disease in SLE that is resistant to the above agents, systemic therapies such as oral corticosteroids (prednisone) and many other immunosuppressant agents have been used (Callen 2002; Callen 2004; Callen 2005). Results have been highly variable depending on the extent and type of cutaneous symptoms (Callen 2002; Callen 2004; Callen 2005). Fairley 2020 presents a similar suggested treatment algorithm that has been updated based on findings of the most recent studies.

In an international survey of 153 lupus centres worldwide, the percentages of respondents using the following interventions for cutaneous lupus manifestations were as follows: hydroxychloroquine 85%, azathioprine 59%, dapsone 41%, thalidomide 35%, pulse steroids 27%, cyclosporin A 22%, and pulsed cyclophosphamide 13% (Vitali 1996).

Considerable toxicities are known for some of the more aggressive systemic treatments including kidney damage, liver damage, cancer, bone destruction, infection, nerve damage, birth defects in children born to women on the medications (teratogenicity), deep vein thrombosis, and death (Wolverton 2001).

How the intervention might work
Pathophysiology of SLE and its cutaneous manifestations
Systemic lupus erythematosus is associated with polynuclear B-cell activation (Wallace 2007). Abnormal circulating T cells are also observed in SLE, and experimental evidence shows that T cells are important in skin and kidney manifestations of SLE (Wolverton 2001). Cytotoxic T cells are also involved in generalised DLE (Wenzel 2005). Deficiencies in different complement factors
(C1q, C2, C3, C4, C5) have been associated with SLE, DLE, and lupus erythematosus-associated panniculitis (fat inflammation) (Wallace 2007). Photosensitivity is associated with abnormal tumour necrosis factor-alpha (TNF-α) expression (Wallace 2007). In newer information reviewed in Gardet 2019, interferon-1 (IFN-1) dysregulation is now known to be a key factor in both SLE and CLE pathogenesis. Recent focus has turned to the role of plasmacytoid dendritic cells (pDCs) - specialised cells that secrete interferon-1 in response to toll-like receptors (TLRs) types 7/8 and 9 by nucleic acid ligands, accumulating in skin and setting off numerous cascades of reactions that lead to cutaneous lupus pathogenesis (Gardet 2019).

**Mechanism of action of different treatment interventions**

Interventions for cutaneous disease in SLE are hypothesised to work through various mechanisms to restore disease-induced imbalances in B cells, T cells, complement, TNF-α, interferon-α, interleukins, and immunoglobulins (Wolverton 2001). Nutan 2017 reviews in detail some of the newest information on mechanisms of action. Following is a brief summary of the mechanisms of action for different interventions; these are also presented in Table 2.

**Antibiotics**

The antibiotic clofazimine may work on cutaneous disease in SLE due to its concomitant anti-inflammatory and immunosuppressant properties (Nutan 2017).

**Antimalarials (oral)**

Oral antimalarial therapies, such as chloroquine and hydroxychloroquine, are thought to act as immunosuppressant and anti-inflammatory agents, affecting light filtration and DNA binding, inhibiting formation of antigen-antibody complexes, and decreasing lymphocyte responsiveness (Kalla 2007). One of the mechanisms of action of antimalarials involves inhibition of endosomal TLR signalling, limiting B-cell and dendritic cell activation (Kalla 2007). Another mechanism of action of antimalarials may involve inhibition of angiogenesis (Lesiak 2008). The antimalarial hydroxychloroquine immunomodulates lysosome stabilisation and reduces interferon production by pDCs (Ponticelli 2017).

**Beta-2-adrenergic receptor agonists (topical)**

Levosalbutamol cream (R-salbutamol sulfate 0.05% cream) is a topical formulation of the well-known beta-2-adrenergic receptor agonist molecule albuterol (aka salbutamol) used in lung conditions (Jemec 2009). Albuterol/salbutamol has anti-inflammatory effects and has been shown to help cutaneous SLE (Jemec 2009). Biologic therapies (intravenous)

Abatacept is a "fully human, soluble fusion protein that consists of the extracellular domain of human cytotoxic T lymphocyte-associated (CTLA) linked to IgG1, which selectively modulates the CD80/CD86:CD28 costimulatory signal" (Merrill 2010b).

Atacicept is a "recombinant fusion protein containing the extracellular, ligand-binding portion of the transmembrane activator, calcium modulator, and cyclophilin-ligand interactor receptor, and the Fc portion of human immunoglobulin (IgG, and is designed to block the activity of B-cell-mediated diseases such as SLE" (Pena-Rossi 2009).

Blisibimod, also known as A-623 or AMG-623, is "a biologic therapeutic agent composed of two high-affinity BAFF binding domains fused to the Fc (fragment crystallisable) region (tail region) domain of IgG1". It works as a selective antagonist of BAFF. "BAFF is upregulated in SLE and peripheral BAFF concentrations have been shown to correlate with disease activity" (Furie 2015b).

A novel recombinant, soluble, human FcYIIIB receptor called SM101 binds to the Fc part of autoimmune complexes and inhibits the binding of immunocomplexes to cell-standing Fcg receptors (Tillmanns 2014).

**Calcineurin inhibitors (topical and oral)**

Topical calcineurin inhibitor creams, such as tacrolimus or pimecrolimus, as well as oral ciclosporin, decrease the responsiveness of T lymphocytes to foreign antigens by inhibiting the intracellular enzyme calcineurin (Wolverton 2001; Wolverton 2020).

**Calcium channel blockers (oral)**

Calcium channel blockers such as nicardipine - Rupp 1987 - and nifedipine (Kahan 1985), which are used for the Raynaud's phenomenon disease manifestation of CLE in SLE, work by "preventing Ca2+transport across the plasma cell membrane" of blood vessel smooth muscle cells, thus "inhibiting excitation contraction coupling and muscle constriction" (Wolverton 2020).

**Cereblon inhibitor (oral)**

A cereblon inhibitor used in cutaneous disease in SLE, CC-220 (also known as ibedomide hydrochloride, or IBER), may work by decreasing B-cell subsets and plasmacytoid dendritic cells (Werth 2017a).

**Chemotherapy (intravenous and oral)**

Bortezomib is a chemotherapy agent that is a "proteasome inhibitor targeting plasma cells widely used in the treatment of plasma cell tumours". It is now being used as SLE treatment due to its ability to target the "antibody-producing B-cell line" (Ishii 2015).

Lenalidomide, a derivative of thalidomide and a chemotherapy agent used to treat myelodysplastic syndrome (MDS), multiple myeloma, and mantle cell lymphoma (MCL), may work in SLE by "inhibiting the synthesis of tumor necrosis factor alpha (TNF-α)" (Nutan 2017).

**Corticosteroids (oral or intravenous)**

Corticosteroids (oral or systemic) have effects on both B cells and T cells, lowering immunoglobulin production and decreasing TNF-α (Wolverton 2001).

**Hormones (oral, repository injection, or gel)**

Corticoterpin is a "prolonged-release formulation containing a highly purified porcine adrenocorticotropic hormone (ACTH) analogue" (Furie 2016a). "ACTH may increase levels of the anti-inflammatory cytokine interleukin (IL)-10 and decrease B-lymphocyte proliferation and differentiation, as reflected by significant reductions in splenic B-lymphocyte follicular and
germinal centre cells and decreased levels of anti-double-stranded DNA (dsDNA) autoantibodies in a rodent model of lupus" (Furie 2016a). Also in humans, it was found that corticosteroids "attenuated IL-4/C40 ligand-induced proliferation and immunoglobulin production in B-lymphocytes isolated from healthy human volunteers" (Furie 2016a).

Oral dehydroepiandrosterone (DHEA), also known as prasterone, is an adrenal steroid hormone that tends to be reduced by about 50% in people with SLE. "DHEA has an immunomodulatory role, including the upregulation of IL-2 and downregulation of IL-6, both of which have been reported to be abnormal in SLE" (Greco 2013; Petri 2004; Van Vollenhoven 1995).

**Immunomodulatory agents (oral)**

**Alkylation cytotoxic agents**

Cyclophosphamide acts by "cross linking DNA leading to cell death by apoptosis", "preferentially affecting proliferating cells", although "it acts independently of the cell cycle" (Wolverton 2020).

**Antimetabolite cytotoxic agents**

Azathioprine is a purine analogue that works by depressing T-cell, B-cell, and antigen-presenting cell functions (Wolverton 2020).

Methotrexate binds to the dihydrofolate reductase enzyme, inhibiting cell division in the DNA synthesis phase in immune cells, suppressing primary and secondary antibody production (Wolverton 2020).

Mycophenolate sodium "inhibits purine biosynthesis, targeting the lymphocytes most responsible for disease" (Wolverton 2020).

**Anti-TNFs**

Thalidomide works to improve cutaneous SLE by inhibiting "the synthesis of tumor necrosis factor alpha and ultraviolet B induced keratinocyte apoptosis with inhibition of interferon gamma" (Nutan 2017).

**Myeloperoxidase inhibitor**

Dapsone inhibits myeloperoxidase found in neutrophils, eosinophils, and monocytes (Wolverton 2020).

**JAK inhibitors (oral)**

Barticitinib is an "oral selective Janus kinase (JAK)-1 and JAK-2 inhibitor" that blocks proinflammatory cytokines (Wallace 2018).

**Leukotriene synthesis inhibitors (oral)**

Zileuton is a leukotriene synthesis inhibitor, specifically an inhibitor of 5-lipoxygenase. Leukotrienes are found to be abnormally elevated in SLE (Hackshaw 1995).

**Monoclonal antibodies (intravenous)**

The mechanism of action of the monoclonal antibodies can be divided into groups based on the main target antigen: B cell-activating factor (BAFF), aka B-cell lymphocyte stimulator (BLys), CD molecules, IFN-alpha, immunoglobulins, or interleukins.

B cell-activating factor (BAFF), aka B-cell lymphocyte stimulator (BLys)

"BAFF is upregulated in SLE, and peripheral BAFF concentrations have been shown to correlate with disease activity" (Furie 2015b). The following monoclonal antibodies block BAFF.

Belimumab is a humanised IgG1y monoclonal antibody directed against "the target soluble B lymphocyte stimulator (BllyS)", also known as B cell-activating factor (BAFF), which is "a soluble ligand of the TNF cytokine family, and is a prominent factor in B cell differentiation, homeostasis, and selection" (Furie 2011).

Tabulamab (LY-2127399) is a fully human immunoglobulin G subclass 4 (IgG4) monoclonal antibody that binds and neutralises both soluble and membrane-bound BAFF (Merrill 2016).

**CD molecules**

Epratuzumab is a "humanized anti-CD22 monoclonal antibody that modulates B-cell signalling without total B-cell depletion" (Closse 2015). Rituximab is a chimeric anti-CD20 monoclonal antibody (Nutan 2017). Lulizumab pegol is an anti-CD28 domain antagonist (Merrill 2018). CD28 is a "T-cell co-stimulatory molecule critical for the activation of pathogenic T cells in autoimmune diseases" (Merrill 2018).

**Dendritic cells**

BLII659 is a fully humanised IgG1 monoclonal antibody targeting blood dendritic cell antigen-2 (BDCA-2) expressed on plasmacytoid dendritic cells (Furie 2015b).

**IFN-alpha**

Examples of IFN-alpha inhibitors are anifrolumab (anti-IFN-alpha-1a receptor) - Nutan 2017 - and sifalimumab (humanised anti-IFN-alpha) (Nutan 2017).

**Interleukins**

The following therapies are monoclonal antibodies against interleukin-associated proteins: ustekinumab works against an interleukin (IL)-12 and IL-23 binding protein (Nutan 2017). Sirukumab is an anti-IL-6 monoclonal antibody (Nutan 2017).

**Retinoid (oral)**

Acitretin is a systemic retinoid that may work in cutaneous SLE - Ruzicka 1992 - via its "ability to affect pathways involved in inflammation, cellular differentiation and apoptosis" (Wolverton 2020).

**Supplements (oral)**

Cholecalciferol (vitamin D) deficiencies have been noted in SLE (Lima 2016). Specifically, cholecalciferol may play a role in "B-cell regulation and antibody secretion" and may act on receptors on dendritic cells and T cells as well (Lima 2016).

Although the effect of copper in SLE is not well understood, copper is used in the treatment of inflammatory disease (Duffy 2004). SLE patients have been observed to have higher mean serum copper concentrations, thought to be "directly related to disease activity" and a tissue "inflammatory response", where tissue copper is consumed at higher than normal rates, reading to localised (tissue) deficiencies (Duffy 2004). "Exogenous copper decreases formation of lupus erythematosus cells in rats" (Duffy 2004).
Animal studies have shown that consumption of an "omega-3 fatty acid-rich" diet leads to "an increased lifespan, reduced autoantibody levels and decreased levels of inflammatory cytokines" (Duffy 2004). Fish oil has also been noted to improve endothelial function that is beneficial in autoimmune diseases such as SLE (Wright 2008).

**Behavioural interventions**

Smoking and ultraviolet light exposure are risk factors for the development of SLE. Behaviour modifications such as smoking cessation and sun avoidance, with the use of sunscreen (high SPF with UVA protection) and protective clothing, help control cutaneous SLE (Callen 2005).

Certain medications (procoainamide, hydralazine, minocycline, isoniazid, TNF inhibitors (etanercept and infliximab), and others) are also well-known risk factors for SLE (Dalle Vedove 2012; Merola 2012; Werth 2017b), and avoidance of these risk factors is central to controlling cutaneous SLE (Callen 2005).

**Camouflage**

Camouflage therapy is used to treat a variety of skin conditions (Levy 2012), including cutaneous SLE (Lanna 2019). Studies show rapid and dramatic improved quality of life (Levy 2012; Lanna 2019). The mechanisms of action for improved quality of life from camouflage therapy, especially when initiated at the "onset of treatment", are hypothesised to relieve suffering "from skin lesions causing emotional distress" on an immediate/rapid basis to help "build confidence in the patient-physician relationship", "increasing patient satisfaction" and "compliance with concurrent medical therapies", especially for those treatments that may take weeks to months to show results.

**Complementary and alternative therapies**

Complementary and alternative therapies have largely unknown mechanisms of action with some exceptions (Greco 2013). Green tea extract (Camellia sinensis) has "antiinflammatory and immunomodulatory benefits" (Shamekhi 2017).

**Laser therapy**

The mechanism of action of a pulsed dye laser (with wavelength of 595 NM) on CLE lesions is thought to be the "destruction of blood vessels", leading to "decreased inflammation" and "disease regression" (Winkelmann 2013).

**Phototherapy**

UVB and UVA-2 (320 NM to 340 NM) exposures are known triggers of SLE. However, specifically UVA-1 phototherapy (limited to 340 to 400 NM) delivered dermally and at low levels is observed to relieve SLE (McGrath 1996; Polderman 2001). The hypothesis for the difference in effect is that only the more deeply penetrating UVA-1 photons induce an "immediate non-transcriptional" apoptosis and therefore a "clean and non-inflammatory" apoptosis that focuses on local disease while minimising collateral damage and unwanted "spill-over" effects (McGrath 1996).

**Traditional Chinese Medicine (TCM)**

The mechanisms of action of various Traditional Chinese Medicine therapies vary greatly. The Zì Shèn Qìng is thought to result from regulation of CD4 and CD25 (Liu 2007).

"Ginsenosides, the major pharmacologically active ingredients of ginseng, appear to be responsible for most of the activities of ginseng including vasorelaxation, antioxidation, anti-inflammation and anti-cancer" (Lu 2009). Ginsenosides (from ginseng stem and leaves) have also been reported to enhance transactivation of the glucocorticoid receptor (You 2010).

**Emerging treatment options for cutaneous disease in SLE**

New treatments for cutaneous disease in SLE are continually being developed and have been reviewed by various authors, including Kalunian 2009; Robak 2012; NHS 2014; Durcan 2016; Presto 2017; and Felten 2018. The most recent detailed reviews include Durcan 2016, which reviewed immunomodulators in SLE; Presto 2017, which reviewed new biological therapies in CLE; and Felten 2018, which provided a recent systematic review of ongoing trials in SLE.

The sections below briefly summarise some of the emerging therapies that are most relevant to this review, along with their mechanisms of action. We also reference relevant upcoming studies of interest featuring these emerging therapies.

The major classes of interventions that are currently emerging include alternative and complementary therapies, antiplatelet agents, biological agents, interleukins, JAK inhibitors, monoclonal antibodies, nanobodies, muteins, tyrosine kinase 2 (TYK2) inhibitors, tyrosine kinase 2/JAK-1 inhibitor combination agents, and vaccines.

**Alternative and complementary therapies**

The following alternative and complementary therapy is under investigation: the cholinergic anti-inflammatory pathway in lupus (NCT02822989).

**Antiplatelet agents**

Dipyridamole is an antiplatelet agent that inhibits phosphodiesterase (PDE)3 and nucleoside transport and is being studied in cutaneous SLE (NCT01781611).

**Biological agents**

AMG 570 is a "bisspecific molecule targeting T-cell and B-cell activity through inhibition of the inducible co-stimulator ligand (ICOSL) and the B cell activating factor (BAFF)" (NCT04058028).

Forgerimod acetate (also known as Lupuzor, Rigenmod, IP-201101, peptide P140, CEP-33457, and Syb1001) is a novel therapeutic agent (oligopeptide/therapeutic nucleolin) called a spliceosomal peptide that modulates autoregulation of T cells. Trials in SLE are ongoing, however none so far with skin outcomes.

RSLV-132 is a novel fully human biologic Fc fusion protein that comprises human RNase fused to the Fc domain of human IgG1. This acts by slicing apart inflammatory RNA/antibody complexes, thereby reducing inflammation in SLE (NCT02660944).

**Interleukins**

He 2019 is an RCT featuring low-dose IL-2, which has been shown to induce "expansion of regulatory T cells and NK cells, which may contribute to the restoration of immune homeostasis in SLE patients".
JAK inhibitors

Delgocitinib cream is a new topical pan-JAK inhibitor that blocks activation of the JAK/signal transducers and activators of transcription (JAK-STAT) pathway (NCT03958955).

Upadacitinib (ABT-494 or Rinvoq) is a JAK selective inhibitor (NCT03978520).

Monoclonal antibodies

Monoclonal antibodies that are being studied for cutaneous SLE include a humanised anti-IgE called omalizumab (Hasni 2019), a humanised monoclonal antibody that selectively neutralises human interleukin-10 (IL-10), called BT-063 (NCT02554019a), and a humanised monoclonal antibody against IL-6 called tocilizumab (Nutan 2017). AMG 811 (a human anti-interferon-γ antibody) is being studied in participants with SLE and DLE (Werth 2017c). BT063 is a humanised monoclonal antibody that specifically binds to and neutralises IL-10 (NCT02554019).

Combination therapy of subcutaneous belimumab administered in combination with rituximab is currently being investigated by two trials: Teng 2019 and ISRCTN47873003.

Nanobodies

ALX-0061, also known as vobarilizumab, is an anti-IL-6R Nanobody (or single domain antibody) that binds monovalently to IL-6R and serum albumin, effectively neutralising the IL-6 pathway; it is currently being studied for use in SLE (NCT02437890).

Muteins

AMG 592 is an IL-2 mutein (a protein with an altered amino acid sequence) that works by selectively inducing expansion of regulatory T cells that may play a role in SLE (NCT03451422).

Tyrosine kinase 2 (TYK2) inhibitors

BMS-986165 is an oral, selective TYK2 inhibitor that blocks cytokine-signalling pathways that lead to SLE (NCT03252587).

Elsubsrtinib (ABBV-105) is a Bruton tyrosine kinase inhibitor (NCT03978520).

Tyrosine kinase 2 and JAK-1 inhibitors (combinations)

PF-06700841 is a combination selective TYK2 and JAK-1 inhibitor (NCT03845517).

ABBV-599 is the combination of elsubsrtinib (a Bruton tyrosine kinase inhibitor) and upadacitinib (a JAK selective inhibitor) (NCT03978520).

Vaccines

Vaccines are being studied for treatment of SLE. A study if under way to evaluate an IFN-α kinaseoid vaccine that induces neutralising anti-IFN-α2b antibodies (Houssiau 2020).

Why it is important to do this review

To date, narrative and evidence-based reviews of treatment options for cutaneous disease in SLE have been completed, including Callen 2002; Callen 2004; Callen 2005; Callen 2006; Chang 2016b; Fabbri 2003; Kalunian 2009; Kuhn 2010a; Kuhn 2010b; Kuhn 2017; McCauliffe 2001; Mok 2007; Presto 2017; Tzellos 2008; and Walling 2009.

However, only three systematic reviews have examined interventions for cutaneous disease in SLE (Fairley 2020; Heath 2004; Jessop 2003), and one Cochrane Review has explored DLE (Jessop 2009, with the most recent update Jessop 2017).

This systematic review aims to provide a thorough assessment of the effectiveness of treatments for cutaneous disease in SLE, to identify areas where further investigation is needed to better focus research, and to avoid unnecessary repetition of clinical trials.

Plans for this review were published as a protocol titled "Interventions for cutaneous disease in systemic lupus erythematosus" (Hannon 2008b).

OBJECTIVES

To assess the effects of interventions for cutaneous disease in systemic lupus erythematosus (SLE).

METHODS

Criteria for considering studies for this review

Types of studies

We considered all randomised controlled trials (RCTs).

Types of participants

Inclusion criteria

We included participants of any age (including those with child-onset lupus), gender, or race who met the following criteria.

- Diagnosis of systemic lupus erythematosus (SLE) based on criteria of the American College of Rheumatology (ACR) for the classification of SLE (Cohen 1971; Hochberg 1997; Tan 1982), or of Systemic Lupus International Collaborating Clinics (SLICC) (Petri 2012), or based on Traditional Chinese Medicine (TCM) (Li 2012).

AND

- Clinical diagnosis of cutaneous lupus erythematosus (CLE).

OR

- Diagnosis of Raynaud’s phenomenon based on 1971 criteria of the ACR (Cohen 1971).

Exclusion criteria

We excluded:

1. CLE patients without a diagnosis of SLE by ACR criteria (Tan 1982 or Hochberg 1997), or by SLICC criteria (Petri 2012), or based on Traditional Chinese Medicine (Li 2012); 2. subacute cutaneous lupus erythematosus (SCLE) patients without a diagnosis of SLE by ACR criteria (Cohen 1971, Tan 1982, or Hochberg 1997) or by SLICC criteria (Petri 2012), or based on Traditional Chinese Medicine (Li 2012); 3. patients with drug-induced lupus erythematosus; and 4. patients with neonatal lupus erythematosus.
Types of interventions
We included all types of interventions. We considered intervention versus placebo trials, comparison trials between different interventions, intervention versus no treatment trials, multi-arm trials including those with factorial designs, trials with different doses of the same intervention, cross-over studies, and trials of split-body-part design with multiple interventions for each participant.

Types of outcome measures

**Timing of outcome assessment**
We measured outcomes in the short term (less than 12 months) and over the long term (12 months or greater). Outcomes were measured from the start of treatment.

**Primary outcomes**
- Complete clinical response, defined as the percentage of participants with SLE with complete resolution of cutaneous disease based on the Gilliam 1981 classification (lupus-specific or lupus-non-specific) (i.e. absence of (cutaneous) rash)
  - Lupus-specific cutaneous disease defined as:
    - malar rash (classic butterfly rash across cheeks) or other form of acute cutaneous lupus erythematosus (ACLE);
    - subacute cutaneous lupus erythematosus (SCLE); or
    - discoid rash (coin-shaped rash) or other form of chronic cutaneous lupus erythematosus (CCLE).
  - Lupus-non-specific cutaneous disease defined as:
  - Partial clinical response, defined as the percentage of participants with SLE with at least 50% improvement in cutaneous disease (lupus-specific or lupus-non-specific)

**Secondary outcomes**
- Reduction (or change) in the number (or percentage) of SLE participants with clinical flares in cutaneous disease (lupus-specific or lupus-non-specific)
- Increase (or change) in time to flare in cutaneous disease (lupus-specific or lupus-non-specific) in SLE participants
- Relapse rate (or percentage of SLE participants with relapse) in cutaneous disease (lupus-specific or lupus-non-specific) when medications are stopped or reduced
- Skin-specific measures of SLE disease activity such as:
  - Cutaneous Lupus Disease Area and Severity Index (CLASI) (Albrecht 2007);
  - Integument domain of the Systemic Lupus Activity Measurement (SLAM) (American College of Rheumatology 2004);
  - Mucocutaneous domain of the British Isles Lupus Assessment Group (BILAG) Disease Activity Index (Hay 1993);
  - Mucocutaneous domain of the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) (Bombardier 1992); and
  - Mucocutaneous domain of the SLE Responder Index (SRI) (Furie 2009).
- Dermatology Quality-of-Life Measures (DLQI) in SLE patients

Adverse events
We collected data on adverse events from interventions that led to both severe and minor events. We looked only at adverse events in included studies.

- Severe events defined as:
  - resulting in discontinuation or withdrawal from the study; or
  - resulting in significant morbidity or mortality.
- Minor events defined as:
  - bothersome to participants but not leading to discontinuation or withdrawal from the study.

Search methods for identification of studies
We aimed to identify all relevant RCTs regardless of language or publication status (published, unpublished, in press, or in progress).

Electronic searches
This review fully incorporates the results of searches conducted up to 27 June 2019. A further 497 reports of trials were identified by a search update conducted to 8 September 2020. Relevant trials identified in the update search have been added to Studies awaiting classification and will be incorporated into this review at the next update.

The Cochrane Skin Information Specialist searched the following databases using strategies based on the draft strategy for MEDLINE in our published protocol (Hannon 2008b).
- Cochrane Skin Group Specialised Register using the following search terms: lupus or ‘sle’ or ‘cle’ or ‘dle’.
- Cochrane Central Register of Controlled Trials (CENTRAL; 2019, Issue 6), in the Cochrane Library, using the strategy provided in Appendix 1
- MEDLINE via Ovid (from 1946), using the strategy presented in Appendix 2.
- Embase via Ovid (from 1974), using the strategy given in Appendix 3.

We (CWH, CM) searched the following databases up to 8 September 2020.
- Wiley Interscience Online Library (onlinelibrary.wiley.com), using the strategy provided in Appendix 4.
- Virtual Health Library (also known as Biblioteca Virtual em Saude, including LILACS, available at bvsalud.org/en), using the strategy presented in Appendix 5.

**Trials registers**
We (CWH, CM) searched the following trials registers up to 8 September 2020, using the search term ‘lupus’.
- ClinicalTrials.gov (www.clinicaltrials.gov).
- International Standard Randomized Controlled Trials Number (ISRCTN) Registry (www.isrctn.com).

The following trial register was not accessible due to technical issues as a result of the COVID-19 situation on 8 September 2020. Our latest search was completed on 27 June 2019.

**Interventions for cutaneous disease in systemic lupus erythematosus (Review)**

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World Health Organization International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch).

**Searching other resources**

**Reference lists**

We checked the bibliographies and citations of included studies, excluded studies, and review articles for further references to relevant trials.

We searched the following online review articles up to 8 September 2020.

- Natural Medicine, using the search term 'lupus'.
- Natural Standard, using the search term 'lupus'.

**Adverse effects**

We did not perform a separate search for adverse effects of interventions for cutaneous disease in SLE. We considered only the adverse effects described in included studies.

**Data collection and analysis**

**Selection of studies**

Titles, abstracts, and key words of records retrieved in the searches were reviewed independently by at least two review authors (CWH, CM, CB). Full articles of all relevant or possibly relevant references were obtained and reviewed to determine eligibility according to predefined selection criteria by at least two review authors independently (CWH, CM, CB). Logs were kept of excluded studies with reasons for exclusion (CWH, CM, CB). PRISMA diagrams were prepared to summarise this process (CWH, CB).

**Data extraction and management**

We extracted the following data from the publications: information about interventions (type of study, medications, dose, duration, experimental groups, type of control), participants (number, sex, age, demographics, types of SLE and CLE), experimental design (inclusions, exclusions, methods, risk of bias), and results (primary outcomes, secondary outcomes, adverse events). We piloted the data extraction forms and refined them as needed to improve the extraction process.

Data were extracted independently from each article by two review authors (CWH, CM) and consensus was obtained (CWH, CM). In the case of differences of opinion to determine two review authors, a third review author served as the final decision maker (CB). Consensus data were summarised qualitatively and quantitatively in the results section (CWH, CB). RevMan was used to prepare the protocol and systematic review for publication as a Cochrane systematic review (CWH, CB). These assessments are reported in the Risk of bias table for each individual study in the Characteristics of included studies section of the review (CWH, CB).

We transformed data on the presence of skin lesions as follows: ‘present’ is equivalent to ‘NOT complete clearance’ or ‘NOT complete absence’. Similarly, ‘NOT present’ is equivalent to ‘complete clearance’ or ‘complete absence’. Upon learning the total number in the group, we transformed the available presence data to the complete clearance outcome as needed.

If studies had subsets of data that could not be included in the meta-analysis, this information was reported narratively. For example, if full quantitative analysis was not possible because key quantitative information was omitted, missing, or unavailable (such as value for ‘n’ or standard deviation), available data were reported narratively along with an explanation of the additional information that would be needed for full analysis. Also, in some cases, data from SLE patients with cutaneous disease were combined with data from excluded groups. If it was not possible to fully separate the data, this was reported narratively, and the nature of the combined data was fully discussed. Any combined data were excluded from quantitative analysis and from meta-analysis.

**Assessment of risk of bias in included studies**

The quality of each study was assessed independently (CWH, CM) and consensus reached by two review authors (CWH, CM), using the Cochrane Risk of bias tools available in RevMan and described in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). Risk of bias domains that were assessed as high, low, or unclear included (1) random sequence generation (selection bias), (2) allocation concealment (selection bias), (3) blinding of participants and personnel (performance bias), (4) blinding of outcome assessment (detection bias), (5) whether incomplete outcome data were addressed (attrition bias), (6) whether the study was free of selective reporting (reporting bias), and (7) whether the study was free of other bias such as a large baseline imbalance between treatment groups.

**Measures of treatment effect**

We presented dichotomous outcomes data as risk ratios (RRs) and risk differences (RDs) along with their associated 95% confidence intervals (CIs). We analysed RRs in RevMan using the Mantel-Haenszel test, unless stated otherwise. We expressed continuous data as mean difference (MD) for the same scales or standardised mean difference (SMD) for similar but different scales. We planned to analyse ordinal outcome data as continuous or dichotomous data if appropriate and necessary for the purposes of meta-analysis. We planned to analyse counts or rates as most appropriate as dichotomous, continuous, or time-to-event or rate data. We also planned to calculate hazard ratios as appropriate.

**Unit of analysis issues**

We encountered special issues in the analysis of studies because not all studies randomised whole participants. In our search process, we encountered some non-standard designs, such as cross-over trials, split-body trials, and studies with multiple treatment groups (multi-arm) including factorial designs.

We analysed cross-over studies using first period data only as recommended by Cochrane Handbook for Systematic Reviews of Interventions guidelines (Higgins 2011 Section 16.4). In the future, if an adequate washout between periods took place and baseline data were presented for each period, then further data may be included in the meta-analysis as deemed appropriate.

For split-body trials, we followed the Cochrane guidelines from the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). Although it was not possible to include data in a meta-analysis, we reported data separately in a narrative fashion.
For multi-arm studies, to assume that analyses are not falsely powered, we partitioned the numbers of participants from the comparison arms into pair-wise comparisons. For example, a three-arm study (A, B, and placebo) with 30 participants in each arm would result in two pair-wise comparisons. The first comparison would consist of 15 participants from the placebo group (one-half of the original placebo group) versus 30 participants from group A. The second comparison would comprise 15 participants from the placebo group (one-half of the original placebo group) versus 30 participants from group B. Mean and standard deviation summary statistics for participants would remain unchanged. If it was not possible to adequately integrate data from multi-arm studies, we reported the results narratively.

For the subset of multi-arm studies that used a factorial design, we followed the procedure recommended in the Cochrane Handbook for Systematic Reviews of Interventions for a 2 × 2 factorial trial that presented “both parts of the trial as if they were just a two-arm parallel group trial” (Section 16.5.6, Factorial trials; Higgins 2011).

Dealing with missing data
We planned to obtain missing data directly from the original researchers. If data on adverse outcomes were unavailable, we planned to use the rule of three to calculate (Hanley 1983). The rule of three states that if none of n participants showed the event, we can be 95% confident that the chance of this event is at most 3/n.

Assessment of heterogeneity
To address clinical heterogeneity, we tabulated the included studies in terms of study characteristics and outcomes, then carefully examined them for quality, similarities, and differences. When we noted a high level of clinical heterogeneity, we did not consider a meta-analysis to be appropriate, and we reported the studies individually.

If meta-analysis was appropriate, we addressed statistical heterogeneity using I² (Higgins 2011). Substantial heterogeneity is defined as I² with a value greater than 50%. If extreme levels of heterogeneity existed between the studies (I² > 80%), we considered reporting the results of studies individually as appropriate and we planned to explore heterogeneity using subgroup analyses, but generally too few studies were included in each meta-analysis to do this.

Assessment of reporting biases
As needed, we planned to assess for possible reporting bias using funnel plots by examining for asymmetry when at least 10 studies were included in a meta-analysis, according to the recommendations on testing for funnel plot asymmetry as described in Section 10.4.3.1 of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). If asymmetry was detected, we planned to explore possible reasons, including selection biases, poor methodological quality of smaller studies, true heterogeneity, artefact, and chance.

Data synthesis
When possible in the future, we plan to conduct a meta-analysis of trials and subgroups, or both, using random-effects models. We will present data in the form of forest plots.

Subgroup analysis and investigation of heterogeneity
We performed subgroup analysis to explore treatment effect size differences by the more specific type of CLE, by lupus-specific (malar, SCLE, discoid lupus) or lupus-non-specific subtypes (such as photosensitivity, oral ulcers, alopecia, Raynaud’s syndrome, or vasculitis), and then by timing of short-term treatment (less than 12 months) and long-term treatment (12 months or longer).

We also planned to examine differences in outcome measures between different interventions and to compare these with the control of ‘no treatment’ (natural history information). As appropriate, analysis was to be carried out at the level of the different interventions; however too few studies were included in each meta-analysis to do this.

For future updates, we may consider subgroup analysis by age, gender, race, geographical location, comorbidity, and treatment factors (e.g. dosage, formulation).

Sensitivity analysis
As needed, we planned to conduct sensitivity analyses to explore the influence of the following factors on effect size.

- Study quality.
- Size of trial.
- Exclusion of studies using the following filters (language of publication, funding sources, etc.).
- Repetition of analyses if ordinal data were dichotomised to certain cut-off points with several options for cut-off points.
- Imputation of missing data.

Number needed to treat for an additional harmful outcome
For dichotomous outcomes and adverse events, we planned to calculate the number needed to treat for an additional harmful outcome from the control group event rate and the relative risk using the Visual Rx NNT Calculator (Cates 2003).

Summary of findings and assessment of the certainty of the evidence
We used the specific evidence grading system presented in Atkins 2004 and GradePro to produce Summary of findings tables as described in Section 12.2 of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). GRADE assesses the certainty (quality) of each outcome through the following domains: study limitations (risk of bias), inconsistency of results, indirectness of evidence, imprecision, and publication bias. An overall quality rating is then assigned to each outcome: high, moderate, low, or very low. Summary of findings tables were created for the main comparisons in this review and included the following outcomes: complete clinical response, partial clinical response, clinical flares, CLASI, quality of life, severe adverse events, and minor adverse events.

RESULTS
Description of studies
Results of the search
We identified 7712 records through database searching, an additional 1972 records through searches of trial registers, and
22 records through bibliographical searching (see Electronic searches). A total of 9706 records were identified through database and bibliographic searching.

After 613 duplicates were removed, we had a total of 9093 records. We screened these 9093 records and discarded 8914 records based on their titles and abstracts.

We obtained the full text of the remaining 179 articles and ongoing study records. We excluded 56 studies (see Characteristics of excluded studies). We identified 16 ongoing studies (see Characteristics of ongoing studies). We added 13 studies to the group included under Characteristics of studies awaiting classification.

We included 61 RCTs reported in 94 references (see Characteristics of included studies). For a further description of our screening process, see the study flow diagram (Figure 1).
Figure 1. Study flow diagram: PRISMA diagram showing the screening process.

- 1227 records identified through database (Cochrane Skin Register, CENTRAL, MEDLINE, Embase)
- 3786 records from Wiley Interscience Online Library
- 2599 records from Virtual Health Library
  Total = 7712

- 1972 additional records identified through searches of trials registers

Bibliographic searching of Natural Medicine and Natural Standard online: 22 records

- 613 duplicate records removed

- 8914 records excluded based on titles and abstracts

- 56 excluded studies
  - 21 non-cutaneous SLE disease
  - 10 non-RCTs
  - 12 non-SLE cutaneous disease
  - 13 Incomplete studies which were terminated, withdrawn or suspended and/or results were never made available or published

- 16 ongoing studies
- 13 studies awaiting classification

- 179 full-text articles assessed for eligibility

- 61 included studies reported in 94 references

- 61 studies included in qualitative synthesis
Included studies
We included 61 RCTs comprising 11,332 total participants. Details about which are included in the Characteristics of included studies tables. Years of publication ranged from 1985 to 2019.

Design

Intervention versus placebo/vehicle trials

Intervention versus intervention trials

Intervention versus no intervention trials

Dose-effect trials
The following dose-effect trials compared multiple (two or more) doses versus each other and versus placebo: Clowse 2015; Furie 2011; Furie 2015b; Khamashta 2016; Merrill 2011; Merrill 2018; Navarra 2011; Pena-Rossi 2009; Petri 2013; Tillmanns 2014; Wallace 2009.

Pena-Rossi 2009 also compared single administration versus multiple administrations. The following dose-effect trial compared multiple doses (low and high) versus each other but did not compare them versus a placebo group: Petri 2010.

Cross-over trials

Split-body-part design trials
Tzung 2007 and Kuhn 2011 were trials with split-body-part design.

Factorial design trials
Duffy 2004 was a factorial design trial.

Dose-timing trials
Bootsma 1995 was the trial of most unusual design that was identified. This study compared the same intervention at different times to assess whether intervention timing made a difference. More specifically, the study assessed whether early treatment based on serological data made a difference in terms of SLE flare severity and adverse effects compared with delayed treatment based on clinical evidence of a flare. To accomplish this, all participants were assessed for disease activity by serology, then were randomly assigned to (1) starting therapy as needed based on any immediate serological evidence of disease versus (2) "putting aside the serological data and delaying any treatment until there was actual clinical evidence of a flare".

Sample size
Studies ranged in size from 11 participants in Polderman 2001 to 1124 participants in Merrill 2016.

Setting
Studies were conducted at outpatient clinics of academic and research institutions in a wide range of countries throughout the world.

Single-site trials
The following studies were performed at a single site in a single country: Bangladesh (Islam 2012), Brazil (Bezerra 2005; Carneiro 1999; Levy 2001; Lima 2016; Meinao 1996), China (You 2010; Zhong 2013), England (Walton 1991), France (Kahan 1985), Italy (Dammacco 2000), Japan (Yokogawa 2015), Malaysia (Yahya 2013), Netherlands (Polderman 2001), Sweden (Westberg 1990), Taiwan (Tzung 2007), and USA (Furie 2015a; Hackshaw 1995; McGrath 1996; Rupp 1987; Tseng 2006; Van Vollenhoven 1995).

Multi-centre trials
The following studies were performed at multiple sites in a single country: Brazil (Lanna 2019), Canada (Tsakonas 1991), Germany (Kuhn 2011), Japan (Ishii 2015), Mexico (Andrade-Ortega 2009), Northern Ireland (Duffy 2004; Wright 2008), Netherlands (Bootsma 1995), Spain (Ordi-Ros 2017), Russia (Pena-Rossi 2009), UK (Griffiths 2010), and USA (Furie 2016a; Furie 2016b; Merrill 2011; Petri 2010; Werth 2017a; Williams 1994).

The following studies were multi-national, multi-centre studies: Clowse 2015; Dilulie 2016; Furie 2011; Furie 2015b; Furie 2015c; Khamashta 2016; Merrill 2010a; Merrill 2010b; Merrill 2016; Merrill 2018; Navarra 2011; Petri 2004; Petri 2013; Stohl 2017; Tillmanns 2014; Van Vollenhoven 2018; Wallace 2009; Wallace 2013; Wallace 2014; Wallace 2018.
Funding sources

Funding sources for RCTs came from pharmaceutical companies, governments, non-profit private foundations, combinations of these groups, or unstated sources. Most studies (29) were funded entirely by pharmaceutical companies (Closew 2015; Duliege 2016; Furie 2011; Furie 2015b; Furie 2015c; Furie 2016a; Furie 2016b; Khamashta 2016; Merrill 2010a; Merrill 2010b; Merrill 2011; Merrill 2016; Merrill 2018; Navarra 2011, Petri 2004; Petri 2013; Stohl 2017; Tillmanns 2014; Van Vollenhoven 2018; Wallace 2013; Wallace 2014; Wallace 2018; Werth 2017a; Yahya 2013; Yokogawa 2015). Other studies (7) were funded entirely by governments (Bootsma 1995; Lima 2016; McGrath 1996; Petri 2010; Tseng 2006; Williams 1994; Zhong 2013). Others (3) were funded entirely by non-profit private foundations (Polderman 2001; Van Vollenhoven 1995; Wright 2008).

Some studies were funded by combinations of different groups, for example, six studies received funds from both pharmaceutical companies and government entities (Bezerra 2005; Furie 2011; Griffiths 2010; Kuhn 2011; Rupp 1987; Wallace 2009). Another three studies were funded by both pharmaceutical companies and non-profit foundations (Fortin 2008; Lanna 2019; Tsakonas 1991). One study received funds from a non-profit foundation and from the government (Walton 1991). In 10 cases, the funding source was not stated (Andrade-Ortega 2009; Carneiro 1999; Dammacco 2000; Duffy 2004; Kahan 1985; Meinao 1996; Ord-Ros 2017; Tzung 2007; Westberg 1990; You 2010). In two cases, study authors reported that they were not funded by certain entities but did not clearly specify where funding had come from. For example, Levy 2001 stated that “the study was not funded by the pharmaceutical company”; however, they did receive medication from the pharmaceutical company. Islam 2012 stated that there was “no funding from industry or government” but did not state exactly where funding came from.

Participants

Sex

Participants in a majority of studies were predominantly women, but the following trials included some men: Andrade-Ortega 2009; Bezerra 2005; Bootsma 1995; Carneiro 1999; Dammacco 2000; Duffy 2004; Duliege 2016; Fortin 2008; Furie 2015b; Furie 2016a; Griffiths 2010; Hackshaw 1995; Islam 2012; Khamashta 2016; Kuhn 2011; Meinao 1996; Merrill 2010a; Merrill 2010b; Merrill 2011; Merrill 2016; Navarra 2011; Pena-Rossi 2009; Petri 2010; Polderman 2001; Rupp 1987; Stohl 2017; Szepiekow Ski 2013; Tsakonas 1991; Tseng 2006; Tzung 2007; Van Vollenhoven 2018; Wallace 2009; Wallace 2013; Wallace 2014; Wallace 2018; Walton 1991; Werth 2017a; Westberg 1990; Williams 1994; Wright 2008; Yahya 2013; You 2010; Zhong 2013.

A few studies included only women (Kahan 1985; Lima 2016; McGrath 1996; Van Vollenhoven 1995). However, this was not necessarily due to the active exclusion of men but rather was due to lack of availability of male participants, except in the case of Petri 2004, which included only women due to the nature of the hormonal treatment (prasterone). Lanna 2019 included only women in a cosmetic camouflage intervention trial.

One study included only pregnant women and the offspring of their pregnancies (boys or girls) that commenced during the study period and were born to study participants with follow-up to the age of three years (Levy 2001).
Severity of CLE in SLE diagnosis reported at baseline

Study authors reported the severity of CLE in SLE at baseline using various methods: CLASI, SLEDAI mucocutaneous domains, SLAM integment domains, or BILAG A or B mucocutaneous criteria, as well as descriptive narratives.

Studies described three categories of CLE in SLE severity: mild (three studies: Dulejík 2016; Szeplietowski 2013; Wright 2008), moderate (13 studies: Carneiro 1999; Fortin 2008; Furie 2016a; Griffiths 2010; Khamashita 2016; Merrill 2010a; Merrill 2011; Rupp 1987; Tzeng 2007; Werth 2017a; Wright 2008; Yahya 2013; Yokogawa 2015), and severe (eight studies: Andrade-Ortega 2009; Bezza 2005; Furie 2015a; Furie 2015b; Furie 2015c; Furie 2016b; Petri 2013; Wallace 2014).

The remainder of the RCTs did not provide sufficient information for assessment of baseline severity of CLE in SLE.

Duration of CLE in SLE diagnosis reported at baseline

Only four studies commented on how long lesions of CLE In SLE had been present before the start of the studies. Bezza 2005 reported that CLE lesions had been present for 3.56 years in the chloroquine group compared with 1.55 years in the chloroquine group. Hackshaw 1995 reported that in more than 50% of participants, CLE lesions had been present longer than four years. Rupp 1987 reported that Raynaud’s lesions had been present for 2 to 40 years before the study. For Clowse 2015, one of the inclusion criteria was that CLE lesions had to be present for at least three weeks. The remainder of the studies did not report information on the duration of CLE in SLE lesions at baseline.

Diagnosis of CLE in SLE reported at baseline

Studies can be divided into four main categories based on the way they reported cutaneous diagnoses at baseline.

Studies that reported specific cutaneous diagnosis directly


The most commonly reported direct diagnosis was discoid lupus, with 13 (of 18) studies reporting a total of 314 participants (Bezza 2005; Bootsma 1995; Dammacco 2000; Duffy 2004; Dulejík 2016; Griffiths 2010; Khamashita 2016; Merrill 2010a; Merrill 2011; Rupp 1987; Tzeng 2007; Van Vollenhoven 1995; You 2010). Next, eight studies reported oral ulcers among a total of 135 participants (Bootsma 1995; Dammacco 2000; Duffy 2004; Griffiths 2010; Khamashita 2016; Merrill 2010a; Merrill 2011; Merrill 2016; Merrill 2018; Pena-Rossi 2009; Polderman 2001; Tseng 2006; Van Vollenhoven 1995; Wallace 2009; Werth 2017a; Yahya 2013), 10 to 15 years (one study: Wright 2008), and 15+ years (one study: Lanna 2019). The remainder of the studies did not report mean duration of SLE diagnosis at baseline.

Interventions for cutaneous disease in systemic lupus erythematosus (Review)

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studies reported cutaneous vasculitis/ivedo reticularis in a total of 18 participants (Andrade-Ortega 2009; McGrath 1996).

Studies that reported cutaneous diagnosis indirectly in the form of the validated Cutaneous Lupus Disease Area and Severity Index (CLASI)

In this category, eight studies reported CLASI qualitatively for a total of 1072 participants (Furie 2015a; Furie 2015c; Khamashta 2016; Merrill 2011; Petri 2013; Polderman 2001; Stohl 2017; Wallace 2013; Wallace 2014; Wallace 2018; Wright 2008).

Studies that reported cutaneous diagnosis indirectly in the form of other validated measures of SLE disease activity such as integument or mucocutaneous domains of Systemic Lupus Activity Measurement (SLAM) (American College of Rheumatology 2004; British Isles Lupus Assessment Group (BILAG) Disease Activity Index (Hay 1993); Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) (Bombardier 1992); and their various updates

In this category, there were 14 studies (Clowse 2015; Fortin 2008; Furie 2016a; Hackshaw 1995; Merrill 2010a; Merrill 2016; Navarra 2011; Petri 2013; Polderman 2001; Stohl 2017; Wallace 2013; Wallace 2014; Wallace 2018; Wright 2008).

Studies that reported cutaneous diagnosis directly or indirectly in the form of non-validated non-standard categorisations that were designed by the authors of each study. Study-specific categorisations range from simple narrative descriptions to combined diagnostic categories (e.g. mucocutaneous disease, malar rash/discoid lupus/oral ulcers photosensitivity) to more complex custom-designed measurement instruments and scoring systems

In this final category, there were 21 studies: Carneiro 1999; Furie 2011; Furie 2015b; Furie 2016b; Ishii 2015; Islam 2012; Lima 2016; Meinao 1996; Merrill 2011; Ordi-Ros 2017; Petri 2004; Petri 2010; Tillmanns 2014; Tsakonas 1991; Tseng 2006; Wallace 2009; Walton 1993; Westberg 1990; Williams 1994; Yahya 2013; Zhong 2013.

Interventions

A total of 42 identified pharmacological interventions are listed in alphabetical order in Table 3, along with doses and treatment course. One identified non-pharmacological intervention (cosmetic camouflage) brought the total number of interventions found for CLE in SLE to 43.

Classes of interventions

Among the 43 interventions, we found 20 different classes of interventions for cutaneous disease in SLE. In summary, we identified one antibiotic, two antimalarials, four biologic therapies, one oral calcineurin inhibitor, one topical calcineurin inhibitor, two oral calcium channel blockers, one cover-up make-up, one cebclon inhibitor, two chemotherapy agents, two systemic corticosteroids, one topical steroid, two hormonal therapies, five immunomodulatory agents, one oral JAK inhibitor, one topical JAK inhibitor, one light therapy, one leukotriene synthesis inhibitor, 10 monoclonal antibodies, three oral supplements, and two Traditional Chinese Medicines.

This information (classes of interventions and associated RCTs) is summarised in Table 2.

Of note, we found no RCTs that assessed the following: behavioural interventions, beta-2-adrenergic receptor agonists, lasers, complementary and alternative therapies such as acupuncture, cognitive-behavioural therapy (CBT), or retinoids.

Some of the RCTs identified in the course of this review for CLE without SLE and SLE without CLE are provided for reference in Table 2, as well as under Characteristics of excluded studies. References to the various detailed reviews that specifically address CLE without SLE and SLE without CLE are provided in the Agreements and disagreements with other studies or reviews and Additional references sections.

Comparisons

Included RCTs conducted the following comparisons: intervention versus placebo/vehicle, intervention versus other intervention, intervention versus no intervention, dose comparison with placebo group, and dose comparison without placebo group.

Intervention versus placebo/vehicle

- Intravenous anifrolumab versus placebo (Furie 2015c)
- Intravenous atacicept versus placebo (Petra-Rossi 2009)
- Intravenous abatacept versus placebo (Merrill 2010b)
- Intravenous baricitinib versus placebo (Wallace 2018)
- Intravenous or subcutaneous belimumab versus placebo (Furie 2011; Navarra 2011; Stohl 2017; Wallace 2009)
- Intravenous blisibimod versus placebo (Furie 2015b)
- Subcutaneous BIB059 versus placebo (Furie 2016b)
- Intravenous bortezomib versus placebo (Ishii 2015)
- Oral cc-220 versus placebo (Wert 2017a)
- Oral chloroquine versus placebo (Meinao 1996)
- Oral cholecalciferol versus placebo (Lima 2016)
- Oral copper versus placebo (Duffy 2004)
- Repository corticotropin injection versus placebo (Furie 2015a; Furie 2016a)
- Oral dehydroepiandrosterone versus placebo (Petri 2004; Van Vollenhoven 1995)
- Intravenous evratuzumab versus placebo (Clowse 2015; Wallace 2013; Wallace 2014)
- Oral fish oil versus placebo (Duffy 2004; Walton 1991; Westberg 1990; Wright 2008)
- Oral ginsenosides versus placebo (You 2010)
- Oral hydroxychloroquine versus placebo (Levy 2001; Williams 1994; Yokogawa 2015)
- Subcutaneous lulizumab pegol versus placebo (Merrill 2018)
- Oral methotrexate versus placebo (Carneiro 1999; Fortin 2008)
- Oral nicardipine versus placebo (Rupp 1987)
- Oral nifedipine versus placebo (Kahan 1985)
- UVA-1 phototherapy versus placebo (McGrath 1996; Polderman 2001)
- Oral prednisone versus placebo (Tseng 2006)
- Topical R932333 versus placebo vehicle (Duliege 2016)
- Intravenous rituximab versus placebo (Merrill 2010a)
- Intravenous sipilumab versus placebo (Khamashta 2016; Merrill 2011; Petri 2013)
- Intravenous sirukumab versus placebo (Szepeitowski 2013)
• Intravenous SM101 versus placebo (Tillmanns 2014)
• Subcutaneous tabalumab versus placebo (Merrill 2016)
• Topical tacrolimus ointment versus placebo vehicle (Kuhn 2011)
• Intravenous versus subcutaneous ustekinumab (Van Vollenhoven 2018)
• Oral zileuton versus placebo (Hackshaw 1995)

**Intervention versus other intervention**

• Oral clofazimine versus oral chloroquine (Bezerra 2005)
• Oral ciclosporin versus oral azathioprine (Griffiths 2010)
• Oral ciclosporin plus intravenous (6-methylprednisolone) and oral steroids (prednisone) versus oral corticosteroids (prednisone) alone (Dammacco 2000)
• Intravenous rituximab versus intravenous cyclophosphamide (Andrade-Ortega 2009)
• Topical tacrolimus versus clobetasol (Tzung 2007)
• Oral methotrexate versus chloroquine (Islam 2012)
• Oral mycophenolate sodium versus azathioprine or dapson (Yahya 2013)
• Oral mycophenolate sodium versus azathioprine (Ordi-Ros 2017)
• Chinese Herbal Medicine (Zi Sen Qing) versus hydroxychloroquine (Zhong 2013)

**Intervention versus no intervention**

• Cosmetic camouflage education versus no cosmetic camouflage education (Lanna 2019)
• Oral hydroxychloroquine (continuation) versus no oral hydroxychloroquine (discontinuation) (Tsakonas 1991)

**Dose comparisons of multiple (two or more) doses of the same intervention versus placebo**

• Intravenous atacicept at various dose levels versus placebo (Pena-Rossi 2009)
• Intravenous belimumab at various dose levels versus placebo (and belimumab at various dose levels versus placebo) (Furie 2011; Navarra 2011; Wallace 2009)
• Intravenous blisibimod at three dose levels versus placebo (Furie 2015b)
• Intravenous epratuzumab at two dose levels versus placebo (Clowse 2015)
• Subcutaneous lulizumab pegol at four dose levels versus placebo (Merrill 2018)
• Intravenous sifalimumab at various dose levels versus placebo (Khamashta 2016; Merrill 2011; Petri 2013)
• Intravenous SM101 at two dose levels versus placebo (Tillmanns 2014)

**Dose comparisons of multiple (two or more) doses of the same intervention but not versus placebo**

One dose comparison study was unique in that it was purely a two-dose comparison study that did not include a placebo group (comparing high dose versus standard dose intravenous cyclophosphamide only) (Petri 2010).

**Treatment duration, post-treatment follow-up, and total trial duration**

**Treatment duration**

Treatment duration for the different RCTs ranged from one week (Kahan 1985) to 24 months in Ordi-Ros 2017 and Petri 2010.

Duration of treatment in order of shortest to longest was as follows: one week (Kahan 1985), three weeks (McGrath 1996; Polderman 2001), one month (Ishii 2015; Rupp 1987), six weeks (Duliege 2016), six weeks and nine weeks (Pena-Rossi 2009), two months (Furie 2015a; Furie 2016a; Hackshaw 1995; Tzung 2007), three months (Furie 2016b; Kuhn 2011; Lanna 2019; Merrill 2011; Van Vollenhoven 1995; Wallace 2013; Walton 1991; You 2010; Zhong 2013), four months (Yahya 2013; Yokogawa 2015), four and one-half months (Szepietowski 2013), six months (Bezerra 2005; Bootasma 1995; Carneiro 1999; Duffy 2004; Islam 2012; Lima 2016; Merrill 2018; Tillmanns 2014; Tsakonas 1991; Van Vollenhoven 2018; Wallace 2018; Werth 2017a; Westberg 1990; Wright 2008), nine months (Merrill 2010b), 10 months (Levy 2001); 12 months (Andrade-Ortega 2009; Clowse 2015; Dammacco 2000; Fortin 2008; Furie 2015b; Furie 2015c; Griffiths 2010; Khamashta 2016; Meinao 1996; Merrill 2010a; Merrill 2016; Navarra 2011; Petri 2004; Petri 2013; Stohl 2017; Wallace 2009; Wallace 2014; Williams 1994), 18 months (Furie 2011; Tseng 2006), and 24 months (Ordi-Ros 2017; Petri 2010).

**Post-treatment follow-up**

Five studies reported a post-treatment follow-up period: Westberg 1990 had a post-treatment follow-up period of three months, Petri 2013 24 weeks (six months), Dammacco 2000 12 months, and Tsakonas 1991 36 months. Levy 2001 had a post-treatment follow-up of up to 36 months on the offspring of pregnancy.

The remaining studies did not report a post-treatment follow-up period.

**Total trial duration**

A few studies had a post-treatment follow-up so total trial duration was calculated as follows. Petri 2013 had a treatment duration of 26 weeks followed by a post-treatment follow-up of 24 weeks for a total of 12.5 months; Dammacco 2000 had a treatment duration of 12 months followed by a post-treatment follow-up period of 12 months for a total trial duration of 24 months; Tsakonas 1991 had a treatment duration of six months followed by a post-treatment follow-up period of 36 months for a total trial duration of 42 months; and Levy 2001 had a treatment duration during pregnancy/postpartum period of 10 months followed by a post-treatment follow-up period of 36 months of offspring for a total trial duration of 46 months.

The following studies were cross-over studies (treatment versus placebo) that did not provide pretreatment run-in periods, washout periods, or post-treatment follow-ups, so the total trial duration was simply twice the treatment duration: Kahan 1985; McGrath 1996; Polderman 2001; Rupp 1987.

Two of the cross-over trials were more complex (Walton 1991; Westberg 1990). Walton 1991 had a pretreatment two-week run-in period of low-fat diet only, followed by three months of treatment with low-fat diet (or placebo), followed by eight weeks of a washout period comprising low-fat diet only, followed by placebo (or treatment) for three months. At the end of the trial, no post-
treatment follow-up period was provided, so the total trial duration was 34 weeks (8.5 months). Westberg 1990 was the most complex cross-over trial, with a pretreatment run-in of three months, followed by treatment with fish oil (or control) for six months, followed by a washout between treatments of three months, followed by treatment with control (or fish oil) for six months, and finally, a three-month post-treatment follow-up period, for a total trial duration of 21 months.

For the remaining studies, total trial duration was the same as treatment duration because no post-treatment follow-up was provided.

Outcomes

Timing of outcome assessment

We measured outcomes from the beginning of treatment to the end of the trial. Short-term outcomes were defined as less than 12 months; long-term outcomes were defined as 12 months or longer.

Most studies reported short-term outcomes, and fewer studies reported long-term outcomes.

Short-term


Long-term


Primary outcomes

Complete clinical response

Definitions

Complete clinical response is defined as the percentage of SLE participants with complete resolution of skin lesions (i.e. absence of (cutaneous) sign).

The complete clinical response outcome was divided into subgroups of clinical interest. The main subgroups of interest were participants with SLE AND lupus-specific OR lupus-non-specific CLE based on the Gilliam classification (Gilliam 1981). Another subgroup was based on timing (short term or long term).

Summary of reported outcomes


The sections that follow describe in greater detail the outcomes reported by each of these studies.

Lupus-specific rashes (malar, SCLE, or discoid) in SLE patients

The following studies reported complete clinical response for lupus-specific rashes in SLE patients. Bezerra 2005 reported on the percentage (or number) of participants with complete clearance of malar, SCLE, or discoid rashes at six months with clofazimine versus chloroquine. Dammacco 2000 reported on complete resolution of erythematous manifestations at three months and 12 months with oral cyclosporin plus intravenous and oral steroids versus oral steroids alone. Islam 2012 reported complete clearance of rash (defined as discoid, butterfly rash, etc.) at six months for oral methotrexate versus chloroquine. You 2010 reported the outcome of complete clearance of facial erythema and complete clearance of erythema of the hands at three months for oral ginsenosides versus placebo.

Some studies reported the complete clinical response for lupus-specific as percentage (or number) of participants with cutaneous lesions present; we transformed these data into a dichotomous outcome of number of participants with skin lesions completely absent or clear (Carneiro 1999; Griffiths 2010; Meinao 1996; Petri 2004).

The following studies reported on complete clinical response for lupus-specific rashes; however, data were provided only in narrative form and could not be used for quantitative analysis (Petri 2010; Walton 1991; Williams 1994).

Lupus-non-specific photosensitivity in SLE patients

No studies reported complete clinical response to photosensitivity.

Lupus-non-specific oral ulcers in SLE patients

The following five studies reported complete clinical response for lupus-non-specific oral ulcers. You 2010 reported the outcome of complete clearance of aphthae at three months for ginsenosides versus placebo. Griffiths 2010 reported the presence of oral ulcers at 12 months for oral cyclosporin versus oral azathioprine. Petri 2004 studied oral stomatitis at 12 months for dehydroepiandrosterone versus placebo. Tseng 2006 reported on a participant with a flare in oral ulcers at 18 months for oral prednisone versus placebo. Walton 1991 provided narrative information for mouth ulcers on one patient only for fish oil.

Lupus-non-specific alopecia in SLE patients

Complete clinical response to alopecia was reported in Meinao 1996 for chloroquine versus placebo in a 12-month study, in Petri 2004 for dehydroepiandrosterone versus placebo in a 12-month study, and in You 2010 for oral ginsenosides versus placebo at three months. Griffiths 2010 reported on alopecia for oral cyclosporin versus oral azathioprine during a 12-month study.

Lupus-non-specific Raynaud’s in SLE patients

Complete clinical response to Raynaud’s attacks were reported by two studies. Kahan 1985 reported severity of Raynaud’s attack...
using a 150-mm visual analogue scale and number of Raynaud’s attacks per day during a two-week study of nifedipine. Rupp 1987 reported on severity of Raynaud’s attack (flares) using a 150-millimetre visual analogue scale and number of Raynaud’s attacks (flares) per day during a one-month study of nicardipine.

Lupus-non-specific vasculitis in SLE patients

We found no reports found on complete clinical response to vasculitis in SLE patients.

Other lupus-non-specific skin findings in SLE patients

Oedema (a sign in Traditional Chinese Medicine) was reported by You 2010, which described complete clearance of oedema at three months for oral ginsenosides versus placebo.

Partial clinical response

Definitions

Partial clinical response is defined as the percentage of SLE participants with at least 50% improvement in skin lesions (lupus-specific or lupus-non-specific).

Summary of reported outcomes


In particular, Levy 2001 reported partial clearance of skin lesions (lupus-specific) in SLE patients during pregnancy for hydroxychloroquine. Bezzera 2005 reported partial clearance of malar, SCLE, or discoid rashes (lupus-specific) at six months for clofazimine versus oral chloroquine. Duliege 2016 reported on partial clearance defined as “at least a 50% decrease from baseline in the total combined ‘erythema and Scaling’ score of all treated lesions” at three months for topical R932333. Petri 2010 reported on partial clearance of skin lesions (lupus-specific), but only in narrative form for high-dose versus standard-dose cyclophosphamide. Yahya 2013 reported on short-term partial clearance (lupus-specific) for oral mycophenolate versus chloroquine. It should be noted that Yahya 2013 defined partial clearance as greater than 20% improvement rather than 50%, as we had specified. Ishii 2015 reported anecdotally that one patient in the study had partial clearance of his skin findings (lupus-specific) for intravenous bortezomib versus placebo. Yokogawa 2015 reported partial improvement in a percentage of participants for oral hydroxychloroquine versus placebo as measured by various global assessment scales (lupus-specific); however, this group pooled data from SLE patients and non-SLE CLE patients and provided insufficient information for separation of data for subgroup analysis.

Secondary outcomes

Reduction (or change) in the number (or percentage) of SLE participants with clinical flares in cutaneous disease (lupus-specific or lupus-non-specific)

Fortin 2008 reported on severe clinical flare requiring discontinuing study during the 12-month study. Merrill 2011 reported on SLE flare for intravenous sifalimumab and placebo groups during the three-month study. Levy 2001 reported on the incidence of systemic lupus flares during pregnancy. Tseng 2006 reported on mild, moderate, and severe flares of SLE-specific rashes (discoid and malar) for non-cutaneous organs and for cutaneous disease subsets during an 18-month study.

Zhong 2013 reported some data on flares (mild, moderate, and severe); however, they pooled data on skin findings with those on other organ systems and did not provide sufficient information to separate data for subgroup analysis. Zhong 2013 also reported on a global Chinese medicine score for which skin was one of the composite criteria; however, this group did not provide enough information for separation of data for skin subgroup analysis.

Bootsma 1995 reported some data on flares; however, they pooled data on skin findings with data on other organ systems and did not provide sufficient information for separation of data for subgroup analysis.

Increase (or change) in time-to-flare in cutaneous disease (lupus-specific or lupus-non-specific) in SLE participants

Tsakonas 1991 reported on increase in time-to-flare in skin lesions.

Relapse rate (or percentage of SLE participants with relapse) in cutaneous disease (lupus-specific or lupus-non-specific) when medications are stopped or reduced

Tsakonas 1991 reported on the relapse rate in skin lesions when hydroxychloroquine was withdrawn for six months compared with placebo with follow-up at six months and 48 months, respectively. Relapse was described as clinical flare in skin disease during the six-month withdrawal study. Relapse was described as a major flare in vasculitis or a major flare in lupus (vasculitis, skin or other system) during the 48-month follow-up study.

Skin-specific measures of SLE disease activity such as the Cutaneous Lupus Disease Area and Severity Index (CLASI); the integument domain of the Systemic Lupus Activity Measurement (SLAM); the mucocutaneous domain of the British Isles Lupus Assessment Group (BILAG) Disease Activity Index; the mucocutaneous domain of the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI); the mucocutaneous domain of the SLE Responder Index (SRI)

Overall disease activity measurements for SLE require composites of scores from the multiple organ systems involved. Some studies reported scores from the individual organ-specific domains that make up the general composite score (e.g. integument or mucocutaneous domain that refers to the skin, mucosa, and hair). Some of the general SLE disease activity measurement instruments commonly used with integument or mucocutaneous domains include the Systemic Lupus Erythematosus Disease Activity Measurement (SLAM) (American College of Rheumatology 2004); the British Isles Lupus Assessment Group (BILAG) Disease Activity Index (Hay 1993); and the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) (Bombardier 1992). These measures can comprise both lupus-specific and lupus-non-specific findings; additional details about the specific definitions are given below.

CLASI scores

Szepietowski 2013 and Furie 2016a reported CLASI scores in a qualitative fashion. Wirth 2017a and Van Vollenhoven 2018 reported CLASI scores in a quantitative manner. Yokogawa 2015 reported CLASI data; however, these investigators pooled data from SLE patients together with data from non-SLE CLE patients and provided insufficient information for separation of data for subgroup analysis. Furie 2015a, Furie 2015c and Khamashta 2016
reported narrative data about CLASI scores. Merrill 2018 reported narrative information about CLASI change from baseline, CLASI-20, and CLASI-50.

**SLAM scores**

The following studies reported on the integument domain of the SLAM score: Duffy 2004; Hackshaw 1995; McGrath 1996; Merrill 2010b; and Polderman 2001. Hackshaw 1995 reported mean changes in the SLAM score integument domain. Duffy 2004 reported qualitatively on the integument domain of the SLAM score. McGrath 1996 narratively reported the SLAM score integument domain. Polderman 2001 narratively reported the SLAM integument domain defined as cutaneous rash (lupus-specific), oral ulcers (lupus-non-specific), alopecia (lupus non-specific), vasculitis (lupus non-specific).

**BILAG scores**

Outcomes reported by Merrill 2010b during a 12-month study were BILAG A or B flare in discoid lesions, new BILAG A score for discoid lesions, and new flare in discoid lesions (based on physician-based assessment). Navarra 2011 reported narratively no new BILAG A or no more than one new BILAG B flare in the mucocutaneous domain. Merrill 2010a reported BILAG B and BILAG A scores for the mucocutaneous domain. Tillmanns 2014 reported narrative data on BILAG scores for the mucocutaneous domain. Wallace 2014 reported data on BILAG scores for the mucocutaneous domain.

**SLEDAI scores**

Navarra 2011 reported in a narrative manner about the SELENA-SLEDAI score mucocutaneous domain. Lima 2016 reported in a narrative manner about the SLEDAI score mucocutaneous domain.

**SLE Responder Index (SRI)**

Stohl 2017 reported on the mucocutaneous domain of the SLE Responder Index (SRI) a composite outcome that incorporates a modification of SELENA-SLEDAI, BILAG, and a 3-cm visual analogue scale of physician-rated disease activity (PGA) to determine patient improvement (Furie 2009).

**Combined manifestations**

Combined manifestations such as the SLAM score integument domain defined as "cutaneous rash (lupus-specific), oral ulcers (lupus-non-specific), alopecia (lupus-non-specific), vasculitis (lupus-non-specific)" were reported for Duffy 2004, Hackshaw 1995, McGrath 1996, Merrill 2010b, and Navarra 2011. Polderman 2001 reported narratively about combined manifestations for SLEDAI scores and BILAG scores. Merrill 2010b also reported combined manifestation BILAG scores.

**Dermatology Quality-of-Life Measures**

Szepietowski 2013 and Lanna 2019 reported on the Dermatology Life Quality Index (DLQI).

**Adverse events**

We collected data on adverse events from interventions that led to both severe and minor events. Severe events were defined as leading to discontinuation or withdrawal from the study, or resulting in significant morbidity or mortality. Minor events were defined as bothersome to participants but not leading to withdrawal from the study.

**Severe events**


The following studies reported narratively (qualitatively) on severe adverse events: Duffy 2004; Furie 2015c; Furie 2016b; Ishii 2015; Lima 2016; McGrath 1996; Ordi-Ros 2017; Polderman 2001; Szepietowski 2013; Tillmanns 2014; Walton 1991, Werth 2017a.

The following studies did not report on whether or not severe adverse events occurred: Clowse 2015, Lanna 2019, Tsung 2007 Wallace 2009 Westberg 1990 or You 2010.

**Minor events**


Minor adverse events were reported narratively (qualitatively) by Duffy 2004; Furie 2015a; Furie 2015b; Furie 2016c; Furie 2016b Lima 2016 Meinao 1996 Petri 2010; Walton 1991; Werth 2017a Westberg 1990; and Wright 2008.

The following studies did not report on whether or not minor adverse events occurred: Clowse 2015; Ishii 2015; Khamashta 2016; Lanna 2019; Levy 2001; McGrath 1996; Navarra 2011; Polderman 2001; Tillmanns 2014; Tsung 2007; Williams 1994; or Yokogawa 2015.

**Excluded studies**

We excluded 56 studies. Study exclusion criteria are detailed in Table 4. Excluded study reports are described in detail under Characteristics of excluded studies.

We excluded RCTs with participants with SLE that, on detailed examination of the full text, did not report a diagnosis of cutaneous disease but rather focused entirely on other non-cutaneous organ manifestations of SLE (Abud-Mendoza 2009; Bhattoa 2004; Cai 2006; Chang 2002; Chang 2016a; Furie 2008; Furie 2011a; Ginzler 2013; Gordon 2008; Liao 2011; Liu 2007; Lu 2015; Nordmark 2005; Partan 2019; Petri 2002; Rovin 2019; Shamekhi 2017; Tsuru 2016; Vietra 2009; Xu 2012; Zhang 2019).

Some studies that appeared to meet initial criteria for inclusion ended up being excluded because closer inspection revealed that they were controlled trials, cohort studies, or case series rather than

The following studies comprised participants with CLE alone and specifically excluded participants with SLE (e.g., studies on DLE or SCLE without a diagnosis of SLE) (Barikbin 2009; Handa 1985; Hummers 2013; Jemec 2009; Kuhn 2011a; NCT00523588; Potthinamthong 2012; Presto 2018; Roenigk 1980; Ruzicka 1992; Sticherling 2007; Werth 2013).

The following studies were listed in trial registries as completed or terminated; however, results were never posted or published, and they were therefore excluded. Sometimes reasons for termination were given; at other times they were not. For example, NCT01498406 (a study about vitamin D) and NCT01470313 (a study on a new compound called PD-0360324) were listed as terminated for financial reasons. NCT01709474 was listed as terminated due to slow enrolment. A study of the selective JAK-1 inhibitor called GS525861S was terminated due to lack of efficacy and due to safety concerns (Kahl 2016). The following studies were also terminated but with no reason given: NCT01689025 NCT02711813 NCT02256744 NCT02514967 NCT02975336. NCT02074020 was reported as withdrawn, and no data were available. NCT00775476 was suspended, and no published data were available. ChiCTR-12002402 and NCT01135459 were never published.

Ongoing studies

We identified 16 ongoing studies. Details are given in the Characteristics of ongoing studies tables.

Ongoing studies are currently in process for the following new interventions: dipyridamole (NCT01781611), RSLV-132 (RNase-Fc fusion protein) (NCT02660944), the cholinergic anti-inflammatory pathway for pain relief in lupus (NCT02822989), oral selective tyrosine kinase 2 (TYK2) inhibition with bms-986165 (NCT03252587), a combination selective tyrosine kinase 2 and JAK-1 inhibitor called PF-06700841 (NCT03845517), an interleukin-2-mutein-Fc fusion protein called AMG 592 (NCT03451422), and a bispecific molecule targeting T-cell and B-cell activity through inhibition of the inducible costimulator ligand (ICOSL) and the B cell-activating factor (BAFF) called AMG 570 (NCT04058028). Studies are under way for elsulbrutinib (ABBV-105), which is a Bruton tyrosine kinase inhibitor (NCT03978520), and upadacitinib (ABT-494 or Rinvoq), which is a Janus kinase selective inhibitor (NCT03978520). ABBV-599 (the combination of elsulbrutinib and upadacitinib) is also being studied (NCT03978520).

ISRCTN47873003 and Teng 2019 are assessing new aspects of belimumab, namely, belimumab after B-cell depletion therapy (subcutaneous belimumab administered in combination with rituximab).

Other studies will further assess established therapies: abatacept (NCT02270957) and CC-220 (NCT03161483). In addition, two studies are evaluating the monoclonal ustekinumab (NCT03517722 and NCT04060888), and another two studies are evaluating the oral JAK inhibitor, baricitinib (NCT03616912 (Brave I) and NCT03616964 (Brave II)).

Most of the ongoing studies state that they will include CLASI outcomes: NCT01781611 NCT02270957 NCT02660944 NCT03161483 NCT03252587; NCT03616912; NCT03451422; NCT03616912; NCT03616964; NCT03845517; NCT03978520; NCT04058028; NCT04060888.

Studies awaiting classification

Thirteen studies are awaiting classification (see Characteristics of studies awaiting classification).

Most of the studies awaiting classification are monoclonal antibody studies: some involving established monoclonal antibodies and others new monoclonal antibodies. Two studies are assessing the established monoclonal antibody anifrolumab (NCT02446899; NCT02446912). Another two studies are assessing belimumab in new populations: Brunner 2020 in children, and Tanaka 2020 in Japan. NCT02847598 is an RCT of the established monoclonal antibody called BIB009 (a fully humanised IgG1 monoclonal antibody targeting blood dendritic cell antigen-2 (BDCA-2) expressed on plasmacytoid dendritic cells). The remainder of the monoclonal studies are investigating new monoclonal antibodies: Werth 2017c is an RCT of AMG 811 (a new human anti-interferon-γ antibody); Hasni 2019 is an RCT of omalizumab (a new humanised anti-IgE monoclonal antibody); and NCT02554019 is testing a new humanised monoclonal antibody that specifically binds to and neutralises interleukin 10.

Some of the studies awaiting classification feature new interventions: NCT03958955 is an RCT about delgocitinib cream (JAK inhibitor); He 2019 is an RCT about low-dose interleukin-2 (IL-2); Houssiau 2020 is an interferon-α (IFN-α) kineoid vaccine trial; and NCT02437890 is an RCT for vobarilizumab (ALX-0061), which is a bispecific interleukin-6R (IL-6R) targeting nanobody with monovalent binding to IL-6R and serum albumin.

One study is examining an already established intervention: Askenase 2019 is an RCT on repository corticotropin injection (RCI).

Risk of bias in included studies

Each included study was assessed according to the risk of bias criteria described in detail in the Methods section. The risk of bias assessment for each individual study is available in the Characteristics of included studies section in the corresponding risk of bias table. Summary data about overall risk of bias of all studies are reported in the summary risk of bias graph (Figure 2) and table (Figure 3).
Figure 2. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

- Random sequence generation (selection bias)
- Allocation concealment (selection bias)
- Blinding of participants and personnel (performance bias): All outcomes
- Blinding of outcome assessment (detection bias): All outcomes
- Incomplete outcome data (attrition bias): All outcomes
- Selective reporting (reporting bias)
- Other bias

Legend:
- Low risk of bias
- Unclear risk of bias
- High risk of bias
Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.
The following studies were rated as having low risk of bias in all domains except one that had unclear risk: Fortin 2008. The following studies had low risk of bias in all domains except two that had unclear risk: Furie 2015b; Van Vollenhoven 2018. Most studies had a mixture of low and unclear risks for the various domains.

Of the included studies, the following had at least one domain rated as having high risk of bias: Andrade-Ortega 2009; Bootsma 1995; Clowse 2015; Dammacco 2000; Duffy 2004; Duliege 2016; Furie 2015c; Griffiths 2010; Hackshaw 1995; Ishii 2015; Islam 2012; Kahan 1985; Khamashta 2016; Kuhn 2011; Lanna 2019; Levy 2001; Merrill 2010a; Merrill 2011; Ordi-Ros 2017; Petri 2010; Tillmanns 2014; Tzung 2007; Walton 1991; Westberg 1990; Williams 1994; Yahya 2013; Yokogawa 2015.

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Interventions for cutaneous disease in systemic lupus erythematosus (Review)
Allocation
The allocation assessment is divided into the categories of random sequence generation and allocation concealment.

Random sequence generation

We rated the majority of the studies as having unclear risk of bias (n = 44) due to insufficient details reported about the randomisation method used.

We considered none of the studies to have high risk of bias in random sequence generation.

Allocation concealment
The following studies were rated as having low risk of allocation concealment bias (n = 16): Bootsma 1995; Fortin 2008; Furie 2011; Furie 2015b; Griffiths 2010; Hackshaw 1995; Khamashta 2016; Kuhn 2011; Navarra 2011; Petri 2013; Tsakonas 1991; Van Vollenhoven 2018; Wallace 2013; Wright 2008; Yahya 2013; Zhong 2013.


None of the studies was considered to have high risk of bias in allocation concealment.

Blinding
Assessment of blinding is divided into the categories of performance bias and detection bias.

Performance bias
For criteria of blinding of participants and personnel (performance bias), the following studies were reported as double-blind and were therefore rated as having low risk (n = 44): Bezerra 2005; Carneiro 1999; Clowse 2015; Duffy 2004; Duliege 2016; Fortin 2008; Furie 2011; Furie 2015a; Furie 2015b; Furie 2015c; Furie 2016a; Furie 2016b; Hackshaw 1995; Kahan 1985; Khamashta 2016; Kuhn 2011; Lima 2016; Merrill 2010a; Merrill 2010b; Merrill 2011; Merrill 2016; Navarra 2011; Pena-Rossi 2009; Petri 2004; Petri 2013; Polderman 2001; Rupp 1987; Stohl 2017; Szepeitowski 2013; Tillmanns 2014; Tsakonas 1991; Tseng 2006; Tzung 2007; Van Vollenhoven 1995; Van Vollenhoven 2018; Wallace 2013; Wallace 2014; Walton 1991; Werth 2017a; Westberg 1990; Wright 2008; Yokogawa 2015; You 2010.

The following double-blind studies were rated as having unclear risk of performance bias due to study investigators reporting insufficient details about the blinding process for participants and personnel and lack of further available data (n = 6): Levy 2001; Meinao 1996; Merrill 2018; Wallace 2009; Williams 1994; Zhong 2013. McGrath 1996 was also rated as having unclear risk of bias because although the first phase of the study was blinded, the second phase was unblinded.

The following studies were unblinded; we therefore rated them as high risk (n = 10): Andrade-Ortega 2009; Bootsma 1995; Dammacco 2000; Griffiths 2010; Ishii 2015; Islam 2012; Lanna 2019; Ordi-Ros 2017; Petri 2010; Yahya 2013.

Detection bias
The following studies blinded outcome assessors and were rated as having low risk for detection bias (n = 13): Bezerra 2005; Carneiro 1999; Duliege 2016; Fortin 2008; Furie 2011; Furie 2015b; Hackshaw 1995; Van Vollenhoven 2018; Wallace 2013; Wallace 2014; Walton 1991; Wright 2008; Zhong 2013.

The following studies were at unclear risk of detection bias (n = 38): Clowse 2015; Duffy 2004; Furie 2015a; Furie 2015c; Furie 2016a; Furie 2016b; Kahan 1985; Khamashta 2016; Kuhn 2011; Levy 2001; Lima 2016; McGrath 1996; Meinao 1996; Merrill 2010a; Merrill 2010b; Merrill 2011; Merrill 2016; Merris 2018; Navarra 2011; Ordi-Ros 2017; Pena-Rossi 2009; Petri 2004; Petri 2013; Polderman 2001; Rupp 1987; Stohl 2017; Szepeitowski 2013; Tillmanns 2014; Tseng 2006; Tzung 2007; Van Vollenhoven 1995; Wallace 2009; Werth 2017a; Westberg 1990; Williams 1994; Yokogawa 2015; You 2010.

The following studies had high risk of detection bias (n = 9): Andrade-Ortega 2009; Bootsma 1995; Dammacco 2000; Griffiths 2010; Ishii 2015; Islam 2012; Lanna 2019; Petri 2010; Yahya 2013.

Incomplete outcome data
For the criterion of incomplete outcome data, we rated most studies as having low risk of attrition bias (n = 42): Andrade-Ortega 2009; Bezerra 2005; Bootsma 1995; Dammacco 2000; Fortin 2008; Furie 2011; Furie 2015a; Furie 2015b; Furie 2016a; Furie 2016b; Hackshaw 1995; Kahan 1985; Khamashta 2016; Kuhn 2011; Levy 2001; Meinao 1996; Merrill 2010a; Merrill 2010b; Merrill 2011; Merrill 2016; Merris 2018; Navarra 2011; Pena-Rossi 2009; Petri 2004; Petri 2013; Polderman 2001; Rupp 1987; Stohl 2017; Szepeitowski 2013; Tillmanns 2014; Tsakonas 1991; Tseng 2006; Van Vollenhoven 2018; Wallace 2009; Wallace 2014; Wallace 2018; Walton 1991; Werth 2017a; Williams 1994; Wright 2008; Yahya 2013; You 2010; Zhong 2013.

We rated the following studies as having unclear risk of attrition bias due to lack of sufficient details about withdrawals from studies or issues with per-protocol analyses (n = 14): Carneiro 1999; Clowse 2015; Furie 2015c; Islam 2012; Lanna 2019; Lima 2016; McGrath 1996; Merrill 2011; Merrill 2018; Ordi-Ros 2017; Petri 2010; Van Vollenhoven 1995; Wallace 2013; Westberg 1990.

The following studies were at high risk of attrition bias due to high rates of dropouts that were not further discussed/justified in the study report or due to serious concerns about per-protocol analysis (n = 5): Duffy 2004; Duliege 2016; Ishii 2015; Tseng 2007; Yokogawa 2015.
Summary of intent-to-treat versus per-protocol analysis

The following studies performed an intention-to-treat analysis or provided sufficient data that allowed us to perform an intention-to-treat analysis (n = 29): Bezerra 2005; Bootsma 1995; Cloose 2015; Fortin 2008; Furie 2016b; Griffiths 2010; Kahan 1985; Kuhn 2011; Meinao 1996; Merrill 2010a; Merrill 2010b; Merrill 2016; Pena-Rossi 2009; Petri 2004; Polderman 2001; Rupp 1987; Szepiekowska 2013; Tillmanns 2014; Tsakonas 1991; Tseng 2006; Wallace 2013; Wallace 2014; Wallace 2018; Werth 2017a; Williams 1994; Wright 2008; Yahya 2013; You 2010; Zhong 2013.

The following studies used a modified intention-to-treat analysis defined as excluding participants who had never received any study treatment (n = 16): Andrade-Ortega 2009; Carneiro 1999; Damaggio 2010; Furie 2011; Furie 2015a; Furie 2015b; Furie 2015c; Furie 2016a; Hackshaw 1995; McGrath 1996; Navarra 2011; Stohl 2017; Van Vollenhoven 1995; Van Vollenhoven 2018; Wallace 2009; Walton 1991.

The following studies used a per-protocol rather than an intention-to-treat analysis (n = 12): Duffy 2004; Ishii 2015; Islam 2012; Lanna 2019; Levy 2001; Lima 2016; Merrill 2010a; Merrill 2018; Petri 2010; Tzung 2007; Westberg 1990; Yokogawa 2015.

Selective reporting

We were not able to assess whether many of the studies deviated from their protocols because most did not have protocols available.

One study was at low risk for reporting bias because the study protocol was available and all outcomes reported in the protocol were published by study authors (Pena-Rossi 2009).

Sixteen studies were at high risk for reporting bias due to evidence of incomplete reporting in the form of missing data or incompletely reported data (Cloose 2015; Duliege 2016; Furie 2015c; Hackshaw 1995; Kahan 1985; Khamashta 2016; Kuhn 2011; Levy 2001; Merrill 2010a; Merrill 2011; Tillmanns 2014; Tzung 2007; Walton 1991; Westberg 1990; Williams 1994; Yokogawa 2015).

The remaining studies (n = 44) were at unclear risk for reporting bias.

Other potential sources of bias

In Fortin 2008 there was evidence that study authors carefully considered the potential other sources of bias and took precautions to minimise these biases (or at the very least, to acknowledge the nature and direction of bias); therefore Fortin 2008 was the only study in this review that was rated at low risk (n = 1).

The remaining studies had unclear risk of other bias due to insufficient information provided for assessment of bias (n = 60).

Effects of interventions

See: Summary of findings 1 Oral methotrexate versus placebo for cutaneous disease in systemic lupus erythematosus; Summary of findings 2 Oral hydroxychloroquine versus placebo for cutaneous disease in systemic lupus erythematosus; Summary of findings 3 Oral dehydroepiandrosterone versus placebo for cutaneous disease in systemic lupus erythematosus; Summary of findings 4 Oral chloroquine versus placebo for cutaneous disease in systemic lupus erythematosus; Summary of findings 5 Oral ciclosporin versus oral azathioprine for cutaneous disease in systemic lupus erythematosus; Summary of findings 6 Oral methotrexate versus oral chloroquine for cutaneous disease in systemic lupus erythematosus

Comparison groups were created for the analysis of primary and secondary outcomes (for details of outcomes, please see Types of outcome measures).

We have organised this section into:

- intervention versus placebo comparisons;
- dose response comparisons; and
- comparisons of two interventions.

If no trials were found for a particular comparison, this was stated. If only one trial was available for a comparison, or if data were unsuitable for combination for meta-analysis, the individual trial was described. For comparisons in which data could not be combined in a useful and methodologically appropriate way, we stated this and described the results of the included study or studies. If a study is not cited for an outcome, it is because the study did not report the outcome.

Numbers given show the total numbers of participants included in the analyses. When it was possible to calculate an effect size, we reported this with the 95% confidence interval. When the calculated effect size was statistically significant (P < 0.05), we stated whether the result favoured the intervention group or the control condition. In the text below, we report I² statistical values for heterogeneity; substantial heterogeneity is defined as I² greater than 50%.

Studies relevant to this review fall into 46 comparisons.

A. Comparisons of intervention versus placebo

Comparison 1 Oral methotrexate versus placebo

Two studies contributed to this comparison (Carneiro 1999; Fortin 2008).

This particular comparison has three outcomes: one primary outcome, one secondary outcome, and adverse events.

1.1 Primary outcome: complete clinical response (absence of malar or discoid rash, lupus-specific)

We identified one study relevant to the primary outcome of complete clinical response and categorised data into one subgroup (Carneiro 1999). No studies reported on the other primary outcome of partial clinical response.

1.1.1 Short term (six months)

A single trial in this subgroup included a total of 41 participants (Carneiro 1999). More participants (17/20) in the methotrexate group than in the placebo group (5/21) had complete clinical resolution of malar or discoid rash at the time of outcome assessment. We found evidence of large benefit for oral methotrexate over placebo within this subgroup (risk ratio (RR) 3.57, 95% confidence interval (CI) 1.63 to 7.84; P = 0.002; low-quality evidence; Analysis 1.1). See Summary of findings 1.
1.2 Secondary outcome: clinical flare (lupus-specific)

For this outcome, we found a single study and categorised data into one subgroup (Fortin 2008).

1.2.1 Long term (12 months)

We identified a single trial in this subgroup with a total of 86 participants (Fortin 2008). More participants (45/86) in the placebo group than in the methotrexate group (41/86) experienced a severe clinical flare requiring discontinuation from the study, favouring methotrexate over placebo. However, we did not find sufficient evidence of a clear difference between oral methotrexate and placebo within this subgroup due to wide confidence intervals and could not rule out higher risk of flares in the methotrexate group (RR 0.77, 95% CI 0.32 to 1.83; P = 0.55; moderate-quality evidence; Analysis 1.2). See Summary of findings 1.

1.3 Adverse events

We identified two studies (Carneiro 1999; Fortin 2008) with data relevant to this outcome.

Fortin 2008 noted narratively that “methotrexate was generally well tolerated, except for some excess in mild to moderate gastrointestinal and psychological toxicity” compared with placebo (P = 0.05).

We categorised the quantitative data into four subgroups.

1.3.1 Severe short term (six months)

We found one trial that was relevant to this subgroup with a total of 41 participants (Carneiro 1999). In the placebo group, two participants had lupus flares resulting in withdrawal from the study. The methotrexate group reported two adverse events (one case of pulmonary tuberculosis, one case of urticaria and dyspepsia). For this subgroup, we did not find evidence of a distinct difference between the two treatment groups because the risk ratio was very close to 1 (RR 1.05, 95% CI 0.16 to 6.76; low-quality evidence; Analysis 1.3.1).

1.3.2 Severe long term (12 months)

We found one trial relevant to this subgroup, which included a total of 86 participants (Fortin 2008). Results show that 5/41 in the methotrexate group compared with 0/45 in the placebo group experienced severe adverse effects in the long term (12 months). For this subgroup, results show evidence of increased harm in the methotrexate group compared with the placebo group; however confidence intervals were wide, so the estimate is uncertain (RR 12.05, 95% CI 0.69 to 211.36; moderate-quality evidence; Analysis 1.3.2). See Summary of findings 1.

1.3.3 Minor short term (six months)

A single trial in this subgroup included a total of 41 people (Carneiro 1999). For this outcome, within this subgroup, we found strong evidence that overall, oral methotrexate was more harmful in the total number of minor short-term effects compared with placebo, with more participants in the methotrexate group (11/20) than in the placebo group (3/21) experiencing an adverse event (RR 3.85, 95% CI 1.26 to 11.80; P = 0.02; low-quality evidence; Analysis 1.3.3). For example, with regard to gastrointestinal symptoms (mainly dyspepsia and increased hepatic enzyme serum levels), 14 methotrexate patients (70%) presented with side effects compared with only 3 placebo patients (14%).

On the other hand, 16 placebo patients presented with articular complaints compared with only 1 methotrexate patient (P < 0.001), and 11 placebo patients presented with hypocomplementaemia compared with only 4 methotrexate patients (P < 0.001).

1.3.4 Minor long-term (12 months) adverse mucocutaneous events

We identified a single trial in this subgroup, which included a total of 86 participants (Fortin 2008). For this subgroup, results do not show sufficient evidence of a distinct difference between the two treatments (RR 0.68, 95% CI 0.39 to 1.17; moderate-quality evidence; Analysis 1.3.4), although more participants in the placebo group (21/45) than in the methotrexate group (13/41) experienced an adverse mucocutaneous event (harm). See Summary of findings 1.

Comparison 2 Oral hydroxychloroquine versus placebo

Four studies contributed to this outcome (Levy 2001; Tsakonas 1991; Williams 1994; Yokogaw a 2015).

This particular comparison involved 14 outcomes reported in the categories of primary outcomes, secondary outcomes, and adverse events.

2.1 Primary outcome: partial clinical response (skin lesions, lupus-specific, during pregnancy)

For this outcome, we found a single study and categorised data into one subgroup (Levy 2001).

2.1.1 Long term (12 months)

We found one trial that was relevant to this subgroup with a total of 20 pregnant participants (Levy 2001). Three out of 10 participants in the hydroxychloroquine group compared with no participants of the 10 in the placebo group experienced partial improvement in skin lesions (during pregnancy), favouring hydroxychloroquine as beneficial. However, results do not show sufficient evidence of a distinct difference between the two treatments due to wide confidence intervals that included RR = 1 (RR 7.00, 95% CI 0.41 to 120.16; low-quality evidence; Analysis 2.1). See Summary of findings 2.

2.2 Primary outcome: partial clinical response (skin lesions, lupus-specific)

For this outcome, we found a single study and categorised data into one subgroup (Yokogaw a 2015).

2.2.1 Short term (four months)

We found one trial that was relevant to this subgroup and included a total of 103 participants (Yokogaw a 2015). Data that were presented grouped together 56 patients with cutaneous disease in SLE and 40 CLE patients without SLE. It was not possible to separate data for SLE patients from CLE patient data. Study authors noted that a greater proportion of patients in this combined group who showed the benefit of partial improvement were included in the hydroxychloroquine treatment group compared with the placebo group. Assessment involved three different scales.

- SkinDex - a 7-point global assessment scale completed by the patient (52/72 compared with 12/24).
- Central photo evaluation (43/72 compared with 7/24).
- Global assessment (GA) by investigators (36/72 compared with 2/24).
2.3 Secondary outcome: clinical flare (skin disease, lupus-specific)

We identified one study relevant to this outcome and organised these trial data into one subgroup.

2.3.1 Short term (six months)

We found one trial that was relevant to this subgroup with a total of 47 participants (Tsakonas 1991). Only nine out of 25 participants in the hydroxychloroquine group experienced a clinical flare compared with 16 out of 22 in the placebo group (RR 0.49, 95% CI 0.28 to 0.89; P = 0.02; moderate-quality evidence; Analysis 2.2). See Summary of findings 2.

2.4 Secondary outcome: clinical flare (vasculitis, lupus-non-specific)

We identified one trial that was relevant to this outcome and categorised the data into one subgroup (Tsakonas 1991).

2.4.1 Long term (48 months)

A single trial in this subgroup included a total of 47 participants (Tsakonas 1991). The oral hydroxychloroquine group had fewer clinical flares of vasculitis compared with the placebo group (RR 0.59, 95% CI 0.11 to 3.20; moderate-quality evidence; Analysis 2.3). However due to wide confidence intervals, evidence was not strong for a distinct difference between groups.

2.5 Secondary outcome: clinical flare (skin vasculitis or other system, lupus-specific and lupus-non-specific)

For this outcome, we found a single study and organised the data into one subgroup (Tsakonas 1991).

2.5.1 Long term (48 months)

We found one trial that was relevant to this subgroup with a total of 47 participants (Tsakonas 1991). Only seven out of 25 participants in the hydroxychloroquine group compared with 11 out of 22 in the placebo group experienced a major flare in lupus (vasculitis, skin or other system) (RR 0.56, 95% CI 0.26 to 1.19; moderate-quality evidence; Analysis 2.4); however confidence intervals were wide; therefore there is no strong evidence of a distinct difference between groups.

2.6 Secondary outcome: clinical flare (systemic lupus flare, lupus-specific, during pregnancy)

For this outcome, we found a single study and organised the data into one subgroup (Levy 2001).

2.6.1 Long term (12 months)

We found one trial that was relevant to this subgroup and included a total of 20 pregnant participants (Levy 2001). For this subgroup, results do not show evidence of a distinct difference between the two treatments (RR 0.14, 95% CI 0.01 to 2.45; low-quality evidence; Analysis 2.5). Three out of 10 participants in the placebo group compared with none of the participants in the hydroxychloroquine group experienced a systemic lupus flare during pregnancy.

2.7 Secondary outcome: CLASI (skin-specific measures of SLE disease activity)

For this outcome, we found a single study and categorised data into one subgroup (Yokogawa 2015).

2.7.1 Short term (four months)

We found one trial that was relevant to this subgroup and included a total of 103 participants (Yokogawa 2015). Data that were presented grouped 56 patients with cutaneous disease in SLE together with 40 CLE patients without SLE. It was not possible to separate the data for SLE patients. In the combined group, study authors noted that there was statistically significant improvement on the CLASI activity scale from baseline compared with four months later in both the hydroxychloroquine group (-4.6 ± 6.4 with P < 0.0001) and the placebo group (-3.2 ± 4.5 with P = 0.002). Data for the comparison between hydroxychloroquine and placebo groups were not reported by study authors.

2.8 Adverse events: severe toxaemia during pregnancy study

For this outcome, we found a single study and categorised data into one subgroup (Levy 2001).

2.8.1 Long term (12 months)

We found one trial that was relevant to this subgroup, which included a total of 20 pregnant participants (Levy 2001). None of the participants (n = 10) in the hydroxychloroquine group compared with 3 out of 10 in the placebo group experienced severe toxaemia during pregnancy, suggesting that hydroxychloroquine was favoured over placebo. However, we did not find strong evidence of a distinct difference between the two treatments due to wide confidence intervals (RR 0.14, 95% CI 0.01 to 2.45; low-quality evidence; Analysis 2.6).

2.9 Adverse events: severe adverse events related to medication

For this outcome, we found a single study and categorised data into one subgroup (Williams 1994).

2.9.1 Long term (12 months)

We found one trial to be relevant to this subgroup with a total of 71 participants (Williams 1994). Two out of 40 participants in the hydroxychloroquine group compared with zero in the placebo group (n = 21) experienced severe adverse events related to medication, indicating increased harms in the hydroxychloroquine group. However, there was no strong evidence of a difference between oral hydroxychloroquine and placebo within this subgroup due to wide confidence intervals, and benefit of hydroxychloroquine cannot be ruled out (RR 3.90, 95% CI 0.19 to 78.46; moderate-quality evidence; Analysis 2.7). See Summary of findings 2.

2.10 Adverse events: severe - any

For this outcome, we found a single study and organised the data into one subgroup (Williams 1994).

2.10.1 Short term (six months)

We identified a single trial in this subgroup with a total of 47 participants (Williams 1994). Only one of 25 participants in the hydroxychloroquine group compared with 5 of 22 in the placebo group experienced any kind of severe adverse event, favouring hydroxychloroquine over placebo. However, results show insufficient evidence of a distinct difference between oral hydroxychloroquine and placebo within this subgroup due to wide confidence intervals (RR 0.18, 95% CI 0.02 to 1.39; moderate-quality evidence; Analysis 2.8).
2.11 Adverse events: severe rash

We identified one study that was relevant to this outcome and categorised data into one subgroup (Williams 1994).

2.11.1 Long term (12 months)

We found one trial that was relevant to this subgroup with a total of 71 participants (Williams 1994). Only one participant in the hydroxychloroquine group compared with none of the 31 participants in the placebo group experienced the adverse effect of a severe rash, indicating increased harms from hydroxychloroquine. However, results provide insufficient evidence of a clear difference between oral hydroxychloroquine and placebo within this subgroup due to wide confidence intervals (RR 2.34, 95% CI 0.10 to 55.58; moderate-quality evidence; Analysis 2.9).

2.12 Adverse events: severe symptoms leading to study withdrawal (lack of efficacy)

For this outcome, we found a single study and organised study data into one subgroup (Williams 1994).

2.12.1 Long term (12 months)

We found one trial that was relevant to this subgroup, which included a total of 71 participants (Williams 1994). Five out of 40 in the hydroxychloroquine group compared with 7 of 31 in the placebo group experienced severe "symptoms leading to study withdrawal (lack of treatment efficacy)"; favouring hydroxychloroquine over placebo. However, results provide insufficient evidence of a clear difference between oral hydroxychloroquine and placebo within this subgroup (RR 0.55, 95% CI 0.19 to 1.58; moderate-quality evidence; Analysis 2.10).

2.13 Adverse events: severe sudden death - not thought to be related to medication

For this outcome, we found a single study and organised the data into one subgroup (Williams 1994).

2.13.1 Long term (12 months)

We found one trial to be relevant to this subgroup with a total of 71 participants (Williams 1994). One sudden death was not thought to be related to medication among the 40 participants in the hydroxychloroquine group compared with no sudden deaths among the 31 participants in the placebo group, indicating higher risk of the harm of sudden death in the hydroxychloroquine group. However, we did not find strong evidence of a distinct difference between the two treatments (RR 2.34, 95% CI 0.10 to 55.58; moderate-quality evidence; Analysis 2.11).

2.14 Adverse events: minor

We identified one study that was relevant to this outcome and organised the data into one subgroup (Tsakonas 1991).

2.14.1 Short term (six months)

We identified a single trial in this subgroup with a total of 47 participants (Tsakonas 1991). Three participants out of 25 in the hydroxychloroquine compared with 2 out of 22 in the placebo group experienced adverse minor events, indicating an increased risk of harms in the hydroxychloroquine group. However, we did not find strong evidence of a distinct difference between the two treatments due to wide confidence intervals and could not rule out an increased risk of harms in the placebo group (RR 1.32, 95% CI 0.24 to 7.19; moderate-quality evidence; Analysis 2.12). See Summary of findings 2.

Comparison 3 Oral dehydroepiandrosterone (DHEA) versus placebo

Two studies contributed to this comparison (Petri 2004; Van Vollenhoven 1995). This comparison has 11 outcomes divided into the categories of primary outcomes and adverse events. No secondary outcomes were reported for this comparison.

3.1 Primary outcome: complete clinical response (oral stomatitis, lupus-non-specific)

For this outcome, we found a single study and organised the data into one subgroup (Petri 2004).

3.1.1 Long term (12 months)

We identified a single trial in this subgroup with a total of 381 participants (Petri 2004). We found evidence of a clear difference between oral dehydroepiandrosterone and placebo within this subgroup, with more participants in the DHEA group experiencing the benefit of the complete clinical response of absence of oral stomatitis, specifically, 161 out of 189 in the oral dehydroepiandrosterone group compared with 148 out of 192 in the placebo group (RR 1.11, 95% CI 1.00 to 1.22; P = 0.04; moderate-quality evidence; Analysis 3.1). Therefore DHEA was favoured over placebo. See Summary of findings 3.

3.2 Primary outcome: complete clinical response (cutaneous rash, lupus-specific)

We identified one study that was relevant to this outcome and categorised data into one subgroup (Petri 2004).

3.2.1 Long term (12 months)

We found one trial that was relevant to this subgroup and included a total of 381 participants (Petri 2004). Only 114 of 189 in the DHEA group compared with 130 of 192 in the placebo group experienced complete clinical response (cutaneous rash) - a desirable/beneficial outcome. However, we did not find strong evidence of a distinct difference between the two treatments due to wide confidence intervals (RR 0.89, 95% CI 0.77 to 1.04; moderate-quality evidence; Analysis 3.2).

3.3 Primary outcome: complete clinical response (alopecia, lupus-non-specific)

We identified one study that was relevant to this outcome and categorised data into one subgroup (Petri 2004).

3.3.1 Long term (12 months)

We identified a single trial in this subgroup, which included a total of 381 participants (Petri 2004). We did not find strong evidence of a distinct difference between the two treatments (RR 1.07, 95% CI 0.97 to 1.17; moderate-quality evidence; Analysis 3.3), although more participants in the DHEA group (161/189) compared with the placebo group (153/192) experienced a complete clinical response of absence of alopecia (a desirable outcome).

3.4 Adverse events: severe - any

For this severe adverse events outcome, we found two relevant studies (Petri 2004; Van Vollenhoven 1995) (overall: RR 0.89, 95% CI
0.45 to 1.77; 409 participants, 2 studies; moderate-quality evidence (Petri 2004); low-quality evidence (Van Vollenhoven 1995)). Only 14 of 203 in the oral DHEA group compared with 16 of 206 in the placebo group experienced a severe adverse event, indicating that DHEA may cause fewer side effects when compared with placebo; however, due to wide confidence intervals, we did not find strong evidence of a distinct difference between the two groups.

We categorised data into two subgroups - short term and long term - for further analysis.

### 3.4.1 Short term (three months)

We found one trial that was relevant to this subgroup, which included a total of 28 participants (Van Vollenhoven 1995). For this outcome, within this subgroup, results show no events of this type; therefore no effect could be estimated and no forest plot produced.

### 3.4.2 Long term (12 months)

We found one trial that was relevant to this subgroup, with a total of 381 participants (Petri 2004). Results show only 14 out of 189 events in the oral DHEA group compared with 16 of 192 events in the placebo group, favouring DHEA over placebo. However, we did not find evidence of a distinct difference between the two treatments due to wide confidence intervals (RR 0.89, 95% CI 0.45 to 1.77; moderate-quality evidence; Analysis 3.4.2).

### 3.5 Adverse events: severe - death

We identified one study that was relevant to this outcome and categorised data into one subgroup (Petri 2004).

#### 3.5.1 Long term (12 months)

We identified a single trial in this subgroup with a total of 381 participants (Petri 2004). Five deaths out of 192 participants were reported in the placebo group compared with no deaths in the oral DHEA group, favouring DHEA over placebo. However, results show insufficient evidence of a clear difference between oral dehydroepiandrosterone and placebo (RR 0.09, 95% CI 0.01 to 1.66; moderate-quality evidence; Analysis 3.5). See Summary of findings 3.

### 3.6 Adverse events: severe - cancer diagnosis

For this outcome, we found a single study and categorised data into one subgroup (Petri 2004).

#### 3.6.1 Long term (12 months)

We identified a single trial in this subgroup, which included a total of 381 participants (Petri 2004). No participants among the 189 in the oral DHEA group had a cancer diagnosis compared with 3 cancer diagnoses among 192 participants in the placebo group, favouring DHEA over placebo; however, we did not find strong evidence of a distinct difference between the two treatments due to wide confidence intervals (RR 0.15, 95% CI 0.01 to 2.79; moderate-quality evidence; Analysis 3.6).

### 3.7 Adverse events: minor presence of acne

We identified two studies that were relevant to this outcome and categorised data into two subgroups (Petri 2004; Van Vollenhoven 1995). We did a meta-analysis combining short-term (3 months) and long-term (12 months) data. Combined data show that 63 of 189 participants in the oral DHEA group had acne compared with 28 of 206 participants in the placebo group developed acne. Overall, strong evidence indicates that participants receiving DHEA were more likely to experience the harm of acne (RR 2.98, 95% CI 1.16 to 7.62; 409 participants, 2 studies; I² = 32%; P = 0.02 (for effect); moderate-quality evidence (Petri 2004); low-quality evidence (Van Vollenhoven 1995; Analysis 3.7).

We divided the data into subgroups as follows.

#### 3.7.1 Short term (three months)

We identified a single trial in this subgroup with a total of 28 participants (Van Vollenhoven 1995). Eight of the 14 participants in the oral DHEA group had acne compared with only 1 of the 14 participants in the placebo group. We found strong evidence that the oral dehydroepiandrosterone group had increased risk of the harm of acne compared with the placebo group (RR 8.00, 95% CI 1.15 to 55.8; P < 0.0001; low-quality evidence; Analysis 3.7).

#### 3.7.2 Long term (12 months)

We found one trial that was relevant to this subgroup, which included a total of 381 participants (Petri 2004). Acne was present in 63 out of 189 in the oral DHEA group compared with only 28 out of 206 in the placebo group. We found strong evidence that oral dehydroepiandrosterone was associated with increased risk of the harm of acne compared with placebo (RR 2.37, 95% CI 1.58 to 3.55; moderate-quality evidence; P < 0.0001; Analysis 3.7).

### 3.8 Adverse events: minor - presence of hirsutism

For this outcome, we found two studies and organised the data into two subgroups (Petri 2004; Van Vollenhoven 1995).

#### 3.8.1 Short term (three months)

We identified a single trial in this subgroup with a total of 28 participants (Van Vollenhoven 1995). Two of 14 in the oral DHEA group compared with 7 of 26 in the placebo group developed hirsutism. The oral dehydroepiandrosterone group had increased risk of the harm of hirsutism compared with the placebo group. However due to wide confidence intervals, results show insufficient evidence of a clear difference between groups, and we could not rule out harm in the placebo group (RR 0.50, 95% CI 0.11 to 2.30; low-quality evidence; Analysis 3.8.1).

#### 3.8.2 Long term (12 months)

We found one trial that was relevant to this subgroup with a total of 381 participants (Petri 2004). This is an undesirable effect that favours the placebo group, with only 3 of 192 in the placebo group compared with 31 of 191 in the oral DHEA group developing hirsutism. We found strong evidence of significantly more hirsutism (a harm) in the DHEA group compared with the placebo group at 12 months (RR 10.5, 95% CI 3.26 to 33.75; moderate-quality evidence; P < 0.0001; Analysis 3.8.2). See Summary of findings 3.

### Combined data

When data were combined for the purposes of meta-analysis, they showed that 33 of 203 in the oral DHEA group compared with 7 of 206 in the placebo group developed hirsutism. Overall, participants receiving DHEA were more likely to experience the harm of hirsutism, but levels of statistical heterogeneity in this analysis were important (RR 2.38, 95% CI 0.11 to 50.74; 409 participants, 2 studies; I² = 90%; P = 0.001; moderate-quality evidence (Petri 2004); low-quality evidence (Van Vollenhoven 1995)). It is unclear if the
3.9 Adverse events: minor - presence of rash

For this outcome, we found a single study and categorised data into one subgroup (Van Vollenhoven 1995).

3.9.1 Short term (three months)

We found one trial that was relevant to this subgroup, which included a total of 28 participants (Van Vollenhoven 1995). Zero of 14 participants in the oral DHEA group compared with 2 of 14 in the placebo group developed a rash. Oral dehydroepiandrosterone was favoured over placebo, with fewer harmful side effects of rash within this subgroup; however results provided insufficient evidence of a difference between groups due to wide confidence intervals, and benefit of placebo could not be ruled out (RR 0.20, 95% CI 0.01 to 3.82; low-quality evidence; Analysis 3.9).

Petri 2004 also reported that the placebo group had qualitatively more stomatitis, myalgia, and cholesterol issues.

Comparison 4 Intravenous belimumab (intravenous or subcutaneous) versus placebo

Three studies of intravenous belimumab - Furie 2011; Navarra 2011; Wallace 2009 - and one study of subcutaneous belimumab - Stohl 2017 - contributed to this comparison. No primary outcomes were reported. The following secondary outcomes and adverse events were reported.

4.1 Secondary outcome: skin-specific measures of SLE disease activity (SELENA/SLEDAI, BILAG, and SRI)

Navarra 2011 reported narrative data on secondary outcomes with IV belimumab. We would prefer to report the results in the form of risk ratios; however this article provided insufficient data to allow transformation from odds ratios (ORs) to risk ratios (RRs). Data were as follows. More participants in the belimumab 1 mg/kg dose group had "SELENA/SLEDAI scores reduced by at least four points" in the mucocutaneous domain compared with the placebo group (OR 1.51, 95% CI 1.07 to 2.14; P = 0.0128). More participants in the belimumab 10 mg/kg group had "SELENA/SLEDAI scores reduced by 4 points" in the mucocutaneous domain compared with the placebo group (OR 1.71, 95% CI 1.21 to 2.41; P = 0.0024). More participants in the belimumab 10 mg/kg dose group had "no new BILAG A" in the mucocutaneous domain or "no more than 1 new BILAG B flare" in the mucocutaneous domain than did those in the placebo group (OR 1.62, 95% CI 1.09 to 2.42; P = 0.0181). However, the number of participants in the belimumab 1 mg/kg dose group with "no new BILAG A" or "no more than one new BILAG B flare" was not statistically significantly different from the number in the placebo group (OR 1.38, 95% CI 0.93 to 2.04; P = 0.1064).

Stohl 2017 reported on subcutaneous belimumab, noting that "all components of the SR4 (Systemic Lupus Erythematosus Responder Index (SR4)) showed statistical significance at week 52" and that "the immunologic, musculoskeletal, mucocutaneous, and vascular SELENA--SLEDAI organ systems improved significantly more in the belimumab group than in the placebo group at week 52 (data not shown)."

These outcomes were graded as moderate quality and were downgraded due to risk of bias, namely, insufficient details about randomisation.

4.2 Adverse events: severe - at belimumab 1 mg/kg IV or 2 to 4 mg/kg SC dose

For this outcome, we found three relevant studies for intravenous injections (Furie 2011; Navarra 2011; Wallace 2009). We organised the data into two subgroups in accordance with our protocol. Overall, we noted no differences between the two groups at any of the time points (RR 0.86, 95% CI 0.62 to 1.21; 1348 participants, 3 studies; I² = 0%; P = 0.10 for heterogeneity and P = 0.40 for effect; Analysis 4.1; moderate-quality evidence (Wallace 2009); moderate-quality evidence (Furie 2011); moderate-quality evidence (Navarra 2011)).

We also found one study for subcutaneous injection (Stohl 2017).

4.2.1 Long term (12 months)

We identified two relevant trials for this subgroup, which included a total of 802 participants (Navarra 2011; Wallace 2009). In all, 37 of 402 participants in the belimumab group compared with 41 of 400 in the placebo group had severe adverse events. In our meta-analysis, we noted no clear differences between intravenous belimumab and placebo within this subgroup due to RR close to 1 and wide confidence intervals (RR 0.90, 95% CI 0.60 to 1.36; I² = 0%; P = 0.78 for heterogeneity; P = 0.62 for effect; Analysis 4.1.1; moderate-quality evidence (Wallace 2009); moderate-quality evidence (Navarra 2011)).

We also found one relevant study for subcutaneous belimumab versus placebo (Stohl 2017). In this study, 25 of 280 participants in the placebo group and 40 of 556 in the belimumab group had severe adverse events.

4.2.2 Long term (18 months)

We found one trial that was relevant to this subgroup, which included a total of 546 participants (Furie 2011). A total of 18 of 271 participants in the belimumab group compared with 23 of 275 in the placebo group had severe adverse events. There was no clear difference between intravenous belimumab and placebo within this subgroup (RR 0.79, 95% CI 0.44 to 1.44; moderate-quality evidence; Analysis 4.1.2).

4.3 Adverse events: severe - at belimumab 10 mg/kg IV dose

For this outcome, we found three relevant studies for intravenous belimumab (Furie 2011; Navarra 2011; Wallace 2009), and we categorised data into two subgroups (in keeping with our protocol). We noted that 56 of 674 participants in the belimumab group compared with 64 of 675 in the placebo group had severe adverse events, favouring belimumab for fewer harmful side effects. However, there was no clear difference between the two groups at any of the time points due to wide confidence intervals (RR 0.88, 95% CI 0.63 to 1.23; 1349 participants, 3 studies; I² = 0%; P = 0.82 for heterogeneity; P = 0.46 for effect; Analysis 4.2 moderate-quality evidence (Furie 2011); moderate-quality evidence (Navarra 2011); moderate quality evidence (Wallace 2009)).

4.3.1 Long term (12 months)

Two relevant trials in this subgroup included a total of 802 participants (Navarra 2011; Wallace 2009). Results show that 33 of 401 participants in the belimumab group compared with 41 of 400 in the placebo group had severe adverse events. In this meta-analysis, although belimumab was favoured with fewer harmful side effects, there was no clear difference between
intravenous belimumab and placebo within this subgroup due to wide confidence intervals (RR 0.81, 95% CI 0.53 to 1.24; 802 participants, 2 studies; I² = 0%; P = 0.88 for heterogeneity; P = 0.34 for effect; Analysis 4.2.1; moderate-quality evidence [Wallace 2009]; moderate-quality evidence [Navarra 2011].

4.3.2 Long term (18 months)
A single trial in this subgroup included a total of 548 participants (Furie 2011). Results show that 23 of 273 participants in the belimumab group compared with 23 of 275 in the placebo group had severe adverse events. There was no clear difference between intravenous belimumab and placebo within this subgroup, with RR close to 1 and wide confidence intervals (RR 1.01, 95% CI 0.58 to 1.75; moderate-quality evidence; Analysis 4.2.2).

4.4 Adverse events: minor - skin and subcutaneous skin combined data at doses of 1.0 mg/kg, 4 mg/kg, and 10 mg/kg
We identified one intravenous study that was relevant to this outcome and categorised data into one subgroup (Wallace 2009).

We also found one relevant study for subcutaneous belimumab (Stohl 2017).

4.4.1 Long term (12 months)
We identified a single trial in this subgroup for intravenous injection, which included a total of 449 participants (Wallace 2009). Only 57 out of 113 participants in the placebo group experienced minor “skin and subcutaneous skin” adverse events compared with 192 out of 336 participants in the belimumab groups. Specifically, for the belimumab subgroups, minor adverse events were experienced in 72 out of 114 participants in the 1 mg/kg group, in 65 out of 111 participants in the 4 mg/kg group, and in 55 out of 111 participants in the 10.0 mg/kg group, respectively. Although there were more side effects (harms) in the belimumab group, favouring placebo, results show insufficient evidence of a difference between intravenous belimumab and placebo (RR 1.13, 95% CI 0.92 to 1.39; moderate-quality evidence; Analysis 4.3.1).

We also found one relevant study for subcutaneous belimumab (Stohl 2017), in which 182 of 280 participants in the treatment group compared with 389 of 556 participants in the belimumab group had minor adverse events.

Comparison 5 Oral prednisone versus placebo
One study contributed to this comparison (Tseng 2006). No primary outcomes were reported. Only secondary outcomes and adverse events were reported. This particular comparison has three outcomes.

5.1 Secondary outcome: clinical flare (skin disease, lupus-specific)
We identified one study that was relevant to this outcome and categorised data into one subgroup (Tseng 2006).

5.1.1 Long term (18 months)
We identified a single trial in this subgroup, which included a total of 41 participants (Tseng 2006). In all, 2 of 21 participants in the prednisone group compared with 2 of 20 in the placebo group had a flare (harm) in skin disease. There was no clear difference between oral prednisone and placebo within this subgroup with RR close to 1 (RR 0.95, 95% CI 0.15 to 6.13; Analysis 5.1). Outcomes in this study were graded at low risk, downgraded due to risk of bias (unclear methods of sequence generation and allocation concealment) and imprecision (only one small study).

5.2 Adverse events: minor
We identified one study that was relevant to this outcome and organised the data into one subgroup (Tseng 2006).

5.2.1 Long term (18 months)
We identified a single trial in this subgroup with a total of 41 participants (Tseng 2006). A total of 12 of 21 participants in the prednisone group compared with 11 of 20 in the placebo group had a minor adverse event. There was no clear difference between oral prednisone and placebo within this subgroup with wide confidence intervals and risk ratio close to 1 (RR 1.04, 95% CI 0.60 to 1.79; low-quality evidence; Analysis 5.2).

5.3 Adverse events: severe
For this outcome, we found a single study and categorised data into one subgroup (Tseng 2006).

5.3.1 Long term (18 months)
We identified a single trial in this subgroup with a total of 41 participants (Tseng 2006). One of 21 participants in the prednisone group compared with zero of 20 participants in the placebo group had severe adverse events, showing increased harms in the prednisone group and favouring the placebo group. However, we did not find strong evidence of a difference between the two treatments due to wide confidence intervals (RR 2.86, 95% CI 0.12 to 66.44; Analysis 5.3).

Comparison 6 Oral chloroquine versus placebo
For this comparison, one study contributed data (Meinao 1996).

For this comparison, three primary outcomes and adverse events were reported. No secondary outcomes were reported.

6.1 Primary outcome: complete clinical response (skin lesions, lupus-specific)
We identified one study relevant to this outcome and organised the data into one subgroup (Meinao 1996).

6.1.1 Long term (12 months)
We identified a single trial in this subgroup, which included a total of 24 participants (Meinao 1996). Results show that 13 of 12 participants in the chloroquine group compared with 7 of 12 participants in the placebo group had complete clinical response (absence of skin lesions), favouring chloroquine as beneficial. However, we did not find sufficient evidence of a distinct difference between the two treatments due to wide confidence intervals (RR 1.57, 95% CI 0.92 to 2.61; low-quality evidence; Analysis 6.1). See Summary of findings 4.

The outcomes in this study were graded as low risk, downgraded due to risk of bias (insufficient details about methods of sequence generation and allocation concealment) and imprecision (one small study).

6.2 Primary outcome: complete clinical response (alopecia, lupus-non-specific)
We identified one study relevant to this outcome and organised the data into one subgroup (Meinao 1996).
6.2.1 Long term (12 months)

We found one trial that was relevant to this subgroup with a total of 24 participants (Meinao 1996). In all, 11 of 12 participants in the chloroquine group compared with 11 of 12 participants in the placebo group had the benefit of a complete clinical response (absence of alopecia). There was no clear difference between oral chloroquine and placebo within this subgroup with risk ratio of 1 and wide confidence intervals (RR 1.00, 95% CI 0.79 to 1.27; low-quality evidence; Analysis 6.2).

6.3 Adverse events: severe

For this outcome, we found a single study and categorised data into one subgroup (Meinao 1996).

6.3.1 Long term (12 months)

We found one trial that was relevant to this subgroup, which included a total of 24 participants (Meinao 1996). None of the 12 participants in the chloroquine group compared with 1 of the 12 participants in the placebo group had severe adverse events, indicating more harms in the placebo group and favouring chloroquine as beneficial. However, there was no strong evidence of a clear difference between oral chloroquine and placebo within this subgroup (RR 0.33, 95% CI 0.01 to 7.45; low-quality evidence; Analysis 6.3) due to wide confidence intervals. See Summary of findings 4.

Comparison 7 Oral fish oil versus placebo

We identified four trials for this comparison (Duffy 2004; Walton 1991; Westberg 1990; Wright 2008). Primary outcomes, secondary outcomes, and adverse events were reported.

Of note, Duffy 2004 was a multi-arm 2 × 2 factorial design study of both copper and fish oil. As recommended, for the purposes of analysis, we split the study into two parallel-group studies and analysed the data separately under each intervention respectively.

Walton 1991 was a cross-over study that reported data narratively providing insufficient data for integration into meta-analysis at this time. In the future, if meta-analysis is undertaken, we plan to use only first period data.

7.1 Primary outcomes

Walton 1991 individualised outcomes for each participant. For example, one participant was described as having "ideal improvement, useful improvement, no change or deterioration". The only specific reported data relevant to skin was seen in the example provided for sample "patient 12". This patient was noted in the first phase (diet only for two weeks followed by 12 weeks with treatment or placebo) to have "no active rash, no mouth ulcers", and in the second phase (diet only followed by 12 weeks with treatment or placebo) had "no rash". Outcomes were graded as low quality due to risk of bias (unclear risk in multiple domains) and imprecision.

Westberg 1990 reported that during the first three months of Max Eicosapentaenoic Acid (MaxEPA), 8 out of 17 in the MaxEPA group and only two out of 17 in the control group had improved clinical scores, a composite general score specific for this study, comprising ratings from 0 to +++ for skin, joints, and kidneys. At six months, there was no difference. Study investigators concluded that the beneficial effect was short-lived. They did not identify any particular subgroup (skin or otherwise) that responded well to MaxEPA. Outcomes were graded as low quality due to risk of bias (unclear risk in multiple domains) and imprecision.

Williams 1994 was initially designed to determine the effects of fish oil on arthropathy. Cutaneous manifestations were discussed in the text: "no significant differences were found between the two treatment groups in cutaneous... manifestations of SLE with the exception of an erythematous maculopapular skin eruption". These rashes were more severe in the placebo group at the beginning (P = 0.02) and at the end (P = 0.02) of the study. No specific extractable analysable data were given in the study beyond these P values. Outcomes were graded as moderate quality due to risk of bias (unclear risk in multiple domains) and imprecision (randomisation details not given).

7.2 Secondary outcomes

Duffy 2004 reported that one of the components of the SLAM-R score that was most affected by fish oil supplementation was the integument domain, along with neuromotor and laboratory domains. However quantitative details were not given for the integument domain. The general SLAM score for the fish oil treatment group compared with the group not taking fish oil showed a significant decrease from a mean (standard error of the mean (SEM)) of 6.12 to 4.69 (P < 0.05) after six months (24 weeks).

This outcome was graded as low quality due to risk of bias that was high in multiple domains (very serious limitations).

7.3 Adverse events: severe - various, requiring withdrawal from study

7.3.1 Short term (six months)

Duffy 2004 narratively reported nine severe adverse events among 65 participants, including three withdrawals (no details given) and three hospital admissions (one for stroke and two for chest infection).

Walton 1991 narratively reported that 10 participants withdrew due to the following severe adverse events: bacterial diarrhoea, inability to swallow capsules, gallstones, vomiting back-up capsules, and inability to comply with a low-fat diet.

Westberg 1990 did not report any severe adverse events.

7.4 Adverse event: severe - GI side effect, requiring withdrawal from study

For this outcome, we found a single study and organised the data into one subgroup (Wright 2008).

7.4.1 Short term (six months)

We found one trial that was relevant to this subgroup and included a total of 60 participants (Wright 2008). A total of 3 of 30 participants in the fish oil group compared with none of the participants in the placebo group had severe gastrointestinal adverse events requiring withdrawal from the study, favouring the placebo group. However, results show no evidence of a clear difference in the fish oil group compared with the placebo group during the six-month study due to wide confidence intervals, and benefits of fish oil could not be ruled out (RR 7.0, 95% CI 0.38 to 129.93; Analysis 7.1).

This outcome was graded as moderate evidence quality, downgraded due to risk of bias (randomisation details not given).
7.5 Adverse events: minor

7.5.1 Short term (six months)
No outcomes were reported.

**Comparison 8 Oral nicardipine versus placebo**

One study contributed to this comparison (Rupp 1987). No primary outcomes were reported. This particular comparison consists of four outcomes, including secondary outcomes and adverse events.

*Rupp 1987* was a cross-over study. Data were insufficient for integration into meta-analysis at this time. In the future, if meta-analysis is undertaken, we plan to use only first period data.

**8.1 Secondary outcome: clinical flare (severity of Raynaud’s attacks assessed by visual analogue scale, lupus-non-specific)**

We identified one study that was relevant to this outcome and organised the data into one subgroup (Rupp 1987).

8.1.1 Short term (one month)

We found one trial that was relevant to this subgroup with a total of 30 participants (Rupp 1987). For this outcome, within this subgroup, we found no evidence that oral nicardipine was different in its effects compared with placebo (mean difference (MD) -0.49, 95% CI -1.16 to 0.18; Analysis 8.2). The mean severity of Raynaud’s attacks assessed by visual analogue scale was 0.84 with standard deviation of 0.77 for the 15 participants in the nicardipine group compared with a mean of 1.33 with standard deviation of 1.08 for the 15 participants in the placebo group.

Outcomes in this study were graded as low-quality evidence due to risk of bias (randomisation method details not given) and imprecision (one small study).

8.2 Secondary outcome: clinical flare (number of Raynaud’s attacks per day, lupus-non-specific)

For this outcome, we found a single study and categorised that data into one subgroup (Rupp 1987).

8.2.1 Short term (one month)

We identified a single trial in this subgroup with a total of 30 participants (Rupp 1987). The mean number of Raynaud’s attacks per day was less at 0.62 with standard deviation of 0.89 for the 15 participants in the nicardipine group compared with a mean of 0.96 with standard deviation of 1.26 for the 15 participants in the placebo group, showing benefits of nicardipine over placebo. However for this outcome, within this subgroup, we did not find strong evidence to suggest that oral nicardipine was different in its effects compared with placebo due to wide confidence intervals, and we could not exclude benefit for the placebo group (MD -0.34, 95% CI -1.12 to 0.44; low-quality evidence; Analysis 8.2).

8.3 Adverse events: severe

We identified one study that was relevant to this outcome and organised the data into one subgroup (Rupp 1987).

8.3.1 Short term (one month)

We identified a single trial in this subgroup with a total of 30 participants (Rupp 1987). None of the 15 participants in the nicardipine group had severe adverse events, favouring the nicardipine group with fewer severe side effects. However for this subgroup, we did not find evidence of a distinct difference between the two treatments due to wide confidence intervals (RR 0.33, 95% CI 0.01 to 7.58; low-quality evidence; Analysis 8.3).

8.4 Adverse events: minor - cardiovascular or GI side effect

We identified one study that was relevant to this outcome and categorised the data into one subgroup (Rupp 1987).

8.4.1 Short term (one month)

We identified a single trial in this subgroup, which included a total of 30 participants (Rupp 1987). In all, 7 of 15 participants in the nicardipine group compared with only 4 of 15 participants in the placebo group had minor cardiovascular or gastrointestinal adverse events, favouring the placebo group, with fewer minor side effects. However, results show no clear evidence of a difference between oral nicardipine and placebo within this subgroup due to wide confidence intervals (RR 1.75, 95% CI 0.64 to 4.75; low-quality evidence; Analysis 8.4).

**Comparison 9 Oral ginsenosides versus placebo**

One study contributed to this comparison (You 2010).

In this comparison, seven outcomes were divided among primary outcomes and adverse events. No secondary outcomes were reported.

9.1 Primary outcome: complete clinical resolution (facial erythema, lupus-specific)

For this outcome, we found a single study and organised the data into one subgroup (You 2010).

9.1.1 Short term (three months)

We identified a single trial in this subgroup, which included a total of 60 participants. More (9/30) participants in the ginsenosides group compared with only 5 of 30 in the placebo group had "complete clearance of facial erythema", favouring ginsenosides. However for this subgroup, we found no evidence of a distinct difference between the two treatments due to wide confidence intervals (RR 1.80, 95% CI 0.68 to 4.74; moderate-quality evidence; Analysis 9.1).

Outcomes were graded as moderate quality due to risk of bias (no blinding of assessors).

9.2 Primary outcome: complete clinical resolution (aphthae, lupus-non-specific)

For this outcome we found a single study, You 2010, and organised the data into one subgroup.

9.2.1 Short term (three months)

We identified a single trial in this subgroup with a total of 60 participants (You 2010). In all, 5 of 30 participants in the ginsenosides group compared with none of 30 participants in the placebo group had "complete clearance of aphthae", favouring ginsenosides. However, we found insufficient evidence of a distinct difference between the two treatments due to wide confidence intervals (RR 11.0, 95% CI 0.64 to 190.53; moderate-quality evidence; Analysis 9.2).
9.3 Primary outcome: complete clinical resolution (erythema (hands), lupus-specific)

For this outcome, we found a single study and organised the data into one subgroup (You 2010).

9.3.1 Short term (three months)

We found one trial that was relevant to this subgroup, which included a total of 60 participants (You 2010). A total of 4 of 30 participants in the ginsenosides group compared with only 3 of 30 participants in the placebo group had "complete clearance of erythema of hands", favouring ginsenosides. However, there was no clear difference between oral ginsenosides and placebo due to wide confidence intervals (RR 1.33, 95% CI 0.33 to 5.45; moderate-quality evidence; Analysis 9.3).

9.4 Primary outcome: complete clinical resolution (alopecia, lupus-non-specific)

We identified one study that was relevant to this outcome and categorised data into one subgroup (You 2010).

9.4.1 Short term (three months)

We identified a single trial in this subgroup with a total of 60 participants (You 2010). Results show that 5 of 30 participants in the ginsenosides group compared with none of the participants in the placebo group had "complete clearance of alopecia", favouring ginsenosides. However, insufficient evidence of a clear difference between oral ginsenosides and placebo was insufficient due to wide confidence intervals (RR 11.0, 95% CI 0.64 to 190.53; moderate-quality evidence; Analysis 9.4).

9.5 Primary outcome: complete clinical resolution (oedema, lupus-non-specific)

For this outcome, we found a single study and categorised data into one subgroup (You 2010).

9.5.1 Short term (three months)

We found one trial to be relevant to this subgroup with a total of 60 participants (You 2010). In all, 3 of 30 participants in the ginsenosides group compared with 4 of 30 in the placebo group had complete clearance of oedema, favouring placebo. However, we did not find sufficient evidence of a distinct difference between the two treatments due to wide confidence intervals (RR 0.75, 95% CI 0.18 to 3.07; moderate-quality evidence; Analysis 9.5).

9.6 Adverse events: minor - side effect from medication

For this outcome, we found a single study and categorised data into one subgroup (You 2010).

9.6.1 Short term (three months)

We found one trial that was relevant to this subgroup with a total of 60 participants (You 2010). None of the 30 participants in the ginsenosides group compared with 1 of 30 of the participants in the placebo group had the undesirable mild adverse event of side effects from the medication (intervention), favouring ginsenosides as beneficial. There was no clear difference between oral ginsenosides and placebo within this subgroup (RR 0.33, 95% CI 0.01 to 7.87; moderate-quality evidence; Analysis 9.6).

Comparison 10 Intravenous rituximab versus placebo

One study contributed to this outcome (Merrill 2010a). No primary outcomes were reported. The following secondary and adverse events were reported.

10.1 Secondary outcome: skin-specific measures of SLE disease activity (BILAG)

Merrill 2010a reported narrative secondary outcomes including BILAG B and BILAG A scores for the mucocutaneous domain. At baseline in the rituximab group, 56.2% had BILAG B and 16% had BILAG A. At baseline in the placebo group, 58.0% had BILAG B and 13.6% had BILAG A. Subgroup analysis of the primary endpoint (BILAG A and BILAG B) was performed for the preplanned subgroup "mucocutaneous system involvement", and study investigators reported no differences during the 12-month study.

Outcomes were graded as moderate quality, downgraded to risk of bias (insufficient details about methods of randomisation and allocation concealment).

10.2 Adverse events: severe event - not including death

We identified one study that was relevant to this outcome and categorised data into one subgroup (Merrill 2010a).

10.2.1 Long term (12 months)

We identified a single trial in this subgroup with a total of 257 participants (Merrill 2010a). In all, 19 of 169 participants in the rituximab group compared with 13 of 88 in the placebo group had severe adverse events (not including death), favouring rituximab over placebo. However, we did not find sufficient evidence of a distinct difference between the two treatments due to wide confidence intervals (RR 0.76, 95% CI 0.39 to 1.47; moderate-quality evidence; Analysis 10.1).

10.3 Adverse events: severe - death

We identified one study that was relevant to this outcome and categorised data into one subgroup (Merrill 2010a).

10.3.1 Long term (12 months)

We found one trial that was relevant to this subgroup with a total of 257 participants (Merrill 2010a). A total of 4 of 169 participants in the rituximab group compared with 1 of 88 participants in the placebo group died. Although the placebo group was favoured over the rituximab group, we found insufficient evidence of a clear difference between intravenous rituximab and placebo (RR 2.08, 95% CI 0.24 to 18.35; moderate-quality evidence; Analysis 10.2).

10.4 Adverse events: minor

Merrill 2010a reported that the most common adverse events were "nervous system (13.6%), general (10.2%), and gastrointestinal (10.2%) disorders [in the placebo group], compared with nervous system (14.2%), gastrointestinal (14.2%), skin and subcutaneous tissue (11.8%), and general disorders (10.7%) in the rituximab group".

Comparison 11 Intravenous abatacept versus placebo

One study contributed to this outcome (Merrill 2010b). There were no primary outcome reports. Four secondary outcomes and adverse events were reported.
11.1 Secondary outcome: skin-specific measures of SLE disease activity (BILAG A or B flare in discoid lesions)

We identified one study that was relevant to this outcome and categorised data into one subgroup (Merrill 2010b).

11.1.1 Long term (12 months)

We found one trial that was relevant to this subgroup with a total of 60 participants (Merrill 2010b). Results show that 35 of 41 participants in the abatacept group compared with 15 of 19 in the placebo group had a BILAG A or B flare in discoid lesions. For this subgroup, we did not find evidence of a distinct difference between the two treatments due to a risk ratio close to 1 and wide confidence intervals (RR 1.08, 95% CI 0.83 to 1.41; moderate-quality evidence; Analysis 11.1).

This outcome was graded as moderate quality, downgraded due to risk of bias, specifically due to insufficient details about the methods of sequence generation and allocation concealment used.

11.2 Secondary outcome: skin-specific measures of SLE disease activity (new BILAG A score for discoid lesions)

We identified one study that was relevant to this outcome and organised the data into one subgroup (Merrill 2010b).

11.2.1 Long term (12 months)

We found one trial that was relevant to this subgroup with a total of 60 participants (Merrill 2010b). Results show that 20 of 41 participants in the abatacept group compared with 8 of 19 in the placebo group had a new BILAG A score for discoid lesions (a harmful outcome), so placebo was favoured. However, we did not find sufficient evidence of a distinct difference between the two treatments due to wide confidence intervals (RR 1.16, 95% CI 0.63 to 2.14; moderate-quality evidence; Analysis 11.2).

11.3 Secondary outcome: clinical flare (in discoid lesions, based on physician-based assessment)

For this outcome, we found a single study and categorised data into one subgroup (Merrill 2010b).

11.3.1 Long term (12 months)

We identified a single trial for this subgroup with a total of 60 participants (Merrill 2010b). In all, only 28 of 41 participants in the abatacept group compared with 15 of 19 in the placebo group had a new flare in discoid lesions based on physician-based assessment - a harmful outcome. Although abatacept was favoured over placebo for fewer flares, we did not find sufficient evidence of a distinct difference between the two treatments due to wide confidence intervals (RR 0.87, 95% CI 0.63 to 1.18; moderate-quality evidence; Analysis 11.3).

11.4 Adverse events: severe - any

For this outcome, we found a single study and organised the data into one subgroup (Merrill 2010b).

11.4.1 Long term (12 months)

We found one trial that was relevant to this subgroup, which included a total of 180 participants (Merrill 2010b). Examples of these side effects in the abatacept group include facial oedema, hand oedema, pyrexia, alveolitis, polyneuropathy, diverticulitis, bronchitis, drug hypersensitivity, and dehydration, and in the placebo group angio-oedema, lupus vasculitis, and lupus peritonitis. Results show that 10 of 121 participants in the abatacept group compared with 3 of 59 in the placebo group had severe adverse events, favouring the placebo group, with fewer side effects. However, evidence of a clear difference between intravenous abatacept and placebo within this subgroup was insufficient due to wide confidence intervals (RR 1.63, 95% CI 0.46 to 5.68; moderate-quality evidence; Analysis 11.4).

11.5 Adverse events: minor

Given the higher proportion of serious adverse events (SAEs) in the abatacept group, further post hoc analyses were performed, which revealed that 17 of the 24 patients in the abatacept group who had SAEs developed the SAEs between the start of the steroid taper and month 6. In the placebo group, two of the four patients had SAEs that occurred between the start of the steroid taper and month 6. Seven patients in the abatacept group (5.8%) and 1 patient in the placebo group (1.7%) discontinued the study because of SAEs.

**Comparison 12 Oral zileuton versus placebo**

One study contributed to this comparison (Hackshaw 1995). No primary outcomes were reported. This comparison reported two secondary outcomes and adverse events.

12.1 Secondary outcome: skin-specific measures of SLE disease activity (SLAM score integument domain)

We identified one study that was relevant to this outcome and categorised data into one subgroup (Hackshaw 1995). We transformed reported standard error (SE) values to standard deviation (SD) values for these analyses.

12.1.1 Short term (two months - 57 days)

We found one trial that was relevant to this subgroup with a total of 30 participants (Hackshaw 1995). There was no clear difference between oral zileuton and placebo within this subgroup (MD -0.53, 95% CI -1.42 to 0.36; low-quality evidence; Analysis 12.1). The mean change from baseline in SLAM score (integument domain) was -0.2 with standard deviation of 1.2394 for the 15 participants in the zileuton group compared with a mean change from baseline in SLAM score (integument domain) of 0.33 with standard deviation of 1.2394 for the 15 participants in the placebo group.

These outcomes were graded as low-quality evidence with downgrading due to risk of bias (unclear method of allocation concealment) and imprecision (one small study).

12.2 Adverse events: severe

For this outcome, we found a single study and categorised data into one subgroup (Hackshaw 1995).

12.2.1 Short term (three months)

We identified a single trial in this subgroup, which included a total of 40 participants (Hackshaw 1995). In all, 2 of 20 participants in the zileuton group compared with none of 20 participants in the placebo group had severe adverse events, favouring placebo due to lower risk of side effects (fewer harms). However, we found insufficient evidence of a difference between oral zileuton and placebo within this subgroup with wide confidence intervals (RR 5.00, 95% CI 0.26 to 98.0; low-quality evidence; Analysis 12.2).
Comparison 13 Intravenous sifalimumab versus placebo

Three studies contributed to this comparison (Khamashta 2016; Merrill 2011; Petri 2013). No primary outcomes were reported. A total of 11 secondary outcomes and adverse events were reported.

13.1 Secondary outcome: clinical flare (SLE, for combined doses versus placebo)

For this outcome, we found a single study and organised the data into one subgroup (Merrill 2011).

13.1.1 Short term (three months)

We found one trial that was relevant to this subgroup, which included a total of 50 participants (Merrill 2011). A total of 9 of 33 participants in the sifalimumab group compared with 8 of 17 in the placebo group had SLE flares, favouring sifalimumab over placebo for fewer flares. However results provided insufficient evidence of a difference between intravenous sifalimumab and placebo due to wide confidence intervals (RR 0.58, 95% CI 0.27 to 1.23; low-quality evidence; Analysis 13.1).

This outcome is graded as low-quality evidence, downgraded due to risk of bias (insufficient details about randomisation and allocation concealment).

13.2 Secondary outcome: skin-specific measures of SLE disease activity (CLASI)

For this outcome, we found a single study and organised the data into one subgroup (Khamashta 2016). Although CLASI data are normally continuous, study authors provided insufficient information for this type of analysis. However, they provided sufficient data (modified intention-to-treat (ITT)) for a dichotomous analysis to compare the proportion of participants in each group with CLASI activity score greater than 10 at baseline who achieved a 4-point or greater reduction in CLASI (improvement).

13.2.1 Long term (12 months) at 200 mg dose versus placebo

We found one trial that was relevant to this subgroup with a total of 68 participants (Khamashta 2016). A significantly greater proportion of participants in the sifalimumab group (24/33) with baseline activity scores greater than or equal to 10 achieved reduction greater than or equal to 4 points in CLASI (improvement) compared with those in the placebo group (17/35). We found evidence of a difference between intravenous sifalimumab and placebo within this subgroup (RR 1.50, 95% CI 1.00 to 2.23; P = 0.05; high-quality evidence; Analysis 13.2).

13.2.2 Long term (12 months) at 600 mg dose versus placebo

We found one trial that was relevant to this subgroup with a total of 68 participants (Khamashta 2016). In all, 19 of 33 participants in the sifalimumab group compared with 17 of 35 in the placebo group had baseline activity scores greater than or equal to 10 and achieved reduction of 4 or more points in CLASI (improvement), favouring sifalimumab. However, results show insufficient evidence of a clear difference between intravenous sifalimumab and placebo due to wide confidence intervals (RR 1.19, 95% CI 0.76 to 1.86; high-quality evidence; Analysis 13.3).

13.2.3 Long term (12 months) at 1200 mg dose versus placebo

We found one trial that was relevant to this subgroup with a total of 61 participants (Khamashta 2016). A significantly greater proportion of participants (19/26) with baseline activity scores greater than or equal to 10 in the sifalimumab group achieved reduction greater than or equal to 4 points in CLASI (improvement) compared with the placebo group (17/35). We found evidence of the superiority of intravenous sifalimumab over placebo (RR 1.50, 95% CI 1.00 to 2.27; P = 0.05; high-quality evidence; Analysis 13.4).

13.2.4 Long term (12 months) at combined doses (200 mg, 600 mg, and 1200 mg) versus placebo

We found one trial that was relevant to this subgroup with a total of 127 participants (Khamashta 2016). A total of 19 of 26 participants in the sifalimumab group compared with 17 of 35 in the placebo group had baseline activity scores greater than or equal to 10 and achieved reduction greater than or equal to 4 points in CLASI (improvement), favouring placebo. However we found insufficient evidence of a difference between intravenous sifalimumab and placebo due to wide confidence intervals (RR 1.39, 95% CI 0.96 to 2.01; high-quality evidence; Analysis 13.5).

13.3 Adverse events: severe - death

For this outcome, we found a single study and categorised data into two subgroups (in keeping with our protocol) (Petri 2013).

13.3.1 Long term (12 months) at 3 mg/kg dose (approximately 21 mg dose)

We found one trial that was relevant to this subgroup with a total of 67 participants (Petri 2013). No events were reported in either group; therefore no forest plot was produced.

13.3.2 Long term (12 months) at 10 mg/kg dose (approximately 70 mg dose)

We identified a single trial in this subgroup with a total of 83 participants (Petri 2013). Results show that 2 of 43 participants in the sifalimumab group compared with none of 40 participants in the placebo group died, favouring placebo. However, we noted insufficient evidence of a clear difference between intravenous sifalimumab and placebo within this subgroup due to wide confidence intervals (RR 4.66, 95% CI 0.23 to 94.18; moderate-quality evidence; Analysis 13.6.1).

This outcome was graded as moderate quality, downgraded for risk of bias with multiple domains that were at unclear risk.

13.4 Adverse events: severe - for combined doses

We identified one study that was relevant to this outcome and organised the data into one subgroup (Merrill 2011).

13.4.1 Short term (3 months)

We found one trial that was relevant to this subgroup with a total of 50 participants (Merrill 2011). No events were reported in either group, so no forest plot could be produced.

13.5 Adverse events: severe - all, including death

For this outcome, we found a single study with dosing/kg weight and categorised the data into four subgroups (in keeping with our protocol) (Petri 2013).

13.5.1 Long term (12 months) at 0.3 mg/kg dose (approximately 21 mg dose)

We found one trial that was relevant to this subgroup with a total of 66 participants (Petri 2013). In all, 7 of 26 participants in
the sifalimumab group compared with 12 of 40 in the placebo group had severe adverse events, including death, indicating that sifalimumab was favoured over placebo. However, evidence of a clear difference between intravenous sifalimumab and placebo was insufficient due to wide confidence intervals (RR 0.90, 95% CI 0.41 to 1.98; moderate-quality evidence; Analysis 13.7.1).

13.5.2 Long term (12 months) at 1 mg/kg dose (approximately 70 mg dose)

We identified a single trial in this subgroup, which included a total of 65 participants (Petri 2013). A total of 3 of 25 participants in the sifalimumab group compared with 12 of 40 in the placebo group had severe adverse events, including death, indicating that sifalimumab was favoured over placebo. However, evidence of a clear difference between intravenous sifalimumab and placebo was insufficient within this subgroup (RR 0.40, 95% CI 0.13 to 1.28; moderate-quality evidence; Analysis 13.7.2).

13.5.3 Long term (12 months) at 3 mg/kg dose (approximately 200 mg dose)

We identified a single trial in this subgroup, which included a total of 67 participants (Petri 2013). In all, 7 of 27 participants in the sifalimumab group compared with 12 of 40 in the placebo group had severe adverse events, including death, favouring sifalimumab over placebo. However, results show insufficient evidence of a clear difference between intravenous sifalimumab and placebo due to wide confidence intervals (RR 0.86, 95% CI 0.39 to 1.91; moderate-quality evidence; Analysis 13.7.3).

13.5.4 Long term (12 months) at 10 mg/kg dose (approximately 700 mg dose)

We identified a single trial in this subgroup, which included a total of 83 participants (Petri 2013). Results show that 10 of 43 participants in the sifalimumab group compared with 12 of 40 in the placebo group had severe adverse events, including death, favouring sifalimumab over placebo. However, we noted insufficient evidence of a clear difference between intravenous sifalimumab and placebo due to wide confidence intervals (RR 0.78, 95% CI 0.38 to 1.59; moderate-quality evidence; Analysis 13.7.4).

13.6 Adverse events: severe - all events

We identified one study that was relevant to this outcome expressed in dosing per kg/weight and organised the data into two subgroups in accordance with our protocol for a total of 131 participants (Petri 2013). We found another study that was dosed in milligrams (not by weight) and categorised data into four additional subgroups (in keeping with our protocol) (Khamashta 2016).

13.6.1 Long term (12 months) at 0.3 mg/kg dose (approximately 21 mg dose)

We found one trial that was relevant to this subgroup, which included a total of 66 participants (Petri 2013). No events were included in this analysis, so no forest plot could be produced.

13.6.2 Long term (12 months) at 1 mg/kg dose (approximately 70 mg dose)

We found one trial that was relevant to this subgroup, which included a total of 65 participants (Petri 2013). A total of 1 of 25 participants in the sifalimumab group compared with none of 40 participants in the placebo group had severe adverse events, favouring the placebo group; however, evidence of a difference between intravenous sifalimumab and placebo within this subgroup was insufficient due to wide confidence intervals (RR 4.73, 95% CI 0.20 to 111.8; moderate-quality evidence; Analysis 13.8.2).

13.6.3 Long term (12 months) at 200 mg dose

We found a single trial in this subgroup, which included a total of 216 participants (Khamashta 2016). In all, 16 of 108 participants in the sifalimumab group compared with 19 of 108 in the placebo group had severe adverse events, favouring sifalimumab; however, we found insufficient evidence of a clear difference between intravenous sifalimumab and placebo due to wide confidence intervals (RR 0.84, 95% CI 0.46 to 1.55; high-quality evidence; Analysis 13.8.3).

13.6.4 Long term (12 months) at 600 mg dose

We identified a single trial in this subgroup, which included a total of 216 participants (Khamashta 2016). Results show that 22 of 108 participants in the sifalimumab group compared with 19 of 108 in the placebo group had severe adverse events, favouring placebo; however, evidence of a clear difference between intravenous sifalimumab and placebo within this subgroup was insufficient (RR 1.16, 95% CI 0.67 to 2.01; high-quality evidence; Analysis 13.8.4).

13.6.5 Long term (12 months) at 1200 mg dose

We found a single trial in this subgroup with a total of 215 participants (Khamashta 2016). A total of 21 of 107 participants in the sifalimumab group compared with 19 of 108 in the placebo group had severe adverse events, favouring placebo for fewer adverse events; however evidence of a clear difference between intravenous sifalimumab and placebo within this subgroup was insufficient (RR 1.12, 95% CI 0.64 to 1.95; high-quality evidence; Analysis 13.8.5).

13.6.7 Long term (12 months) at three doses combined (200 mg, 600 mg, and 1200 mg)

We identified a single trial in this subgroup with a total of 431 participants (Khamashta 2016). In all, 59 of 323 participants in the sifalimumab group compared with 19 of 108 in the placebo group had severe adverse events, favouring placebo due to fewer adverse events; however results show insufficient evidence of a clear difference between intravenous sifalimumab and placebo within this subgroup (RR 1.04, 95% CI 0.65 to 1.66; high-quality evidence; Analysis 13.8.6).

13.7 Adverse events: minor - pruritus, papular rash, or pruritic rash for combined doses

For this outcome, we found a single study and organised the data into one subgroup.

13.7.1 Short term (three months)

We found a single trial in this subgroup with a total of 50 participants (Merrill 2011). Results show that 4 of 33 participants in the sifalimumab group compared with 3 of 17 in the placebo group had minor adverse events of pruritus, papular rash, or pruritic rash, favouring sifalimumab over placebo. However, evidence of a clear difference between intravenous sifalimumab and placebo within this subgroup was insufficient (RR 0.69, 95% CI 0.17 to 2.72; high-quality evidence; Analysis 13.9).
13.8 Adverse events: minor - viral infection rash such as herpes zoster or herpes simplex for combined doses

We identified one study that was relevant to this outcome and categorised data into one subgroup (Merrill 2011).

13.8.1 Short term (three months)

We identified a single trial in this subgroup, with a total of 50 participants (Merrill 2011). A total of 2 of 33 participants in the sifalimumab group compared with 1 of 17 in the placebo group had minor adverse events of viral infection rash, such as herpes zoster or herpes simplex, favouring the placebo group. However, evidence of a clear difference between intravenous sifalimumab and placebo within this subgroup was insufficient with RR close to 1 and wide confidence intervals (RR 1.03, 95% CI 0.1 to 10.57; high-quality evidence; Analysis 13.10).

13.9 Adverse events: minor - for all combined doses

For this outcome, we found a single study and organised the data into one subgroup (Petri 2013).

13.9.1 Long term (12 months)

We found one trial that was relevant to this subgroup with a total of 161 people (Petri 2013). In all, 85 of 121 participants in the sifalimumab group compared with 26 of 40 in the placebo group had minor adverse events, favouring placebo due to fewer minor adverse events. However evidence of a clear difference between intravenous sifalimumab and placebo within this subgroup was insufficient (RR 1.08, 95% CI 0.84 to 1.4; moderate-quality evidence; Analysis 13.11).

13.10 Adverse events: minor - zoster

We identified one study that was relevant to this outcome and organised the data into two subgroups in accordance with our protocol (Petri 2013).

13.10.1 Long term (12 months) at 0.3 mg/kg dose (approximately 21 mg dose)

We found a single trial in this subgroup with a total of 66 participants (Petri 2013). No events were reported in either group, so the effect was not estimable, and no forest plots could be produced.

13.10.2 Long term (12 months) at 1 mg/kg dose (approximately 70 mg dose)

We identified a single trial in this subgroup with a total of 65 participants (Petri 2013). No events were reported in either group, so the effect was not estimable, and no forest plots could be produced.

13.11 Adverse events: minor

We identified one study that was relevant to this outcome and organised the data into two subgroups in accordance with our protocol (Petri 2013).

13.11.1 Long term (12 months) at 3 mg/kg dose (approximately 210 mg dose)

We found one trial that was relevant to this subgroup with a total of 67 participants (Petri 2013). Results show that 2 of 27 participants in the sifalimumab group compared with none of 40 participants in the placebo group had minor adverse events, favouring placebo due to less bothersome minor adverse events. However, evidence of a clear difference between treatment groups was insufficient (RR 7.32, 95% CI 0.37 to 146.78; moderate-quality evidence; Analysis 13.12.1).

13.11.2 Long term (12 months) at 10 mg/kg dose (approximately 700 mg dose)

We found one trial that was relevant to this subgroup with a total of 83 participants (Petri 2013). In all, 2 of 43 participants in the sifalimumab group compared with none of 40 participants in the placebo group had minor adverse events, favouring placebo due to less bothersome minor adverse events. However, evidence of a clear difference between treatment groups was insufficient (RR 4.66, 95% CI 0.23 to 94.18; moderate-quality evidence; Analysis 13.12.2).

Comparison 14 Intravenous sirukumab versus placebo

One study contributed to this comparison (Szepietowski 2013). No primary outcomes were reported. This comparison had four secondary outcomes and secondary events.

14.1 Secondary outcome: skin-specific measures of SLE disease activity (CLASI)

One trial described this outcome (Szepietowski 2013). Szepietowski 2013 reported on CLASI in a quantitative fashion during a four and one-half month study of sirukumab versus placebo. However data (no standard deviations reported) given for a repeat analysis were insufficient, so study investigators’ data were reported narratively. At baseline, CLASI was 4 for the sirukumab group (n = 10) compared with CLASI of 2 for the placebo group (n = 5). At 22 weeks, CLASI was 1.5 for the sirukumab group (n = 10) compared with 1 for the placebo group (n = 5). CLASI improved in both groups during the study. No clinically or statistically significant difference from baseline was noted in the CLASI. Szepietowski 2013 also reported narratively on CLASI with no clinically or statistically significant differences from baseline.

The quality of evidence of this outcome was graded as low, downgraded due to risk of bias (unclear risk in most domains and high risk in some) and imprecision (one study of small sample size).

14.2 Secondary outcome: dermatology quality of life measure

One trial described this outcome (Szepietowski 2013). Szepietowski 2013 reported on the Dermatology Life Quality Index (DLQI) during a four and one-half month study of sirukumab versus placebo. At baseline, DLQI was 2 for the sirukumab group (n = 10) compared with 0 for the placebo group (n = 5). At 22 weeks, DLQI was 2.5 for the sirukumab group (n = 10) compared with 4 for the placebo group (n = 5). Study investigators noted that “DLQI scores remained low and stable in CLE and SLE patients treated with sirukumab but worsened in SLE patients treated with placebo”.

The quality of evidence for this outcome was graded as low, downgraded due to risk of bias (unclear risk in most domains and high risk in some) and imprecision (one study of small sample size).

14.3 Adverse events: severe - for combined doses versus placebo

For this outcome, we found a single study and categorised the data into one subgroup (Szepietowski 2013).
14.3 Short term (4.5 months)
We found one trial that was relevant to this subgroup with a total of 15 participants (Szepietowski 2013). A total of 2 of 10 participants in the sirukumab group had severe adverse events (pneumonia in the 10 mg/kg treated group, iatrogenic wound infection in the 4 mg/kg treated group), favouring the placebo group with fewer severe adverse events. However, evidence of a clear difference between intravenous sirukumab and placebo within this subgroup was insufficient (RR 2.73, 95% CI 0.15 to 48.04; low-quality evidence; Analysis 14.1).

14.4 Adverse events: minor – for combined doses versus placebo
We identified one study that was relevant to this outcome and categorised data into one subgroup (Szepietowski 2013).

14.4.1 Short term (4.5 months)
We found a single trial for this subgroup with a total of 15 participants (Szepietowski 2013). Results show that 4 of 5 participants in the sirukumab group compared with 9 of 10 participants in the placebo group had minor adverse events, favouring sirukumab with fewer minor adverse events. However, evidence of a clear difference between intravenous sirukumab and placebo was insufficient with wide confidence intervals (RR 0.89, 95% CI 0.55 to 1.44; low-quality evidence; Analysis 14.2).

Szepietowski also compared SLE patients with CLE patients with regard to minor adverse events, noting that minor “adverse events (AEs) occurred more often with sirukumab than placebo in CLE patients (91% versus 63%) and in SLE patients (90% versus 80%). Sirukumab led to sustained, dose-independent decreases in white blood cell counts, absolute neutrophil counts (neutropenia), and platelet counts (thrombocytopenia) and to minor elevations in total cholesterol levels. The majority of infections were mild respiratory infections, which were reported similarly across CLE cohorts but more often in sirukumab-treated than in placebo-treated SLE patients.

Comparison 15 Intravenous atacicept versus placebo
One study contributed to this comparison (Pena-Rossi 2009). No primary or secondary outcomes were reported. This comparison reported four adverse events.

15.1 Adverse events: severe - death and other severe events
We identified one study that was relevant to this outcome and categorised data into one subgroup (Pena-Rossi 2009).

15.1.1 Short term (two months)
We found one trial that was relevant to this subgroup, which included a total of 28 participants (Pena-Rossi 2009). No events were reported in either group.

15.2 Adverse events: minor - eczema - at atacicept 3 mg/kg dose
For this outcome, we found a single study and categorised data into one subgroup (Pena-Rossi 2009).

15.2.1 Short term (six weeks)
We found one trial that was relevant to this subgroup with a total of nine participants (Pena-Rossi 2009). A total of 1 of 5 participants in the atacicept group compared with none of 4 participants in the placebo group had the minor adverse event of eczema, favouring the placebo group due to fewer side effects of eczema. However, evidence of a clear difference between intravenous atacicept and placebo within this subgroup was insufficient (RR 2.50, 95% CI 0.13 to 48.85; low-quality evidence; Analysis 17.1).

This outcome was graded as low-quality evidence, downgraded due to risk of bias (insufficient details given about sequence generation and allocation concealment, assessors not blinded) and due to imprecision (one small study).

15.3 Adverse events: minor - local site reaction (redness, bruising, tenderness) - for all doses combined
We identified one study that was relevant to this outcome and organised the data into one subgroup (Pena-Rossi 2009).

15.3.1 Short term (six weeks)
We found one trial that was relevant to this subgroup with a total of 24 participants (Pena-Rossi 2009). In all, 7 of 20 participants in the atacicept group compared with 2 of 4 participants in the placebo group had the minor adverse event of local site reaction (redness, bruising, tenderness), favouring atacicept as having fewer adverse events. However for this subgroup, we did not find evidence of a distinct difference between the two treatments (RR 0.70, 95% CI 0.22 to 2.21; low-quality evidence; Analysis 17.2).

15.4 Adverse events: minor - other reaction (not eczema or local site reaction)
For this outcome, we found a single study and categorised data into one subgroup (Pena-Rossi 2009).

15.4.1 Short term (two months)
We identified a single trial in this subgroup with a total of nine participants (Pena-Rossi 2009). None of the 5 participants in the atacicept group compared with 1 of the 4 participants in the placebo group had another minor adverse event (not eczema or local site reaction), favouring atacicept as having fewer adverse events. However, we did not find evidence of a distinct difference between the two treatments (RR 0.28, 95% CI 0.01 to 5.43; low-quality evidence; Analysis 17.3).

Comparison 16 Oral nifedipine versus placebo
We found one trial for this comparison (Kahan 1985). No primary outcomes were reported. This comparison reported two secondary outcomes and adverse events.

16.1 Secondary outcome: clinical flare (vasospasm, lupus-non-specific)
Kahan 1985 reported about the secondary outcome of flares in a qualitative narrative form as "mean number of vasospastic attacks (flares)" per week by participant diary. Study investigators pooled the data for five participants with SLE and three with rheumatoid arthritis because the data were similar. The mean number of vasospastic attacks per week in the nifedipine group was 4.75 ± 2.31 compared with 23.6 ± 4.3 in the placebo group. Using Snedecor’s F test to compare the nifedipine group versus the placebo group, F1,14 = 119, corresponding to P < 0.01.

The quality of evidence for this outcome was rated as low, downgraded for risk of bias (most domains unclear risk, some high risk) and imprecision (one small study).
16.2 Adverse events

16.2.1 Severe

Kahan 1985 reported that no patients discontinued the study due to side effects. Therefore by definition, no severe adverse events were reported in this study.

16.2.2 Minor

For Kahan 1985, the number of participants in the placebo group versus the number in the nifedipine group was not stated. So quantitative information about adverse events could not be calculated. Minor adverse events were reported in narrative form. Minor adverse events such as headache, flushing, nausea, and leg oedema were reported in nine participants in the nifedipine group. Minor adverse events such as nausea and dizziness occurred in three participants in the placebo group.

The quality of evidence for this outcome was rated as low, downgraded for risk of bias (most domains unclear risk, some high risk) and imprecision (one small study).

Comparison 17 Topical tacrolimus ointment versus placebo

We identified one trial for this comparison (Kuhn 2011). This comparison has two outcomes.

Kuhn 2011 was a split-body study. Data were insufficient for integration into meta-analysis at this time (only one trial). In the future, if meta-analysis is deemed appropriate, we plan to account for unit of analysis issues as per Cochrane guidelines.

17.1 Secondary outcome: skin-specific measures of SLE disease activity (total clinical score)

In Kuhn 2011, only a small group of participants, namely, 3 of 30 participants, met ACR criteria for SLE. Of these three participants with SLE, two had DLE and one had acute cutaneous lupus erythematosus (ACLE). The one participant with ACLE was noted to have clinical improvement in cutaneous symptoms with 0.1% tacrolimus ointment, exhibiting a mean change from baseline in total clinical score of 5.00 on the last visit (day 84). No further details on outcomes of the two SLE participants with DLE were reported.

The quality of evidence for this outcome was rated as moderate, downgraded for imprecision (one small study).

17.2 Adverse event

17.2.1 Severe

Kuhn 2011 reported no withdrawals from the study due to adverse events; therefore by definition, no severe adverse events were reported.

17.2.2 Minor

Kuhn 2011 reported minor adverse events included burning, itching, and herpes virus infection. Quantitative adverse events could not be calculated because the number (n) per group (treatment versus placebo) was not stated.

Comparison 18 UVA-1 phototherapy versus placebo

We identified two trials for this comparison (McGrath 1996, Polderman 2001). No primary outcomes were reported. This comparison reported two secondary outcomes and adverse events.

Both McGrath 1996 and Polderman 2001 were cross-over studies. Current data are insufficient for integration into meta-analysis at this time. In the future, if meta-analysis is undertaken, we plan to use only first period data.

18.1 Secondary outcomes: skin-specific measures of SLE disease activity (SLAM scores)

McGrath 1996 was a cross-over study with Group A (UVA-1 treatment first for five days per week for three weeks, then placebo visible light for three weeks) and Group B (placebo visible light treatment first for three weeks, then UVA-1 treatment five days per week for three weeks) followed by an open unblinded second phase in which both groups received UVA-1 irradiation three days per week for six weeks, followed by twice a week for three weeks, and then once a week for three weeks. In Group A, the SLAM score improved during UVA-1 treatments and regressed to baseline during the placebo phase. “Improvement then recurred and progressed” during a six-week period with “three-day-a-week of UVA-1 irradiation”. In Group B (placebo light phase first), there was minimal improvement during the three weeks of visible light. Group B then responded “more sharply” to UVA-1 during the three weeks of five days per week treatment and maximally to six weeks of “three-day-a-week of UVA-1 irradiation”. With twice- and once-weekly UVA-1 irradiation, SLAM scores worsened slightly.

The quality of this outcome was graded as low, downgraded due to risk of bias (most domains unclear risk) and imprecision (few small studies).

Polderman 2001 reported that the SLAM integument domain (oral ulcers, cutaneous rash, vasculitis, and alopecia) was significantly improved (P = 0.04) after UVA-1 light treatment compared with after placebo treatment. Cardiovascular score (Raynaud’s + hypertension + carditis) also improved significantly after UVA-1 treatment compared with placebo (P = 0.03). Improvement in overall SLAM score was not statistically significant, with subdomain improvement in rash (P = 0.08) and Raynaud’s phenomenon (P = 0.06). The overall SLEDAI score was not significant and subdomains were not reported. Study investigators advised caution with interpretation of P values, given that Bonferroni correction was not performed.

The quality of evidence for this outcome was graded as low, downgraded due to risk of bias (most domains unclear risk) and imprecision (few small studies).

18.2 Adverse events

18.2.1 Severe

McGrath 1996 reported one severe adverse event among 26 patients: a patient taking a photosensitising medication (diltiazem) developed a transient rash and discontinued the initial six-week study. During the extended 12-week study, severe adverse events occurred in 6 of 18 patients: 2 withdrew due to “slightly worsening discoid skin lesions” and 4 withdrew due to severe worsening of symptoms (lack of effect).

The quality of this outcome was graded as low, downgraded due to risk of bias (most domains unclear risk) and imprecision (few small studies).

Polderman 2001 reported no severe adverse events during the study.
18.2.2 Minor

McGrath 1996 reported no minor adverse events.

Polderman 2001 reported no minor adverse events. Study investigators noted that “despite the fact that five out of the 11 patients were known to be occasionally photosensitive, no signs of photosensitivity or other side effects occurred during the UVA-1 or placebo treatments”.

The quality of this outcome was graded as low, downgraded due to risk of bias (most domains unclear risk) and imprecision (few small studies).

Comparison 19 Oral copper versus placebo

We included one trial for this comparison (Duffy 2004). Two primary outcomes and adverse events were reported for this comparison. No secondary events were reported.

Duffy 2004 was a multi-arm 2 × 2 factorial design study of both copper and fish oil. As recommended, for the purposes of analysis, we split the study into two parallel-group studies and analysed the data separately.

19.1 Primary outcome - complete clinical response

Duffy 2004 narratively reported "no therapeutic effect from copper".

The quality of this outcome was moderate, downgraded due to risk of bias (most domains were unclear risk, some were low risk).

19.2 Adverse events

19.2.1 Severe

Duffy 2004 reported nine participants out of 65 with severe adverse events, including six withdrawals (no details given) and three hospital admissions (one for stroke and two for chest infection).

Comparison 20 Intravenous epratuzumab versus placebo

Three trials contributed to this comparison (Clowse 2015; Wallace 2013; Wallace 2014). This comparison reported no primary or secondary outcomes. Adverse outcomes are discussed below.

20.1 Adverse events

20.1.2 Severe

Wallace 2013 reported that 3 of 187 participants in the treatment group compared with 2 of 38 in the placebo group had severe adverse events (RR 0.3, 95% CI 0.05 to 1.76; low-quality evidence, Analysis 16.1.1) in this short-term (three-month) study. Severe adverse events included pneumonia, pyelonephritis, and urinary tract infection.

Wallace 2014 reported that 3 of 51 participants in the treatment group compared with 3 of 37 in the placebo group had severe adverse events (RR 0.73, 95% CI 0.16 to 3.4; low-quality evidence, Analysis 16.1.2) in this long-term (12-month) study. No deaths were reported.

20.1.2 Minor

Wallace 2013 reported that overall, 127 of 187 participants in the treatment group compared with 25 of 38 in the placebo group had minor adverse events (RR 1.03, 95% CI 0.8 to 1.32; low-quality evidence, Analysis 16.1.3) in this short-term (three-month) study. Wallace 2013 reported that “after adjusting for duration of exposure, the highest rates of [minor adverse events] AE were for nasopharyngitis, sinusitis, upper respiratory tract infection and urinary tract infection. Infusion-related AEs were reported in 6 (21%) patients in SL0006, corresponding to an infusion-related AE rate of 10.8 per 100 years of exposure”.

Wallace 2014 reported that 44 of 51 participants in the treatment group compared with 34 of 37 in the placebo group had at least one minor adverse event (RR 0.94, 95% CI 0.81 to 1.09; low-quality evidence; Analysis 16.1.4) in this long-term (12-month) study. Wallace 2014 reported that “the most common adverse events (AEs) across all arms were headache, nausea, upper respiratory tract infection and dizziness”.

The quality of evidence for these outcomes was graded as low, downgraded due to risk of bias (most domains unclear risk).

Comparison 21 Subcutaneous repository corticotropin injection (acthar gel) versus placebo

We identified two trials for this comparison (Furie 2015a; Furie 2016a). No primary outcomes were reported. This comparison reported two secondary outcomes and adverse events.

21.1 Secondary outcomes: skin-specific measures of SLE disease activity (CLASI)

Furie 2015a noted CLASI activity improvement for the repository corticotropin injection (combined dose) versus placebo; however, this difference was not statistically significant (P = 0.051) in this small (n = 38) short-term study (2 months). Researchers also reported improvement in hybrid SLEDAI (arthritis and/or skin involvement) and BILAG A or B (for mucocutaneous and/or musculoskeletal systems) scores; however it was not possible to extract purely skin findings from the data provided.

Furie 2016a noted CLASI activity improvement for repository corticotropin injections when the combined dose treatment group was compared with the placebo group in a small (n = 38) short-term study (two months) and after the long-term cross-over open-label extension. Study authors reported, "least squares (LS) mean (SE) changes from baseline" in Cutaneous Lupus Erythematosus Disease Area and Severity Index activity (CLASI) scores on a graph and narratively noted that "corresponding improvements in SLE skin manifestations were reflected by statistically significant improvements in CLASI activity scores in the RCI 40 U (P = 0.030) and combined RCI (P = 0.047) groups compared with the combined placebo group, at week 8". Statistically significant improvement was not seen at four weeks or for the RCI 80 U group alone.

These outcomes were graded as low-quality evidence due to risk of bias (many domains unclear risk) and for imprecision (three small studies).

21.2 Adverse events

21.2.1 Severe

Furie 2015a reported no significant differences between placebo and treatments groups in terms of severe adverse events.

Furie 2016a reported severe adverse events (treatment-emergent adverse events (TEAEs) leading to treatment discontinuation) “during the double-blind treatment period occurred in one patient...”
(7.7%) receiving RCI 40 U and one patient (8.3%) receiving RCI 80 U. The patient in the RCI 40 U group experienced moderate chest discomfort and moderate gastro-oesophageal reflux disease, both of which were considered serious adverse events (SAEs) and related to study medication. During weeks 1–4, three patients (two in the RCI 40 U group and one in the RCI 80 U group) had their RCI dose decreased based on tolerability. All three patients were also taking prednisone 10 mg daily. The events leading to dose reduction included moderate weight gain and mild increased tendency to bruise in the RCI 40 U group, and moderate irritability in the RCI 80 U group”.

21.2.2 Minor

Furie 2015a reported no significant differences between placebo and treatments groups in terms of minor adverse events.

Furie 2016a reported that “the overall incidences of treatment-emergent adverse events (TEAEs) and treatment-related TEAEs in the combined RCI and combined placebo groups were similar…The most commonly reported AE was weight gain, which occurred in seven patients (19.4%) with similar frequencies in each group. The overall incidence of infections was higher in the RCI groups (23.1% in each group) than in the combined placebo group (9.1%), but there were no other differences in AE profiles between the groups. The majority of TEAEs, including infections, were mild or moderate in severity…”

Comparison 22 Intravenous blisibimod versus placebo

We identified one trial for this comparison (Furie 2015b). No primary or secondary outcomes were reported. This comparison reported one adverse event outcome.

22.1 Adverse events: severe - all events including death

For this outcome, we found a single study and categorised data into one subgroup (Furie 2015b).

22.1.1 Long term (12 months)

We found a single trial for this subgroup with a total of 546 participants (Furie 2015b). A total of 16 of 280 participants in the blisibimod group compared with 21 of 266 in the placebo group had a severe adverse event including death, favouring blisibimod over placebo for fewer severe adverse events. However, evidence of a clear difference between intravenous blisibimod and placebo within this subgroup was insufficient with wide confidence intervals (RR 0.72, 95% CI 0.39 to 1.36; high-quality evidence; Analysis 15.1).

This outcome was graded as high quality due to low risk of bias.

Comparison 23 Intravenous anifrolumab versus placebo

We found one trial for this comparison (Furie 2015c). No primary outcomes were reported. This comparison reported two secondary outcomes and adverse events.

23.1 Secondary outcomes

We identified one trial for this comparison with a total of 305 participants (Furie 2015c).

Furie 2015c provided insufficient information for quantitative analysis of minor events (n was not reported for specific groups). However, this group narratively reported on a subset of 77 patients with baseline CLASI scores greater than or equal to 10. In this subset, they noted significant improvement (P = 0.013) in the proportion of patients with 50% reduction in CLASI score in the anifrolumab 300 mg group compared with the placebo group (odds ratio (OR) 4.49, 90% CI 1.67 to 12.12; n = 25). In contrast, evidence of a clear difference between anifrolumab 1000 mg and placebo was not sufficient (OR 2.97, 90% CI 1.08 to 8.19; n = 22; P = 0.077).

These outcomes were graded as low-quality evidence, downgraded due to risk of bias (domains unclear risk or high risk).

23.2 Adverse events

One trial contributed for this comparison with a total of 305 participants (Furie 2015c).

23.2.1 Severe

Furie 2015c gave insufficient information for quantitative analysis of minor events (n was not reported for specific groups); however this group narratively reported that a proportion of severe adverse events were similar for the pooled intervention groups (16.7%) and for the placebo group (18.8%).

23.2.2 Minor

Furie 2015c gave insufficient information for quantitative analysis of minor events (n was not reported for specific groups); however this group narratively reported a minor increase in flu and herpes zoster.

Comparison 24 Bortezomib versus placebo

We identified one trial for this comparison (Ishii 2015). This comparison reported two primary outcomes and adverse events. No secondary outcomes were reported.

24.1 Primary outcome: partial clinical response

We identified one trial for this comparison with a total of 14 participants (Ishii 2015). Study authors noted anecdotally that one patient in the bortezomib treatment group showed improvement in skin symptoms.

This outcome was graded as very low-quality evidence due to risk of bias that was high for most domains (very serious concerns) and imprecision (one small study).

24.2 Adverse events

We found one trial for this comparison with a total of 14 participants (Ishii 2015).

24.2.1 Severe

Ishii 2015 reported narratively that 7 of 8 patients (87.5%) in the treatment group had severe enough side effects that they withdrew from the one-month study. Only one patient in the treatment group completed the one-month study (12.5% completion rate). Study authors did not compare these findings against placebo.

This outcome was graded as very low-quality evidence due to risk of bias that was high for most domains (very serious concerns) and imprecision (one small study).
Comparison 25 Cholecalciferol versus placebo

We found one trial for this comparison (Lima 2016). This comparison reported one secondary outcome and one adverse event. No secondary outcomes were reported.

25.1 Primary outcome: partial clinical response

We identified one trial for this comparison with a total of 45 participants (Lima 2016). Study authors narratively reported a 5% reduction in skin involvement in the cholecalciferol group compared with 0% reduction in the placebo group during this six-month study; however, evidence of a difference was insufficient (P = 0.66).

This outcome was graded as low-quality evidence due to risk of bias (most domains unclear risk) and imprecision (one small study).

25.2 Adverse events

25.2.1 Severe

Lima 2016 reported that 5 of 45 patients (11%) withdrew from the cholecalciferol study (personal reasons or loss to follow-up). Information about group assignment of these withdrawals was not given. No severe side effects were reported in the 40 patients that completed the study (89%).

25.2.2 Minor

Lima 2016 reported that "six patients (4 in the intervention group and 2 in the placebo group) reported epigastric pain but without discontinuation of therapy".

Comparison 26 SM101 versus placebo

We found one trial for this comparison (Tillmanns 2014). No primary outcomes were reported. This comparison reported two secondary outcomes and adverse events.

26.1 Secondary outcome: skin-specific measures of SLE disease activity (BILAG)

We identified one trial for this comparison with a total of 51 participants (Tillmanns 2014).

Tillmanns 2014 narratively reported that one of the "main clinical drivers for response" was improvement in "skin eruption" that was present in 50% of patients according to the BILAG scale. In SM101-treated patients, "improvement or resolution (as measured by the BILAG scale)" occurred in 45% with skin eruption.

This outcome was graded as moderate-quality evidence, downgraded due to risk of bias (most domains unclear risk).

26.2 Adverse events

We found one trial for this comparison with a total of 51 participants (Tillmanns 2014).

26.2.1 Severe

Tillmanns 2014 reported narratively that "no safety signals which could be attributed specifically to SM101 were reported, and no serious adverse events were probably or possibly related to the drug".

Comparison 27 BIIB059 versus placebo

We identified one trial for this comparison (Furie 2016b). This comparison reported no primary outcomes. Secondary outcomes and adverse events were reported.

27.1 Secondary outcome: skin-specific measures of SLE disease activity (CLASI)

We included one trial for this comparison with a total of 12 participants (Furie 2016b).

Furie 2016b narratively reported that "CLASI activity at week 12 was notable decreased in 6/8 BIIB059 treated patients compared with 4 placebo patients (2/4 non-responders, 1/4 lost to follow-up and 1/4 treated with IV steroids for SLE flare".

The quality of evidence for these outcomes was graded as low, downgraded due to risk of bias (most domains unclear risk) and imprecision (small study).

27.2 Adverse events

We found one trial for this comparison with a total of 12 participants (Furie 2016b).

27.2.1 Severe

Furie 2016b noted that no withdrawals occurred due to severe events in the treatment group (0/8 participants) nor in the placebo group (0/4 participants).

27.2.2 Minor

Furie 2016b reported that "BIIB059 was generally well tolerated; the incidence of AEs was similar between BIIB059 and placebo-treated SLE subjects, and most AEs were mild or moderate in severity".

Comparison 28 Subcutaneous tabalumab versus placebo

We identified one trial for this comparison (Merrill 2016). This comparison reported no primary or secondary outcomes. Severe and minor adverse events were reported.

The quality of evidence for these outcomes was graded as low, downgraded due to risk of bias (most domains unclear risk).

28.1 Adverse events

We included one trial for this comparison with a total of 1124 participants (Merrill 2016).

28.1.1 Severe

Merrill 2016 noted that 38 of 745 participants in the tabalumab treatment group had severe adverse events compared with 27 of 376 in the placebo group (RR 0.71, 95% CI 0.44 to 1.15; low-quality evidence; Analysis 18.1.1) in this long-term (12-month) study.

28.1.2 Minor

Merrill 2016 noted that 575 of 745 participants in the tabalumab treatment group had minor adverse events compared with 276 of 376 in the placebo group (RR 1.05, 95% CI 0.98 to 1.13; low-quality evidence; Analysis 18.1.2) in this long-term (12-month) study.
Comparison 29 Oral baricitinib versus placebo

We found one trial for this comparison (Wallace 2018). This comparison reported primary and secondary outcomes and adverse events.

The quality of evidence for these outcomes was graded as low, downgraded due to risk of bias (most domains unclear risk).

29.1 Primary outcome: complete clinical response (rash or arthritis)

We identified one trial for this comparison with a total of 314 participants (Wallace 2018).

Study authors noted that there was complete "resolution of arthritis or rash" in 56 of 105 participants in the placebo group compared with 70 of 104 in the 4 mg orally once daily baricitinib group, with P ≤ 0.05 by week 24 (or at 6 months). However when the placebo group was compared with the 2 mg orally once daily for 6 months baricitinib group with complete "resolution of arthritis or rash" in 61 of 105 participants, the comparison did not meet statistical significance. We were unable to further analyse these data because data for arthritis and for rash were pooled and information provided was insufficient for extraction of rash only data.

29.2 Secondary outcome: skin-specific measures of SLE disease activity (CLASI)

We identified one trial for this comparison with a total of 314 participants (Wallace 2018).

Study authors reported that the difference (least squares mean change) from baseline in CLASI activity score was not significant for the placebo group (-2.68) compared with the 2 mg oral daily baricitinib group (-1.66) or the 4 mg oral daily baricitinib group (-2.27).

29.3 Adverse events

We included one trial for this comparison with a total of 314 participants (Wallace 2018).

29.3.1 Severe

Wallace 2018 noted that 21 of 209 participants in the two combined baricitinib treatment groups had severe adverse events compared with 5 of 105 in the placebo group (RR 0.47, 95% CI 0.18 to 1.22; low-quality evidence; Analysis 19.1.1).

Specifically, “one severe adverse event (SAE) of deep vein thrombosis was reported in a patient with risk factors (Bari 4 mg group)”.

Researchers noted “no deaths, malignancies, major adverse cardiovascular events, tuberculosis, or serious herpes zoster infections”.

29.3.2 Minor

Wallace 2018 noted that 130 of 209 participants in the two combined baricitinib treatment groups had minor adverse events compared with 63 of 105 in the placebo group (RR 0.96, 95% CI 0.8 to 1.16; low-quality evidence; Analysis 19.1.2).

Comparison 30 Oral CC-220 versus placebo

CC-220 is also known as iberdomid hydrochloride. We identified one trial for this comparison with 42 participants (Werth 2017a). This comparison reported no primary outcomes. Secondary outcomes and adverse events were reported.

The quality of evidence of these outcomes was graded as low, downgraded due to risk of bias (most domains unclear risk) and imprecision (one small study).

30.1 Secondary outcome: skin-specific measures of SLE disease activity (CLASI)

We included one trial for this comparison with a total of 42 participants (Werth 2017a).

Study authors reported that "mean CLASI activity score at baseline was 9.8 with mean reductions in the CLASI activity score at day 85 ranging from 4.3 to 7.8 in the CC-220 treatment groups compared to an increase of 0.4 in the placebo group. The reductions in CLASI activity score were even more significant among subjects who had moderate-to-severe skin involvement (CLASI score ≥10 at baseline)". Given that n for individual treatment groups was not provided, we did not carry out further quantitative analysis.

30.2 Adverse events

We included one trial for this comparison with a total of 42 participants (Werth 2017a).

30.2.1 Severe

Werth 2017a noted that “four patients experienced serious adverse events, including two patients in the placebo group and two patients who developed pneumonia at the highest (0.6 mg per day) CC-220 dose. In the two highest-dose groups, two patients also developed grade 3 neutropenia, one patient developed grade 1 neutropenia”.

Given that the forin each subgroup was not specifically stated, we did not perform further quantitative analysis.

30.2.2 Minor

Werth 2017a reported that “the most common treatment-emergent adverse effects were mild to moderate nausea and diarrhoea”. It was also reported that “2 subjects in the highest CC-220 dose group had dermatitis, and 1 subject in the 0.3 mg QD and 1 in the 0.6 mg QD dose groups had urticaria”.

Comparison 31 Intravenous ustekinumab versus placebo

We included one trial for this comparison (Van Vollenhoven 2018). No primary outcomes were reported. Secondary outcomes and adverse events were reported.

The quality of evidence of these outcomes was graded as high (all domains low risk).

31.1 Secondary outcome: skin-specific measures of SLE disease activity (CLASI)

We identified one trial for this comparison with a total of 102 participants (Van Vollenhoven 2018).

Study authors reported on "≥ 50% improvement from baseline in the CLASI activity scores". In the ustekinumab treatment group, 17
of 32 participants (53%) met these criteria compared with only 6 of 17 (35%) in the placebo group (RR 1.51, 95% CI 0.73 to 3.10; high-quality evidence; Analysis 20.1). Study authors further calculated that this constituted "a mean response rate of 64.1% with a SD (standard deviation) of 43.1 to 80.9 versus a response rate of 29.9% (SD = 12 to 57)". Study authors calculated that this corresponded to a P value of 0.032.

### 31.2 Adverse events

We included one trial for this comparison with a total of 102 participants (Van Vollenhoven 2018).

#### 31.2.1 Severe

Van Vollenhoven 2018 noted that 4 of 60 participants in the treatment group had severe adverse events compared with 4 of 42 in the placebo group (RR 0.70, 95% CI 0.19 to 2.64; high-quality evidence; Analysis 20.2.1). Study authors noted that "no deaths or treatment-emergent opportunistic infections, herpes zoster, tuberculosis, or malignancies occurred between weeks 0-24".

#### 31.2.2 Minor

Van Vollenhoven 2018 noted that 43 of 60 participants in the treatment group had minor adverse events compared with 24 of 42 in the placebo group (RR 1.25, 95% CI 0.92 to 1.7; high-quality evidence; Analysis 20.2.2). Study authors reported that "infections were the most common type of adverse event".

**Comparison 32 Topical R932333 versus placebo**

We found one trial for this comparison (Duliege 2016). This comparison reported no primary or secondary outcomes. Adverse events were reported.

The quality of evidence for these outcomes was graded as low, downgraded due to risk of bias (most domains unclear risk or high risk).

#### 32.1 Adverse events

We included one trial for this comparison with a total of 54 participants (Duliege 2016).

#### 32.1.1 Severe

Duliege 2016 noted that 0 of 36 participants in the treatment group had severe adverse events compared with 0 of 18 in the placebo group at the final study endpoint at six weeks. No analysis was performed due to zero values.

#### 32.1.2 Minor

Duliege 2016 noted that 16 of 36 participants in the treatment group had minor adverse events compared with 10 of 18 in the placebo group at the final study endpoint at six weeks (RR 0.8, 95% CI 0.46 to 1.39; high-quality evidence; Analysis 21.1.1).

More specifically, reported minor adverse events for the treatment group included the following: mild leukopenia, mild eyelid crusting, increased lacrimation, gastrointestinal disorders (such as vomiting, nausea, diarrhea, or reflux disease), respiratory infection, musculoskeletal disorders, application site pain, headaches, chest pain, and insomnia.

For the placebo group, reported minor adverse events included mild increased neutrophils, respiratory infection, sinusitis, laryngitis, musculoskeletal disorders, headache, pyrexia, and fatigue.

**Comparison 33 Subcutaneous lulizumab pegol versus placebo**

We identified one trial for this comparison with a total of 349 participants (Merrill 2018). This comparison reported secondary outcomes. Severe adverse events were also reported.

The quality of evidence for these outcomes was graded as low, downgraded due to risk of bias (all domains unclear risk).

#### 33.1 Secondary outcome: skin-specific measures of SLE disease activity (CLASI)

Merrill 2018 reported narratively that "CLASI change from baseline, CLASI20 and CLASI50 also did not reveal significant differences between groups".

#### 33.2 Adverse events

We found one trial for this comparison with a total of 349 participants (Merrill 2018).

#### 33.2.1 Severe

We included a single trial in this subgroup, which included a total of 349 participants (Merrill 2018). A total of 14 of 275 participants in the lulizumab pegol combined dose group compared with 1 of 71 participants in the placebo group had severe adverse events, favouring placebo with fewer severe side effects at six months. However, we did not find sufficient evidence of a distinct difference between the two treatments (RR 3.61, 95% CI 0.48 to 27.03; 349 participants; low-quality evidence (Merrill 2018); Analysis 22.1.1).

Merrill 2018 reported narratively that "2 deaths in 1.25 mg EOW group were due to cerebral haemorrhage and SLE". No deaths were reported in the placebo group or at any other dose level.

#### 33.2.2 Minor

Merrill 2018 reported pooled data for minor and severe adverse events. It is not possible to extract minor adverse events data from the published information. Narrative information on minor side effects was not reported.

**Comparison 34 Cosmetic camouflage versus placebo**

We found one trial for this comparison with a total of 43 participants (Lanna 2019). This comparison reported a secondary outcome. No severe or minor adverse events were reported.

The quality of evidence for these outcomes was graded as low, downgraded due to risk of bias (all domains unclear risk except two (blinding and incomplete outcome data) high risk).

#### 34.1 Secondary outcome: Dermatology Quality of Life Index (DLQI)

Lanna 2019 reported that the Dermatology Quality of Life Index (DLQI) score decreased in the cosmetic camouflage group from baseline (P = 0.008) but there was no variation in the control group (P = 0.196). This group also reported that "the difference on the variations of" dermatology quality of life "scores between group I (cosmetic camouflage intervention) and group II (no intervention) was statistically significant: ΔDLQI: P = 0.03". They reported that "the SLEQoL score variations were on physical function (P = 0.033, humor (P = 0.033) and self-image (P =0.031) domains". We were
unable to perform a quantitative analysis due to insufficient data reported by study authors.

B. Dose response comparisons

**Comparison 35 Intravenous belimumab versus intravenous belimumab dose comparison**

Three trials contributed to this comparison (Furie 2011; Navarra 2011; Wallace 2009). No primary or secondary outcomes were reported. This particular comparison reported four adverse event outcomes.

35.1 Adverse events: severe - for 1 mg/kg versus 10 mg/kg dose

For this outcome, we found two relevant studies and categorised data into two subgroups (in keeping with our protocol) (Furie 2011; Navarra 2011). Results show that 55 of 673 participants in the belimumab 1 mg/kg group compared with 56 of 674 in the belimumab 10 mg/kg group had severe adverse events. Overall, evidence of a clear difference between the two subgroups at any of the time points was insufficient with RR very close to 1 and wide confidence intervals (RR 0.98, 95% CI 0.59 to 1.61; P = 0.77; moderate-quality evidence (Navarra 2011); moderate-quality evidence (Furie 2011); Analysis 23.1.1).

35.1.1 Long term (12 months)

We identified two trials (Navarra 2011; Wallace 2009). In all, 37 of 402 participants in the belimumab 1 mg/kg group compared with 33 of 401 in the belimumab 10 mg/kg group had severe adverse events, favouring placebo. However, evidence of a distinct difference between the two treatments was insufficient with wide confidence intervals (RR 1.11, 95% CI 0.7 to 1.72; 803 participants, 2 studies; Analysis 23.1.1).

35.1.2 Long term (18 months)

We found a single trial in this subgroup, which included a total of 544 participants (Furie 2011). A total of 18 of 271 participants in the belimumab 1 mg/kg group compared with 23 of 273 in the belimumab 10 mg/kg group had severe adverse events, favouring belimumab 1 mg/kg with fewer severe side effects. However, we did not find sufficient evidence of a distinct difference between the two treatments (RR 0.79, 95% CI 0.44 to 1.43; moderate-quality evidence; Analysis 23.1.2).

35.2 Adverse events: minor - skin and subcutaneous tissue - for 1 mg/kg versus 4 mg/kg dose

For this outcome, we found a single study and categorised data into one subgroup (Wallace 2009).

35.2.1 Long term (12 months)

We found one trial that was relevant to this subgroup with a total of 225 people (Wallace 2009). Results show that 72 of 114 participants in the belimumab 1 mg/kg group compared with 65 of 111 participants in the belimumab 4 mg/kg group had minor adverse events, favouring placebo. Evidence of a clear difference between intravenous belimumab and intravenous belimumab dose comparison within this subgroup was insufficient (RR 1.08, 95% CI 0.87 to 1.33; moderate-quality evidence; Analysis 23.2).

35.3 Adverse events: minor - skin and subcutaneous tissue - for 1 mg/kg versus 10 mg/kg dose

For this outcome, we found a single study and organised the data into one subgroup (Wallace 2009).

35.3.1 Long term (12 months)

We found one trial that was relevant to this subgroup, which included a total of 225 participants (Wallace 2009). More minor skin and subcutaneous tissue adverse events occurred in the 1 mg/kg group (in 72 of 114 participants) compared with the belimumab 10 mg/kg group (only 55 of 111 participants), favouring the 10 mg/kg dose with fewer minor events. We found evidence of the superiority of intravenous belimumab 10 mg/kg with fewer minor adverse events than intravenous belimumab 10 mg/kg (RR 1.27, 95% CI 1.01 to 1.61; P = 0.04; moderate-quality evidence; Analysis 23.3).

35.4 Adverse events: minor - skin and subcutaneous tissue - for 4 mg/kg versus 10 mg/kg dose

For this outcome, we found a single study and organised the data into one subgroup (Wallace 2009).

35.4.1 Long term (12 months)

We identified a single trial for this subgroup, which included a total of 225 participants (Wallace 2009). In all, 65 of 111 participants in the belimumab 4 mg/kg group compared with 55 of 111 in the belimumab 10 mg/kg group had minor skin and subcutaneous tissue adverse events, favouring the 10 mg/kg group with fewer minor adverse events. Evidence of a clear difference between the two intravenous belimumab doses within this subgroup was insufficient (RR 1.18, 95% CI 0.93 to 1.51; moderate-quality evidence; Analysis 23.4).

**Comparison 36 Intravenous atacicept versus intravenous atacicept dose comparison**

One trial contributed to this comparison (Pena-Rossi 2009). No primary or secondary outcomes were reported. In this comparison, two adverse event outcomes were reported.

36.1 Adverse events: minor - eczema

For this outcome, we found a single study and categorised data into two subgroups (in keeping with our protocol) (Pena-Rossi 2009).

36.1.1 Short term (two months) 3 mg/kg versus 9 mg/kg dose

We included a single trial in this subgroup (total N = 10) (Pena-Rossi 2009). Results show that 1 of 5 participants in the atacicept 3 mg/kg group compared with none of 5 participants in the atacicept 9 mg/kg group had the minor adverse event of eczema, favouring atacicept 3 mg/kg with less eczema. However, evidence of a clear difference between different intravenous atacicept doses within this subgroup was insufficient (RR 3.00, 95% CI 1.05 to 7.58; low-quality evidence; Analysis 24.1).

This outcome was graded as low-quality evidence, downgraded due to risk of bias (insufficient details of methods of randomisation and allocation concealment) and imprecision (one small study).

36.1.2 Short term (two months) 3 mg/kg versus 18 mg/kg dose

We found one trial that was relevant to this subgroup with a total of 10 people (Pena-Rossi 2009). In all, 1 of 5 participants in the atacicept 3 mg/kg group compared with none of 5 participants in the atacicept...
18 mg/kg group had the minor adverse event of eczema, favouring the atacicept 18 mg/kg dose. However, for this subgroup, we did not find evidence of a distinct difference between the two dose levels (RR 3.00, 95% CI 0.15 to 59.89; low-quality evidence; Analysis 24.1).

36.2 Adverse events: minor - other adverse event (not eczema or local site reaction)

We identified one study that was relevant to this outcome and categorised data into four subgroups (in keeping with our protocol) (Pena-Rossi 2009).

36.2.1 Short term (two months) 9 mg/kg versus 18 mg/kg dose

We found one trial that was relevant to this subgroup, which included a total of 10 participants (Pena-Rossi 2009). A total of 1 of 5 participants in the atacicept 9 mg/kg group compared with 1 of 5 participants in the atacicept 18 mg/kg group had other minor adverse events (not eczema or local site reaction). There was no clear difference between the two intravenous atacicept doses due to RR close to 1 and wide confidence intervals (RR 1.00, 95% CI 0.08 to 11.93; low-quality evidence; Analysis 24.2.1).

36.2.2 Short term (two months) 3 mg/kg versus 18 mg/kg dose

We found one trial that was relevant to this subgroup, which included a total of 10 participants (Pena-Rossi 2009). Results show that 2 of 5 participants in the atacicept 3 mg/kg group compared with 1 of 5 in the atacicept 18 mg/kg group had other minor adverse events (not eczema or local site reaction), favouring atacicept 18 mg/kg. However, we did not find sufficient evidence of a distinct difference between the two doses (RR 2.00, 95% CI 0.26 to 15.62; low-quality evidence; Analysis 24.2.2).

36.2.3 Short term (two months) 3 mg/kg versus 9 mg/kg dose

We included a single trial in this subgroup, which included a total of 10 participants (Pena-Rossi 2009). A total of 2 of 5 participants in the atacicept 3 mg/kg group compared with 1 of 5 in the atacicept 9 mg/kg group had other minor adverse events (not eczema or local site reaction), favouring the 9 mg/kg dose due to fewer side effects. However, evidence of a clear difference between intravenous atacicept doses was insufficient (RR 2.0, 95% CI 0.26 to 15.62; low-quality evidence; Analysis 24.2.3).

36.2.4 Short term (two months) single 9 mg/kg versus two 9 mg/kg doses

We found one trial that was relevant to this subgroup, which included a total of 10 participants (Pena-Rossi 2009). In all, 1 of 5 participants in the atacicept single 9 mg/kg dose group compared with 4 of 5 in the atacicept two doses of 9 mg/kg group had other minor adverse events (not eczema or local site reaction), favouring a single 9 mg/kg dose. However, we did not find sufficient evidence of a distinct difference between the two doses (RR 0.25; 95% CI 0.04 to 1.52; low-quality evidence; Analysis 24.2.4).

36.3 Short-term (two months) - local site reaction of redness, bruising, and swelling

During the two-month study (Pena-Rossi 2009), no quantitative data were obtained by the study. Study investigators stated that no notable differences in the incidence of local injection site reaction was seen between the atacicept groups.

Comparison 37 Intravenous sifalimumab versus intravenous sifalimumab dose comparison

Two studies reported the outcomes (Khamashta 2016; Petri 2013). No primary outcomes were reported.

This comparison includes 22 secondary outcomes and adverse events.

37.1 Secondary outcomes: skin-specific measures of SLE disease activity (CLASI)

We identified one study that was relevant to this outcome and organised the data into one subgroup (Khamashta 2016). Although CLASI data are normally continuous, information provided by study authors was insufficient for this type of analysis. However, sufficient data were provided (modified ITT) for a dichotomous analysis comparing the proportion of participants in each group with CLASI activity score greater than 10 at baseline who achieved a reduction in CLASI of 4 or more points.

37.1.1 Long term (12 months) for 200 mg versus 600 mg dose

We found one trial that was relevant to this subgroup with a total of 66 participants (Khamashta 2016). In all, 24 of 33 participants in the sifalimumab 200 mg dose group compared with 19 of 33 in the sifalimumab 600 mg dose group with CLASI activity score greater than 10 at baseline achieved reduction in CLASI scores of 4 or more points favouring sifalimumab 600 mg. However, we did not find sufficient evidence of a distinct difference between the two doses (RR 1.26, 95% CI 0.88 to 1.81; high-quality evidence; Analysis 25.1).

37.1.2 Long term (12 months) for 600 mg versus 1200 mg dose

We found one trial that was relevant to this subgroup with a total of 59 participants (Khamashta 2016). Results show that 19 of 33 participants in the sifalimumab 600 mg dose group compared with 19 of 26 in the sifalimumab 1200 mg dose group with CLASI activity score greater than 10 at baseline achieved reduction in CLASI scores of 4 or more points, favouring sifalimumab 600 mg. However, we did not find sufficient evidence of a distinct difference between doses (RR 0.79, 95% CI 0.54 to 1.15; high-quality evidence; Analysis 25.2).

37.1.3 Long term (12 months) for 200 mg versus 1200 mg dose

We found one trial that was relevant to this subgroup with a total of 59 participants (Khamashta 2016). A total of 24 of 33 participants in the sifalimumab 200 mg dose group compared with 19 of 26 in the sifalimumab 1200 mg dose group with CLASI activity score greater than 10 at baseline achieved reduction in CLASI score of 4 or more points. However, we did not find sufficient evidence of a distinct difference between the two doses (RR 0.79, 95% CI 0.54 to 1.15; high-quality evidence; Analysis 25.3).

37.2 Adverse events: severe - all, including death - for 200 mg versus 600 mg dose

For this outcome, we found a single study and organised the data into one subgroup (Khamashta 2016).

37.2.1 Long term (12 months)

We identified a single trial in this subgroup with a total of 216 participants (Khamashta 2016). In all, 16 of 108 participants in the sifalimumab 200 mg dose group compared with 22 of 108 in the sifalimumab 600 mg group had severe events including death, favouring the 200 mg dose. However, there was no clear evidence
of a distinct difference between intravenous sifalimumab doses within this subgroup (RR 0.73, 95% CI 0.40 to 1.31; high-quality evidence; Analysis 25.4).

### 37.3 Adverse events: severe - all, including death - for 600 mg versus 1200 mg dose

For this outcome, we found a single study and organised the data into one subgroup (Khamashta 2016).

#### 37.3.1 Long term (12 months)

We found a single trial in this subgroup with a total of 215 participants (Khamashta 2016). Results show that 22 of 108 participants in the sifalimumab 600 mg dose group compared with 21 of 107 in the sifalimumab 1200 mg group had severe events including death, favouring the 1200 mg dose. However, evidence of a clear difference between intravenous sifalimumab and intravenous sifalimumab dose comparison within this subgroup was insufficient (RR 1.04, 95% CI 0.61 to 0.77; high-quality evidence; Analysis 25.5).

### 37.4 Adverse events: severe - all, including death - for 200 mg versus 1200 mg dose

For this outcome, we found a single study and organised the data into one subgroup (Khamashta 2016).

#### 37.4.1 Long term (12 months)

We identified a single trial for this subgroup with a total of 215 participants (Khamashta 2016). In total, 16 of 108 participants in the sifalimumab 200 mg dose group compared with 21 of 107 in the sifalimumab 1200 mg group had severe events including death, favouring the 200 mg dose. However, evidence of a clear difference between intravenous sifalimumab doses within this subgroup was insufficient (RR 0.75, 95% CI 0.42 to 1.37; high-quality evidence; Analysis 25.6).

### 37.5 Adverse events: severe - all, including death - for 0.3 mg/kg versus 1 mg/kg dose

We identified one study that was relevant to this outcome and organised the data into one subgroup (Petri 2013).

#### 37.5.1 Long term (12.5 months)

We found one trial that was relevant to this subgroup with a total of 51 participants (Petri 2013). In all, 7 of 26 participants in the sifalimumab 0.3 mg/kg dose group compared with 3 of 25 in the sifalimumab 1 mg/kg group had severe events including death, favouring the 1 mg/kg dose. However, we did not find evidence of a distinct difference between the two doses (RR 2.24, 95% CI 0.65 to 7.72; high-quality evidence; Analysis 25.7).

### 37.6 Adverse events: severe - all, including death - for 0.3 mg/kg versus 3 mg/kg dose

We identified one study that was relevant to this outcome and categorised data into one subgroup (Petri 2013).

#### 37.6.1 Long term (12.5 months)

We included one trial that was relevant to this subgroup with a total of 53 participants (Petri 2013). Results show that 7 of 26 participants in the sifalimumab 0.3 mg/kg dose group compared with 7 of 27 in the sifalimumab 3 mg/kg group had severe events including death, favouring the 3 mg/kg dose. However, there was no clear difference between intravenous sifalimumab doses within this subgroup (RR 1.04, 95% CI 0.42 to 2.55; high-quality evidence; Analysis 25.8).

### 37.7 Adverse events: severe - all, including death - for 0.3 mg/kg versus 10 mg/kg dose

For this outcome, we found a single study and organised the data into one subgroup (Petri 2013).

#### 37.7.1 Long term (12.5 months)

We found a single trial for this subgroup, which included a total of 52 participants (Petri 2013). In total, 3 of 25 participants in the sifalimumab 1 mg/kg dose group compared with 7 of 27 in the sifalimumab 3 mg/kg group had severe events including death, favouring the 1 mg/kg dose with fewer severe side effects. However, we did not find sufficient evidence of a distinct difference between the two treatments (RR 0.46, 95% CI 0.13 to 1.6; moderate-quality evidence; Analysis 25.10).

### 37.8 Adverse events: severe - all, including death - for 1 mg/kg versus 3 mg/kg dose

We identified one study that was relevant to this outcome and categorised data into one subgroup (Petri 2013).

#### 37.8.1 Long term (12.5 months)

We found a single trial for this subgroup, which included a total of 68 people (Petri 2013). Results show that 3 of 25 participants in the sifalimumab 1 mg/kg dose group compared with 10 of 43 participants in the sifalimumab 10 mg/kg group had severe events including death, favouring the 1 mg/kg dose. However, evidence of a clear difference between intravenous sifalimumab and intravenous sifalimumab dose comparison within this subgroup was insufficient (RR 0.52, 95% CI 0.16 to 1.70; moderate-quality evidence; Analysis 25.11).

### 37.9 Adverse events: severe - all, including death - for 1 mg/kg versus 10 mg/kg dose

We identified one study that was relevant to this outcome and organised the data into one subgroup (Petri 2013).

#### 37.9.1 Long term (12.5 months)

We found one trial that was relevant to this subgroup with a total of 68 people (Petri 2013). Results show that 3 of 25 participants in the sifalimumab 1 mg/kg dose group compared with 10 of 43 participants in the sifalimumab 10 mg/kg group had severe events including death, favouring the 1 mg/kg dose. However, evidence of a clear difference between intravenous sifalimumab and intravenous sifalimumab dose comparison within this subgroup was insufficient (RR 0.52, 95% CI 0.16 to 1.70; moderate-quality evidence; Analysis 25.11).

### 37.10 Adverse events: severe - all, including death - for 3 mg/kg versus 10 mg/kg dose

We identified one study that was relevant to this outcome and categorised data into one subgroup (Petri 2013).

#### 37.10.1 Long term (12.5 months)

We found a single trial for this subgroup with a total of 70 people (Petri 2013). In all, 7 of 27 participants in the sifalimumab 3 mg/kg dose group compared with 10 of 43 in the sifalimumab 10 mg/kg group had severe events including death, favouring the 10 mg/kg dose. However, we did not find sufficient evidence of a distinct difference between the two doses (RR 1.11, 95% CI 0.48 to 2.58; moderate-quality evidence; Analysis 25.12).
37.11 Adverse events: severe - death - for 0.3 mg/kg versus 1 mg/kg dose
For this outcome, we found a single study and categorised data into one subgroup (Petri 2013).

37.11.1 Long term (12.5 months)
We found one trial that was relevant to this subgroup with a total of 51 people (Petri 2013). In total, 1 death in the 1 mg/kg group and no deaths in the 0.3 mg/kg group occurred, favouring the 0.3 mg/kg group, but we found insufficient evidence of a clear difference between intravenous sifalimumab doses within this subgroup (RR 0.32, 95% CI 0.01 to 7.53; moderate-quality evidence; Analysis 25.13).

37.12 Adverse events: severe - death - for 0.3 mg/kg versus 3 mg/kg dose
For this outcome, we found a single study and categorised data into one subgroup (Petri 2013).

37.12.1 Long term (12.5 months)
We included a single trial in this subgroup, which included a total of 53 participants (Petri 2013). No events were reported in either group, so no effect was estimable and no forest plots could be produced.

37.13 Adverse events: severe - death - for 0.3 mg/kg versus 10 mg/kg dose
For this outcome, we found a single study and organised the data into one subgroup (Petri 2013).

37.13.1 Long term (12.5 months)
We found one trial that was relevant to this subgroup, which included a total of 69 participants (Petri 2013). No participants of 26 in the sifalimumab 0.3 mg/kg dose group compared with 2 of 43 in the sifalimumab 10 mg/kg group died, favouring the 0.3 mg/kg dose. However, we found insufficient evidence of a clear difference between intravenous sifalimumab doses within this subgroup (RR 0.33, 95% CI 0.02 to 6.54; moderate-quality evidence; Analysis 25.14).

37.14 Adverse events: severe - death - for 1 mg/kg versus 3 mg/kg dose
For this outcome, we found a single study and categorised data into one subgroup (Petri 2013).

37.14.1 Long term (12.5 months)
We found one trial that was relevant to this subgroup with a total of 52 people (Petri 2013). One participant of 25 in the sifalimumab 1 mg/kg dose group compared with none of 27 in the sifalimumab 3 mg/kg group died, favouring the 3 mg/kg dose. However, we did not find sufficient evidence of a distinct difference between the two doses (RR 3.23, 95% CI 0.14 to 75.83; moderate-quality evidence; Analysis 25.15).

37.15 Adverse events: severe - death - for 1 mg/kg versus 10 mg/kg dose
For this outcome, we found a single study and categorised data into one subgroup (Petri 2013).

37.15.1 Long term (12.5 months)
We found one trial that was relevant to this subgroup (total N = 68). One participant of 25 in the sifalimumab 1 mg/kg dose group compared with 2 of 43 in the sifalimumab 10 mg/kg group died, favouring the 1 mg/kg dose. However, evidence of a clear difference between intravenous sifalimumab and intravenous sifalimumab dose comparison within this subgroup was insufficient (RR 0.86 CI 0.08 to 9.01; moderate-quality evidence; Analysis 25.16).

37.16 Adverse events: severe - death - for 3 mg/kg versus 10 mg/kg dose
For this outcome, we found a single study and organised the data into one subgroup (Petri 2013).

37.16.1 Long term (12.5 months)
We included a single trial in this subgroup (total N = 70) (Petri 2013). Results show no participants of 27 in the sifalimumab 3 mg/kg dose group compared with 2 of 43 in the sifalimumab 10 mg/kg group died, favouring the 3 mg/kg dose. However, evidence of a clear difference between intravenous sifalimumab doses within this subgroup was insufficient (RR 0.31, 95% CI 0.02 to 6.31; moderate-quality evidence; Analysis 25.17).

37.17 Adverse events: minor - zoster - for 0.3 mg/kg versus 1 mg/kg dose
For this outcome, we found a single study and organised the data into one subgroup (Petri 2013).

37.17.1 Long term (12.5 months)
We found one trial that was relevant to this subgroup with a total of 51 people (Petri 2013). No events were reported in either group, so no effect could be estimated and no forest plot produced.

37.18 Adverse events: minor - zoster - for 0.3 mg/kg versus 3 mg/kg dose
For this outcome, we found a single study and categorised data into one subgroup (Petri 2013).

37.18.1 Long term (12.5 months)
We found one trial that was relevant to this subgroup with a total of 53 participants (Petri 2013). In all, no participants of 26 in the sifalimumab 0.3 mg/kg dose group compared with 2 of 27 in the sifalimumab 3 mg/kg group had a minor adverse event of zoster infection, favouring the 0.3 mg/kg dose. However, evidence of a clear difference between intravenous sifalimumab doses within this subgroup was insufficient (RR 0.21, 95% CI 0.01 to 4.12; moderate-quality evidence; Analysis 25.18).

37.19 Adverse events: minor - zoster - for 0.3 mg/kg versus 10 mg/kg dose
For this outcome, we found a single study and categorised data into one subgroup (Petri 2013).

37.19.1 Long term (12.5 months)
We included a single trial in this subgroup with a total of 69 people (Petri 2013). Results show that no participants of 26 in the sifalimumab 0.3 mg/kg dose group compared with 2 of 43 in the sifalimumab 10 mg/kg had a minor adverse event of zoster infection, favouring the 0.3 mg/kg dose. However, we did not find sufficient evidence of a distinct difference between the two doses.
We found one study relevant to this outcome and organised the data into one subgroup (Petri 2013).

37.20 Long term (12.5 months)
A single trial in this subgroup included a total of 68 participants (Petri 2013). No participants out of 25 in the sifalimumab 1 mg/kg dose group compared with 2 of 43 in the sifalimumab 10 mg/kg group had a minor adverse event of zoster infection, favouring the 1 mg/kg dose. However, evidence of a clear difference between intravenous sifalimumab doses within this subgroup was insufficient (RR 0.34, 95% CI 0.01 to 6.78; moderate-quality evidence; Analysis 25.21).

37.21 Adverse events: minor - zoster - for 3 mg/kg versus 10 mg/kg dose
For this outcome, we found a single study and organised the data into one subgroup (Petri 2013).

37.21.1 Long term (12.5 months)
We found one trial that was relevant to this subgroup, which included a total of 68 participants (Petri 2013). No participants out of 25 in the sifalimumab 1 mg/kg dose group compared with 2 of 43 in the sifalimumab 10 mg/kg group had a minor adverse event of zoster infection, favouring the 1 mg/kg dose with fewer cases of zoster. However, we did not find sufficient evidence of a distinct difference between the two doses (RR 0.46, 95% CI 0.14 to 1.46; moderate-quality evidence; Analysis 26.1). This outcome was graded as low-quality evidence, downgraded due to risk of bias (insufficient details about methods of sequence generation and allocation concealment) and imprecision (one small study).

38.2 Primary outcome: partial clinical response (malar, SCLE, or discoid rash, lupus-specific)
For this outcome, we found a single study and organised the data into one subgroup (Bezerra 2005).

38.2.1 Short term (six months)
We found one trial that was relevant to this subgroup (total N = 33) (Bezerra 2005). A total of 12 of 16 participants in the clofazimine group compared with 14 of 17 in the chloroquine group had partial clearance of malar, SCLE, or discoid rash, also favouring chloroquine because more participants had partial clearance (a positive outcome). However, evidence of a clear difference between oral clofazimine and oral chloroquine within this subgroup was insufficient (RR 0.91, 95% CI 0.64 to 1.30; low-quality evidence; Analysis 26.2).

38.3 Adverse events: severe - severe flare in lupus, requiring withdrawal from the study
For this outcome, we found a single study and organised the data into one subgroup (Bezerra 2005).

38.3.1 Short term (six months)
We found one trial for this subgroup, which included a total of 33 participants (Bezerra 2005). Results show that 5 of 16 participants in the clofazimine group compared with 1 of 17 in the chloroquine group had a severe adverse event of flare in lupus requiring withdrawal from the study, favouring chloroquine due to fewer severe flares. However, evidence of a clear difference between oral clofazimine and oral chloroquine within this subgroup was insufficient (RR 5.31, 95% CI 0.69 to 40.68; low-quality evidence; Analysis 26.3).

38.4 Adverse events: minor
We identified one study that was relevant to this outcome and categorised data into one subgroup (Bezerra 2005).

38.4.1 Short term (six months)
We found one trial that was relevant for this subgroup, which included a total of 33 participants (Bezerra 2005). In all, 11 of 16 participants in the clofazimine group compared with 12 of 17 in the chloroquine group had minor adverse events, favouring clofazimine with fewer minor adverse events. However, we did not find sufficient evidence of a distinct difference between the two treatments (RR 0.97, 95% CI 0.62 to 1.53; low-quality evidence; Analysis 26.4).

Comparison 39 Oral cyclosporin versus oral azathioprine
We included one trial that contributed to this comparison (Griffiths 2010). This comparison reported five primary outcomes and adverse events. No secondary outcomes were reported.
39.1 Primary outcome: complete clinical response (malar rash, intent-to-treat analysis)

We identified one study that was relevant to this outcome and organised the data into one subgroup (Griffiths 2010).

39.1.1 Long term (12 months)

We found one trial that was relevant for this subgroup with a total of 89 participants (Griffiths 2010). In total, 14 of 47 participants in the ciclosporin group compared with 15 of 42 in the azathioprine group had complete clearance of malar rash (intent-to-treat analysis), favouring azathioprine. However, we did not find sufficient evidence of a distinct difference between the two treatments (RR 0.83, 95% CI 0.46 to 1.52; low-quality evidence; Analysis 27.1). See Summary of findings 5.

39.2 Primary outcome: complete clinical response (oral ulcers, intent-to-treat analysis)

We identified one study that was relevant to this outcome and organised the data into one subgroup.

39.2.1 Long term (12 months)

We found one trial that was relevant to this subgroup with a total of 89 participants (Griffiths 2010). Results show that 23 of 47 participants in the ciclosporin group compared with 14 of 42 in the azathioprine group had complete clearance of oral ulcers (intent-to-treat analysis), favouring the ciclosporin group. However, we did not find sufficient evidence of a distinct difference between the two treatments (RR 1.47, 95% CI 0.87 to 2.46; low-quality evidence; Analysis 27.2).

39.3 Adverse events: all severe events combined

For this outcome, we found a single study and categorised the data into one subgroup (Griffiths 2010).

39.3.1 Long term (12 months)

We included a single trial for this subgroup with a total of 89 participants (Griffiths 2010). In all, 14 of 47 participants in the ciclosporin group compared with 14 of 42 in the azathioprine group had severe adverse events, favouring ciclosporin. However, we found no evidence of a clear difference between oral ciclosporin and oral azathioprine within this subgroup (RR 0.89, 95% CI 0.48 to 1.65; low-quality evidence; Analysis 27.3). See Summary of findings 5.

39.4 Adverse events: subset of severe adverse events due to lack of effect of medication only

We identified one study that was relevant to this outcome and organised the data into one subgroup (Griffiths 2010).

39.4.1 Long term (12 months)

We found one trial that was relevant to this subgroup with a total of 89 participants (Griffiths 2010). In total, 5 of 47 participants in the ciclosporin group compared with 2 of 42 in the azathioprine group had severe adverse events due to lack of effect of medication only (excluding other severe adverse events), favouring azathioprine. However, we did not find sufficient evidence of a distinct difference between the two treatments (RR 2.23, 95% CI 0.46 to 10.91; low-quality evidence; Analysis 27.4).

39.5 Adverse events: minor

For this outcome, we found a single study and categorised data into six subgroups (in keeping with our protocol) with a total of 623 participants (Griffiths 2010).

39.5.1 Long term (12 months) - gum hypertrophy

We identified a single trial in this subgroup with a total of 89 participants (Griffiths 2010). Results show that 3 of 47 participants in the ciclosporin group compared with none of 42 in the azathioprine group had the minor adverse event of gum hypertrophy, favouring azathioprine. However, we found no clear difference between oral ciclosporin and oral azathioprine within this subgroup (RR 6.27, 95% CI 0.33 to 117.96; low-quality evidence; Analysis 27.5.1).

39.5.2 Long term (12 months) - alopecia (possibly unrelated to lupus)

We found a single trial in this subgroup, which included a total of 89 participants (Griffiths 2010). In all, 6 of 47 participants in the ciclosporin group compared with 7 of 42 in the azathioprine group had alopecia, favouring ciclosporin (less alopecia) over azathioprine. However, we did not find sufficient evidence of a distinct difference between the two treatments (RR 0.77, 95% CI 0.28 to 2.10; low-quality evidence; Analysis 27.5.2).

39.5.3 Long term (12 months) - herpes zoster

We included a single trial in this subgroup, which included a total of 89 participants (Griffiths 2010). In total, none of 47 participants in the ciclosporin group compared with 2 of 42 in the azathioprine group had the minor adverse event of zoster infection, favouring ciclosporin. For this subgroup, however, we did not find sufficient evidence of a distinct difference between the two treatments (RR 0.18, 95% CI 0.01 to 3.63; low-quality evidence; Analysis 27.5.3).

39.5.4 Long term (12 months) - non-lupus rash

We identified a single trial in this subgroup, which included a total of 89 participants (Griffiths 2010). Results show that 9 of 47 participants in the ciclosporin group compared with 12 of 42 in the azathioprine group had the minor adverse event of a non-lupus rash, favouring ciclosporin. However, evidence of a clear difference between oral ciclosporin and oral azathioprine within this subgroup was insufficient (RR 0.67, 95% CI 0.31 to 1.43; low-quality evidence; Analysis 27.5.4).

39.5.5 Long term (12 months) - acne

We included a single trial in this subgroup, which included a total of 89 participants (Griffiths 2010). In all, none of the participants in the ciclosporin group compared with 3 of 42 in the azathioprine group had the minor adverse event of acne, favouring ciclosporin. For this subgroup, however, we did not find sufficient evidence of a distinct difference between the two treatments (RR 0.13, 95% CI 0.01 to 2.41; low-quality evidence; Analysis 27.5.5).

39.5.6 Long term (12 months) - hirsutism

We found a single trial in this subgroup with a total of 89 participants (Griffiths 2010). In total, 11 of 47 participants in the ciclosporin group compared with 1 of 42 in the azathioprine group had the minor adverse event of hirsutism, favouring azathioprine against this harm. We found strong evidence of clear superiority of azathioprine over ciclosporin (RR 9.83, 95% CI 1.32 to 72.95; P = 0.03; low-quality evidence; Analysis 27.5.6). See Summary of findings 5.
39.5.7 Long term (12 months) - herpes simplex

We identified a single trial in this subgroup with a total of 89 participants (Griffiths 2010). Results show that 2 of 47 participants in the ciclosporin group compared with 3 of 42 in the azathioprine group had the minor adverse event of herpes simplex, favouring ciclosporin. However, we did not find sufficient evidence of a distinct difference between the two treatments oral ciclosporin and oral azathioprine (RR 0.60, 95% CI 0.10 to 3.39; low-quality evidence; Analysis 27.5.7).

Comparison 40 Oral methotrexate versus oral chloroquine

One trial contributed to this comparison (Islam 2012). This particular comparison reported four primary outcomes and adverse events. No secondary outcomes were reported.

40.1 Primary outcome: complete clinical response (skin rash, ITT analysis)

We identified one study that was relevant to this outcome and organised the data into one subgroup (Islam 2012).

40.1.1 Short term (six months)

We found a single trial in this subgroup with a total of 41 participants (Islam 2012). In all, 6 of 15 participants in the methotrexate group compared with 16 of 26 in the chloroquine group had complete clearance of skin rash (intent-to-treat analysis), favouring chloroquine due to a greater percentage of patients with complete clearance (a benefit). However, evidence of a clear difference between oral methotrexate and oral chloroquine within this subgroup was insufficient (RR 0.65, 95% CI 0.33 to 1.30; low-quality evidence; Analysis 28.1).

This outcome was graded as low-quality evidence due to risk of bias (high risk due to open-label study (no blinding), unclear allocation concealment, withdrawals occurring without explanation, per-protocol analysis).

40.2 Primary outcome: complete clinical response (skin rash)

We identified one study that was relevant to this outcome and organised the data into one subgroup (Islam 2012).

40.2.1 Short term (six months)

We included a single trial in this subgroup for a total of 37 participants (Islam 2012). In total, 6 of 13 participants in the methotrexate group compared with 16 of 24 in the chloroquine group had complete clearance of skin rash (study investigators’ per-protocol analysis), favouring chloroquine. For this subgroup, however, we did not find sufficient evidence of a distinct difference between the two treatments (RR 0.69, 95% CI 0.36 to 1.33; low-quality evidence; Analysis 28.2).

40.3 Primary outcome: complete clinical response (during six-month study (subset of patients with skin findings at baseline))

We identified one study that was relevant to this outcome and organised the data into one subgroup (Islam 2012).

40.3.1 Short term (six months)

We found one trial that was relevant to this subgroup, which included a total of 25 participants (Islam 2012). Results show that 6 of 6 (100%) participants in the methotrexate group compared with 16 of 19 (84%) in the chloroquine group had complete clearance of skin rash (subset of patients with skin findings at baseline), favouring methotrexate as having higher complete clearance rate. For this subgroup, however, we did not find evidence of a distinct difference between the two treatments with wide confidence intervals (RR 1.13, 95% CI 0.84 to 1.50; low-quality evidence; Analysis 28.3), namely, both were very effective. See Summary of findings 6.

40.4 Adverse events

For this outcome, we identified a single study and organised the data into two subgroups in accordance with our protocol (Islam 2012).

40.4.1 Severe short term (six months)

We found one trial that was relevant to this subgroup, which included a total of 41 participants (Islam 2012). In all, 2 of 15 participants in the methotrexate group compared with 2 of 26 in the chloroquine group had severe adverse events, favouring chloroquine with fewer side effects. For this subgroup, however, we did not find sufficient evidence of a distinct difference between the two treatments (RR 1.73, 95% CI 0.27 to 11.07; low-quality evidence; Analysis 28.4.1). See Summary of findings 6.

40.4.2 Minor short term (six months)

We included one trial that was relevant to this subgroup with a total of 41 people (Islam 2012). We found evidence of a clear difference between oral methotrexate and oral chloroquine within this subgroup in that more cases of minor adverse events (9/15) were reported in the methotrexate group (RR 3.90, 95% CI 1.45 to 10.51; P = 0.007; low-quality evidence, Analysis 28.4.2) than in the chloroquine group (4/26), favouring chloroquine due to fewer minor side effects. See Summary of findings 6.

Comparison 41 Oral mycophenolate versus azathioprine or dapsone

One trial contributed to this comparison (Yahya 2013). This particular comparison reported two primary outcomes and adverse events. No secondary outcomes were reported.

41.1 Primary outcome: partial clinical response

For this outcome, we found a single study and organised the data into one subgroup (Yahya 2013).

41.1.1 Short term (four months)

We found one trial that was relevant to this subgroup with a total of six participants (Yahya 2013). In all, 2 of 3 participants in the mycophenolate group compared with none of 3 in the azathioprine or dapsone group had partial improvement, favouring mycophenolate. For this subgroup, however, we did not find sufficient evidence of a distinct difference between the two treatments (RR 5.0, 95% CI 0.34 to 74.52; low-quality evidence; Analysis 29.1).

This outcome was graded as low-quality evidence, downgraded due to risk of bias (some high risk domains) and for imprecision (one small study).

41.2 Adverse events

For this outcome, we found a single study and categorised data into two subgroups (in keeping with our protocol) (Yahya 2013).
41.2.1 Severe short term (four months)

We found one trial that was relevant to this subgroup with a total of 14 participants (Yahya 2013). None of the 8 participants in the mycophenolate group compared with 2 of 6 in the azathioprine or dapsone group had severe adverse events, favouring mycophenolate. For this subgroup, we did not find sufficient evidence of a distinct difference between the two treatments (RR 0.16, 95% CI 0.01 to 2.75; low-quality evidence; Analysis 29.2.1).

41.2.2 Minor short term (four months)

We found one trial that was relevant to this subgroup, which included a total of 14 participants (Yahya 2013). In all, 1 of 8 participants in the mycophenolate group compared with none of 6 participants in the azathioprine or dapsone group had minor adverse events, favouring the azathioprine/dapsone group. For this subgroup, however, we did not find sufficient evidence of a distinct difference between the two treatments (RR 2.33, 95% CI 0.11 to 48.99; low-quality evidence; Analysis 29.2.2).

Comparison 42 Oral mycophenolate versus azathioprine

One study contributed to this comparison (Ordí-Ros 2017). No primary or secondary outcomes were reported. This comparison reported one adverse event outcome.

42.1 Adverse events

42.1.1 Minor long term (24 months)

For this outcome, we found a single study involving 240 participants (Ordí-Ros 2017). Study authors note that adverse events were "similar in both groups except leucopenia that occurred more frequently with AZA".

These outcomes were graded as low-quality evidence, downgraded due to risk of bias (domains with unclear or high risk).

Comparison 43 Oral Zi Shen Qing (Chinese herbal medicine) versus hydroxychloroquine

One study contributed to this comparison (Zhong 2013). No primary or secondary outcomes were reported. This comparison reported two adverse event outcomes.

43.1 Adverse events: severe

We identified one study that was relevant to this outcome and organised the data into one subgroup (Zhong 2013).

43.1.1 Short term (three months)

We included a single trial for this subgroup, which included a total of 84 participants (Zhong 2013). In total, 4 of 42 participants in the Zi Shen Qing group compared with 3 of 42 in the hydroxychloroquine group had severe adverse events, favouring hydroxychloroquine. For this subgroup, however, we did not find sufficient evidence of a distinct difference between the two treatments (RR 1.33, 95% CI 0.32 to 5.60; high-quality evidence; Analysis 30.1).

43.2 Adverse events: minor

For this outcome, we found a single study and categorised data into one subgroup (Zhong 2013).

43.2.1 Short term (three months)

We found one trial that was relevant to this subgroup, which included a total of 84 participants (Zhong 2013). Results show that 5 of 42 participants in the Zi Shen Qing (Chinese herbal medicine) group compared with 8 of 42 in the hydroxychloroquine group had minor adverse events, favouring Zi Shen Qing with fewer minor adverse events. However, evidence of a clear difference between oral Zi Shen Qing (Chinese herbal medicine) and hydroxychloroquine within this subgroup was insufficient (RR 0.63, 95% CI 0.22 to 1.75; high-quality evidence; Analysis 30.2).

Comparison 44 Oral cyclosporin A plus intravenous and oral steroids versus oral steroids alone

One trial contributed to this comparison (Dammacco 2000). This comparison reported two primary outcomes and adverse events. No secondary outcomes were reported.

44.1 Primary outcome: complete clinical response (erythematous manifestations)

For this outcome, we found a single study and organised the data into two subgroups in accordance with our protocol (Dammacco 2000).

44.1.1 Short term (three months)

We found one trial that was relevant to this subgroup with a total of 18 participants (Dammacco 2000). In all, 1 of 10 participants in the oral cyclosporin A plus intravenous and oral steroids group compared with none of 8 in the oral steroids alone group had complete resolution of erythematous manifestations over the short term (three months), favouring oral cyclosporin plus intravenous and oral steroids. However, results show insufficient evidence of a clear difference between oral cyclosporin A plus intravenous and oral steroids and oral steroids alone within this subgroup (RR 2.45, 95% CI 0.11 to 53.25; P = 0.57; low-quality evidence; Analysis 31.1.1).

44.1.2 Long term (12 months)

We found one trial that was relevant to this subgroup with a total of 18 participants (Dammacco 2000). In total, 7 of 10 participants in the oral cyclosporin A plus intravenous and oral steroids group compared with none of 8 in the oral steroids alone group had complete resolution of erythematous manifestations over the long term (12 months), favouring oral cyclosporin plus intravenous and oral steroids. However, evidence of a clear difference between oral cyclosporin A plus intravenous and oral steroids alone within this subgroup was insufficient (RR 12.27, 95% CI 0.81 to 187.01; P = 0.07; low-quality evidence; Analysis 31.1.2).

44.2 Adverse events

We identified one study that was relevant to this outcome and organised the data into three subgroups in accordance with our protocol (Dammacco 2000).

44.2.1 Severe long term (12 months)

We found a single trial in this subgroup with a total of 18 participants (Dammacco 2000). Results show that 2 of 10 participants in the oral cyclosporin A plus intravenous and oral steroids group compared with 4 of 8 in the oral steroids alone group had severe long-term adverse events, favouring cyclosporin A plus intravenous and oral steroids due to fewer severe side effects. For this subgroup, however, we did not find sufficient evidence of a
44.2.2 Minor long term (12 months) - mucocutaneous alterations only (hypertrichosis, striae rubrae)

We included one trial that was relevant to this subgroup, which included a total of 18 participants (Dammacco 2000). In all, none of 10 participants in the oral ciclosporin A plus intravenous and oral steroids group compared with 4 of 8 in the oral steroids alone group had minor long-term adverse events of mucocutaneous alterations only (hypertrichosis, striae rubrae), favouring oral ciclosporin A plus intravenous and oral steroids. However, we found no clear difference between oral ciclosporin A plus intravenous and oral steroids alone within this subgroup (RR 0.09, 95% CI 0.01 to 1.47; low-quality evidence; Analysis 31.2.4).

44.2.3 Minor long term (12 months) - combined mucocutaneous and other organ systems

We identified a single trial in this subgroup, which included a total of 18 participants (Dammacco 2000). In total, 6 of 10 participants in the oral ciclosporin A plus intravenous and oral steroids group compared with 5 of 8 in the oral steroids alone group had minor long-term adverse events of combined mucocutaneous and other organ systems, favouring ciclosporin A plus intravenous and oral steroids due to fewer minor side effects. For this subgroup, however, we did not find evidence of a distinct difference between the two treatments (RR 0.96, 95% CI 0.46 to 2.01; low-quality evidence; Analysis 31.2.5).

Comparison 45 Intravenous rituximab versus intravenous cyclophosphamide

One trial contributed to this comparison (Andrade-Ortega 2009). No primary or secondary outcomes were reported. In this comparison, two adverse event outcomes were reported.

45.1 Adverse events: severe

For this outcome, we found a single study and organised the data into one subgroup (Andrade-Ortega 2009).

45.1.1 Long term (12 months)

We found a single trial in this subgroup with a total of 20 participants (Andrade-Ortega 2009). No events were reported in either group, so no effect could be estimated nor forest plot produced.

45.2 Adverse events: minor - cutaneous rash, itching

For this outcome, we found a single study and organised the data into one subgroup (Andrade-Ortega 2009).

45.2.1 Long term (12 months)

We included one trial that was relevant to this subgroup with a total of 19 participants (Andrade-Ortega 2009). Results show that 3 of 10 participants in the rituximab group compared with none of 9 in the cyclophosphamide had minor cutaneous rashes/itching, favouring cyclophosphamide. For this subgroup, however, we did not find sufficient evidence of a distinct difference between the two treatments (RR 6.36, 95% CI 0.37 to 108.56; low-quality evidence; Analysis 32.1).

Comparison 46 Early treatment (serology) with prednisone and/or cytotoxic agents versus later treatment (clinical flare)

One trial contributed to this comparison (Bootsma 1995). No primary or secondary outcomes were reported. In this comparison, two adverse event outcomes were reported.

46.1 Adverse events: minor

We identified one study that was relevant to this outcome and organised the data into one subgroup (Bootsma 1995).

46.1.1 Short term (six months)

We found a single trial in this subgroup with a total of 46 participants (Bootsma 1995). In all, 18 of 22 participants in the early treatment (serology) with prednisone and/or cytotoxic agents group compared with 17 of 24 in the later treatment (clinical flare) group had minor adverse events, favouring later treatment. For this subgroup, however, we did not find sufficient evidence of a distinct difference between the two treatments (RR 1.16, 95% CI 0.84 to 1.6; moderate-quality evidence; Analysis 33.1).

46.2 Adverse events: severe

For this outcome, we found a single study and organised the data into one subgroup (Bootsma 1995).

46.2.1 Short term (six months)

We found one trial that was relevant to this subgroup, which included a total of 46 participants (Bootsma 1995). In total, 6 of 22 participants in the early treatment (serology) with prednisone and/or cytotoxic agents group compared with 1 of 24 in the later treatment (clinical flare) group had severe adverse events, favouring later treatment. However, evidence of a clear difference between early treatment (serology) with prednisone and/or cytotoxic agents and later treatment (clinical flare) within this subgroup was insufficient (RR 6.55, 95% CI 0.85 to 50.16; moderate-quality evidence; Analysis 33.2).

Comparison 47 Intravenous pulse high-dose cyclophosphamide versus intravenous monthly lower-dose cyclophosphamide

One trial contributed to this comparison (Petri 2010). No primary or secondary outcomes were reported. This particular comparison reported two adverse events outcomes.

47.1 Adverse events: severe - death

For this outcome, we found a single study and categorised data into one subgroup (Petri 2010).

47.1.1 Long term (24 months)

We found one trial that was relevant to this subgroup with a total of 51 participants (Petri 2010). Results show that 1 of 24 participants in the intravenous pulse high-dose cyclophosphamide group compared with none of 27 in the intravenous monthly lower-dose cyclophosphamide group died, favouring monthly lower-dose cyclophosphamide. However, we found insufficient evidence of a clear difference between intravenous pulse high-dose cyclophosphamide and intravenous monthly lower-dose cyclophosphamide within this subgroup (RR 3.36, 95% CI 0.14 to 78.79; moderate-quality evidence; Analysis 34.1).
47.2 Adverse events: severe - infection, cardiac arrest (not including death)

We identified one study that was relevant to this outcome and categorised data into one subgroup (Petri 2010).

47.2.1 Long term (24 months)

We found one trial that was relevant to this subgroup with a total of 51 participants (Petri 2010). In all, 1 of 24 participants in the intravenous pulse high-dose cyclophosphamide group compared with 1 of 27 in the intravenous monthly lower-dose cyclophosphamide group had severe adverse events including infection and cardiac arrest but excluding deaths, favouring monthly lower-dose cyclophosphamide. However, we found insufficient evidence of a clear difference between intravenous pulse high-dose cyclophosphamide and intravenous monthly lower-dose cyclophosphamide within this subgroup (RR 1.13, 95% CI 0.07 to 18.02; Analysis 34.2).

Comparison 48 Topical tacrolimus versus topical clobetasol

One trial contributed to this comparison (Tzung 2007). This particular comparison reported four primary outcomes. No secondary outcomes or adverse events were reported.

Tzung 2007 was a split-body study. Data were insufficient for integration into meta-analysis at this time (only one trial). In the future, if meta-analysis is deemed appropriate, we will need to take into account unit of analysis issues as per Cochrane guidelines.

48.1 Primary outcome: complete clinical response (erythema)

For this outcome, we found a single study and organised the data into one subgroup (Tzung 2007).

48.1.1 Short term (two months)

We found one trial that was relevant to this subgroup with a total of 36 participants (Tzung 2007). The mean for erythema was 1.17 with a standard deviation of 0.69 for 18 participants in the tacrolimus group compared with a mean for erythema of 1.47 with standard deviation of 0.87 for 18 participants in the topical clobetasol group. We found no evidence of a clear difference between the mean for erythema for topical tacrolimus and topical clobetasol within this subgroup (MD -0.30, 95% CI -0.81 to 0.21; low-quality evidence; Analysis 35.1).

This outcome was rated as low quality due to risk of bias (insufficient details about sequence generation and allocation concealment, risk of attrition, and reasons for dropout not discussed; ITT not performed).

48.2 Primary outcome: complete clinical response (desquamation)

We identified one study as relevant to this outcome and categorised data into one subgroup (Tzung 2007).

48.2.1 Short term (two months)

We found a single trial in this subgroup, which included a total of 36 participants (Tzung 2007). The mean for desquamation was 0.5 with a standard deviation of 0.57 for 18 participants in the tacrolimus group compared with a mean for desquamation of 0.69 with standard deviation of 0.69 for 18 participants in the topical clobetasol group. We found no evidence of a clear difference between topical tacrolimus and topical clobetasol within this subgroup (MD -0.19, 95% CI -0.60 to 0.22; low-quality evidence; Analysis 35.2).

48.3 Primary outcome: complete clinical response (skin induration)

For this outcome, we found a single study and categorised data into one subgroup (Tzung 2007).

48.3.1 Short term (two months)

We included a single trial in this subgroup, which included a total of 36 participants (Tzung 2007). The mean for skin induration was 0.67 with a standard deviation of 0.62 for 18 participants in the tacrolimus group compared with a mean for skin induration of 0.92 with standard deviation of 0.84 for 18 participants in the topical clobetasol group. For this outcome, within this subgroup, we did not find any evidence that topical tacrolimus was different in its effects compared with topical clobetasol (MD -0.25, 95% CI -0.73 to 0.23; low-quality evidence; Analysis 35.3).

48.4 Primary outcome: complete clinical response (telangiectasias)

48.4.1 Short term (two months)

For this outcome, we found a single study involving 18 participants who received the study medications (Tzung 2007). Tacrolimus did not increase telangiectasias (redness and unwanted blood vessels), which is a positive outcome. Study investigators rated no telangiectasias (good outcome) as zero value, then rated the increasing degree of the bad outcome (telangiectasias) created by clobetasol. Study investigators used Wilcoxon’s rank sum test with Bonferroni correction to compare the severity of telangiectasias between tacrolimus and clobetasol at baseline and across five time points. Tzung 2007 reported that for telangiectasias during the two-month study, there was a statistically significant difference between topical tacrolimus and topical clobetasol, that is, by week 3, a statistically significant difference (P = 0.004) between telangiectasias in the tacrolimus group (no telangiectasias, i.e. 0 ± 0) and in the clobetasol group (0.47 ± 0.50). The magnitude of this difference continued to increase each week and reached its maximum at two months (end of study) with a P value of 0.002 in the tacrolimus group (no telangiectasias, i.e. 0 ± 0) compared with the clobetasol group (0.64 ± 0.68).

This outcome was rated as low-quality evidence due to risk of bias (insufficient details about sequence generation and allocation concealment, risk of attrition, and reasons for dropout not discussed; ITT not performed).

DISCUSSION

Summary of main results

We included in this review 61 randomised controlled trials (RCTs), which examined 11,232 participants. We aimed to assess effects of interventions for cutaneous disease in systemic lupus erythematosus (SLE); however, uncertainties remain due to the small number of completed studies on this topic per intervention. In addition, a majority of comparisons were based on only one trial, and included comparisons were widely disparate, which meant there were few opportunities to combine results in meta-analyses. Adverse outcomes that were assessed in each study were inconsistent in type and level of detail, making comparisons between studies challenging; however, when we could pool data, adverse outcomes were the only measures that were eligible.
Moreover, the duration of studies was short in most cases for many interventions; therefore it may be inadequate to demonstrate optimal treatment effect. We found a limited number of head-to-head comparisons to help clinicians decide between treatments.

Many interventions used for cutaneous disease in SLE were not assessed by any included study; the most common treatment, hydroxychloroquine, was assessed by very few studies. Few trials evaluated second-line treatments that are used when resistance to more frequently used agents is shown.

None of the studies addressed more than a few outcomes, and the quality of data reporting was variable. Only a very limited number of skin outcomes were assessed in each study. Most studies focused on global composite outcomes that were designed for research, such as the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), Systemic Lupus Activity Measurement (SLAM), and the British Isles Lupus Assessment Group Disease Activity Index (BILAG). Although these composite measures may provide quantitative and objective outcomes that are useful for analysis, they are considered to be physician-oriented rather than participant-oriented.

Also, although cutaneous disease has been shown to be extremely important for participants with SLE (Tebbe 1997), based on this systematic review, cutaneous disease was less likely to be reported in RCTs than the disease parameters for other organ systems. Several RCTs presented limited data on a composite measure that is specific to the skin (Cutaneous Lupus Disease Area and Severity Index - CLASI) (Furie 2015a; Furie 2015c; Furie 2016a; Furie 2016b; Khamashta 2013; Werth 2017a; Van Volkenhoven 2018; Yokogawa 2015), and only two RCTs included an assessment of dermatology quality of life (Lanna 2019; Szepiekowski 2013), even though cutaneous disease in SLE is known to have a very significant impact on quality of life (Tebbe 1997; Verma 2014).

Interventions compared with placebo

Oral methotrexate versus placebo

Please see Summary of findings 1.

Methotrexate may lead to an increase in the lupus-specific primary outcome of complete clinical response (when defined as resolution of malar or discoid rash) (low-quality evidence). Partial clinical response was not reported by any studies assessing this comparison. When clinical flares are assessed, there may be no difference between methotrexate and placebo, but the 95% confidence interval (CI) indicates that there may also be more or fewer flares with methotrexate (moderate-quality evidence).

Oral hydroxychloroquine versus placebo

Please see Summary of findings 2.

The included studies comparing hydroxychloroquine against placebo did not report complete clinical response. Partial clinical response in pregnant participants may be greater with hydroxychloroquine, but the 95% CI indicates that hydroxychloroquine may also make no difference in or may decrease partial clinical response (low-quality evidence). Hydroxychloroquine probably leads to increased reduction in clinical flares compared to placebo (moderate-quality evidence).

Oral chloroquine versus placebo

Please see Summary of findings 4.

Chloroquine may increase complete clinical clearance, defined as complete resolution of skin lesions (low-quality evidence). The study in this comparison did not report partial clinical response or clinical flare.

Interventions compared head to head

Oral ciclosporin versus oral azathioprine

Please see Summary of findings 5.

There may be little to no difference between ciclosporin and azathioprine in terms of complete clearance, defined as resolution of malar rash (low-quality evidence). The study in this comparison did not report partial clinical response or clinical flares.

Oral methotrexate versus oral chloroquine

Please see Summary of findings 6.

Methotrexate and chloroquine may be comparable for complete clinical response (defined as resolution of skin rash) (low-quality evidence). The study in this comparison did not report partial clinical response nor clinical flares.

Adverse effects

Adverse events were minimal and reporting was dissonant, but well-known adverse effects associated with hydroxychloroquine, chloroquine, and methotrexate include gastrointestinal symptoms, liver problems, and retinopathy for hydroxychloroquine and chloroquine, and teratogenicity during pregnancy for methotrexate.

Overall completeness and applicability of evidence

The studies identified were not sufficient to address all of the objectives of the review question because not all relevant types of participants, interventions, or outcomes have been investigated in the included studies. In addition, the skin manifestations of SLE are very heterogeneous and for the most part were not quantified sufficiently or described in enough detail in most available studies.

The included studies assessed a wide range of classes of interventions (Table 2), including oral and topical calcineurin inhibitors, a topical corticosteroid, topical and oral Janus kinase (JAK) inhibitors, an antibiotic, antimalarials, biologic therapies, calcium channel blockers, chemotheraphy, systemic corticosteroids, ultraviolet light (UVA), a cereblon inhibitor, hormones, immunomodulatory agents, a leukotriene synthesis inhibitor, and monoclonal antibodies. Also assessed were complementary and alternative medicine treatments including camouflage makeup, supplements, and Traditional Chinese Medicine (TCM).

Many routine interventions listed under Description of the intervention have not been assessed sufficiently by the included studies. Hydroxychloroquine, one of the most commonly used treatments for cutaneous lupus manifestations, was assessed by only five trials. Prednisone was assessed by only two trials - one as a comparator. Azathioprine, ciclosporin, cyclophosphamide,
dapsone, and mycophenolate, which are other widely prescribed interventions, were assessed only as comparators.

Some interventions were not assessed at all, such as topical beta-2-adrenergic receptor agonists, naturopathic medicine, retinoids, behavioural therapies, cognitive-behavioral therapy (CBT), and laser therapy. No trials of topical corticosteroids have reported our primary or key secondary outcomes.

At class level, monoclonal antibodies were the most commonly assessed, with 28% of the included studies evaluating this type of immunotherapy. Most therapies were assessed by single studies; however, the following were evaluated in two or three studies: antimalarials (chloroquine), calcineurin inhibitors (oral ciclosporin, tacrolimus ointment), corticosteroids (prednisone), immunosuppressive agents (ciclosporin, mycophenolate sodium, methotrexate, cyclophosphamide, azathioprine), monoclonal therapies (epratuzumab, sipilimumab, rituximab), dehydroepiandrosterone, and UVA-1 phototherapy.

Placebo was the most common comparator. We included only nine head-to-head trials and 12 dose-effect trials. Active comparators included an antibiotic, antimalarial, biologic therapies, calcineurin inhibitors, corticosteroids, immunosuppressives, monoclonal antibodies, and TCM.

Participants were reflective in terms of sex; SLE affects more women than men (9:1), and participants in the majority of studies were primarily women. Twenty-four studies (39%) included participants younger than 40 years of age, which reflects the time SLE is most commonly diagnosed among women. Eleven studies did not report specific details about age. It is difficult to determine if the ethnicity of included participants was characteristic of the real-world SLE population, as one-third of studies did not report race, and those that did included a majority white population.

All (100%) participants had a diagnosis of SLE (since this was an inclusion criterion) and had at least one cutaneous lupus erythematosus (CLE) manifestation (or Raynaud’s) at baseline (or during the course of the study).

The severity of SLE among participants differed greatly both within studies and between studies. The most common scenarios were studies with SLE severities that ranged from mild to moderate, moderate to severe, or mild to severe. Other severity ranges were not represented by the studies. For example, one study included mild SLE only, no studies included moderate SLE only, no studies included severe SLE only, no studies reported on severe/very severe SLE, no studies included very severe SLE only, three studies reported on mild/moderate/severe/very severe SLE, four studies included moderate/severe/very severe SLE, and five studies provided insufficient information needed to characterise the range of SLE severity.

The duration of SLE diagnosis at baseline also varied greatly between studies and within studies; participants had recent diagnoses (the quickest diagnosis was reported at one month) or long-standing SLE (the longest time to diagnosis reported was 38 years), or studies included participants from both groups. Many (28) studies (47%) did not report the mean duration of time to SLE diagnosis at baseline at all. Among studies that did report this information, 20 studies (83%) had a mean duration of SLE diagnosis of between 6 and 10 years.

Most studies (36) did not report the severity of CLE diagnoses at baseline. For the 25 studies (40%) that did report, three studies included mild CLE in SLE disease, 13 had moderate CLE in SLE, and nine studies had severe CLE in SLE disease.

Only 4 of 61 studies (6%) commented on how long lesions of CLE In SLE had been present before the start of the studies. One study reported that lesions had been present for 3.56 years in one intervention group and for only 1.55 years in the comparator group. A second study reported that in more than 50% of participants, CLE lesions had been present for longer than 4 years. The third study reported that Raynaud’s had been present for 2 to 40 years before the start of the study. The last study reported that one of the inclusion criteria was that CLE lesions had to be present for at least 3 weeks.

Studies varied in how they presented CLE diagnoses. Of the 61 studies, 21 studies reported baseline CLE diagnoses in a non-standard fashion (different for every study); 18 reported cutaneous diagnoses “directly”; 14 reported them in the form of SLAM, BILAG, SLEDAI, or SLE Responder Index (SRI) mucocutaneous or integument domain; and 8 reported CLASI. Of the 18 studies that reported cutaneous diagnoses “directly”, the most commonly reported CLE diagnoses were discoid lupus (in 13 studies), malar rash (in 11 studies), oral ulcers (in 8 studies), photosensitivity (in 5 studies), alopecia (in 4 studies), Raynaud’s (in 3 studies), and cutaneous vasculitis/livedo reticularis (2 studies).

Our primary outcome, complete clinical response, was reported by 14 studies (only 23%), with most reporting lupus-specific rashes (malar, discoid, and subacute cutaneous lupus erythematosus (SCLE)) in SLE patients. Seven studies (11.5%) reported our second primary outcome, partial clinical response.

Fewer studies reported our secondary outcomes. Six studies reported a reduction (or change) in the number of flares of skin lesions; however, one-third of these studies did not provide enough information for separation of data for skin subgroup analysis. Only one study reported both an increase (or a change) in time to flare in cutaneous disease and relapse rate (or percentage of participants with relapse) in cutaneous disease when medications were stopped or reduced. The most commonly reported skin-specific measure of SLE disease activity was the CLASI score, with nine studies reporting this outcome. Of the other skin-specific SLE disease activity measures, five studies reported the SLAM integument domain, five reported the BILAG mucocutaneous domain, two the SLEDAI mucocutaneous domain, and one the SRI mucocutaneous domain. Only two studies assessed quality of life.

Adverse events were the outcomes most often reported: 55 studies (90%) reported severe adverse events, and 49 studies (80%) reported minor adverse events.

Some studies were limited by a short duration. Just over 60% of studies measured outcomes after less than a year, which may not have been long enough to identify certain adverse events. One of the main concerns with antimalarial medications is the risk of eye toxicity; however, this is detected only over the long term (over 5 to 20 years) (Marmor 2016), and the longest published study included in this review lasted 42 months (Tsakonas 1991).
Analysis

Finally, study reports did not always provide sufficient information to distinguish exact subsets, meaning that we were unable to separate participants with CLE in SLE from participants with non-SLE CLE in some situations, so we could not separate data for subgroup analysis.

Quality of the evidence

The included studies had notable methodological limitations. Therefore it is important to emphasise that any conclusions that we have drawn are reliant on primary studies with varying degrees of bias, including lack of reporting about allocation concealment methods and blinding of study assessors, and lack of reporting or failure to perform intention-to-treat data analysis. Treatments with demonstrated benefit were derived from evidence of limited quality, and the data are too sparse to allow firm conclusions about their relative efficacy.

When GRADE quality of evidence from comparisons in this review was rated as very low, low, or moderate, further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. The current body of evidence does not, therefore, allow robust conclusions.

Risk of bias

When the results of this review are interpreted, risk of bias in individual trials should be considered (Figure 3), and findings derived from studies with high or unclear risk of bias should be viewed with caution. We give reasons for downgrading the quality of the body of evidence for these comparisons in the Summary of findings tables (Summary of findings 1; Summary of findings 2; Summary of findings 3; Summary of findings 4; Summary of findings 5; Summary of findings 6). None of the included trials had low risk of bias across all domains. The most common reasons for high risk of bias were selective reporting followed by insufficient blinding of participants and personnel.

Indirectness of evidence

Overall, the outcomes presented in this review are fairly direct. Primary outcomes of complete clinical response and partial clinical response; secondary outcomes of clinical flares, time to flare, relapse rate, dermatology quality of life measures, CLASI, and other skin-specific measures of SLE disease activity; and adverse outcomes are of direct importance to patients and clinicians. Therefore, no outcomes were downgraded for indirectness.

Inconsistency of results

It was not possible to compare the statistical consistency or inconsistency of most results at this time due to the small number of studies, with only one study found for most interventions. We did not see unexplained high levels of statistical heterogeneity in pooled data.

Comparisons between studies were difficult to conduct due to differences in the timing of outcome assessments, clinical heterogeneity in skin outcomes reported (types of primary versus secondary outcomes), differences in the clinical populations studied (e.g. differences in disease severity and burden, possible relapsing/detransient disease), differences among clinical cutaneous subgroups noted in each study (lupus-specific versus lupus-non-specific skin symptoms), and heterogeneity in the semantic terms used by different study authors to describe lupus-specific and lupus-non-specific rashes.

We noted some inconsistency in results for chloroquine and methotrexate. For example, methotrexate was found to be more efficacious than placebo (greater resolution of malar or discoid rash) in one trial. Another head-to-head study showed that both methotrexate and chloroquine were efficacious and their efficacy was similar (no statistically significant differences). However, in another trial studying the presence of skin lesions and complete skin clearance, chloroquine was not favoured over placebo. At this time, no clear explanation is available for these inconsistencies. One possibility for the inconsistencies is that outcomes were measured in different ways in different studies or among different study populations. Another possibility is the low power noted in the study of chloroquine versus placebo, meaning that study findings did not reach statistical significance.

Imprecision of results

It was not possible to compare most interventions well because typically only one trial was included per comparison. Also few studies reported outcome data that could be incorporated into meta-analyses.

Most of the included trials had small numbers of participants and were imprecise due to small sample size and wide confidence intervals.

Studies with larger numbers of participants, which were therefore more precise, include the following: Fortin 2008; Petri 2004; Williams 1994. These studies investigated methotrexate versus placebo (Fortin 2008: Summary of findings 1), oral hydroxychloroquine versus placebo (Williams 1994: Summary of findings 2), and oral dehydroepiandrosterone (prasterone) versus placebo (Petri 2004: Summary of findings 3).

Another major contributor to imprecision is that the cutaneous signs found in lupus are varied and can be difficult to describe. In most studies, cutaneous lupus signs were not described with a high degree of precision. Also many studies used validated composite scores with domains for skin. Composite scores led to further challenges in interpreting evidence because data from varied cutaneous signs were pooled, which further decreased precision.

Publication bias

We could not assess for publication bias with statistical methods as each comparison included too few studies to test for this (e.g. by using a funnel plot).

However, by following ongoing studies longitudinally over the years, we have been able to observe the publication process over time from the stage of trial registration to final publication. Over this time, we have detected the following trials that were completed or terminated; however, no published data from these studies were ever made available: NCT00523588; NCT01498406; NCT01470313 NCT01470313; NCT01689025; NCT01709474; NCT02074020; NCT02265744; NCT02514967; NCT02711813, ChiCTR-12002402 NCT02975336; NCT01135459.

Statements from study investigators at http://www.clinicaltrials.gov regarding NCT01498406 (a study about
vitamin D) and NCT01470313 (a study on a new compound called PD-0360324) indicate that these studies were terminated for financial reasons. Both studies had planned CLASI outcomes.

The unpublished trials may constitute evidence of publication bias.

**Potential biases in the review process**

This review was derived from an extensive and broad search encompassing many databases over a significant time period and incorporating a diverse patient population from studies carried out around the world. For example, we searched the Virtual Health Library database, in addition to large biomedical bibliographic databases, and found unique studies that were not cited in other databases.

Our review of the bibliographies of identified randomised controlled trials (RCTs) yielded additional studies for inclusion in this review. One reason why these additional studies were identified in bibliographies and not by database search may be that keywords and abstracts listed for RCTs in the large biomedical databases may not completely reflect all cutaneous variables that are hidden in the full text of articles on SLE.

There is a high likelihood that most of the relevant published studies were identified. We attempted to conduct a comprehensive search for studies, but the fact that 13 studies have not yet been incorporated may be a source of potential bias. Unpublished studies may also constitute some evidence of publication bias. Moreover, the numerous ongoing studies currently in progress may alter the conclusions of this review in the future.

We minimised bias in the review process by ensuring that at least two review authors working independently (CWH and CM) selected studies and performed double data extraction, which helped to reduce the chance of bias during data collection. Two review authors (CW, CB) performed data entry as well as analysis.

Review methods may not have allowed for detection of rare adverse events, which may be a limitation.

Departures from the protocol can also be a source of bias in reviews. Differences between our protocol and our review are reported and examined in the Differences between protocol and review section. Relevant changes from the protocol that could have introduced bias to this review include narrowing of the scope of the search to exclude certain lower-yield databases (Google Scholar, Cochrane Musculoskeletal Register, Allied and Complementary Medicine Database (AMED), unpublished trial correspondence with authors, drug reference books and databases). We decided to exclude these sources for reasons of efficiency and practicality; however, this change may have resulted in some missed studies.

**Agreements and disagreements with other studies or reviews**

To date, three other detailed systematic reviews have examined cutaneous disease in systemic lupus erythematosus (Fairley 2020; Heath 2004; Jessop 2003).

Many other qualitative reviews have been completed: Callen 2004; Chang 2016b; Fett 2011; Kuhn 2010a; Kuhn 2010b; Kuhn 2017; Presto 2017; Walling 2009; Winkelmann 2013.

In addition, systematic reviews have been conducted that had a more limited focus in terms of interventions: Chasset 2017a; Chasset 2017b; Mok 2007; Sato 2001; Tzellos 2008.

Overall, our systematic review supports the conclusions of prior systematic and evidenced-based reviews. Moreover, our review identifies many additional RCTs not found by prior search methods nor cited in prior reviews.

**Systematic reviews**

Jessop 2003 summarised RCTs, observational studies, and case reports for cutaneous lupus erythematosus (discoid lupus erythematosus (DLE), SCLE, and SLE) for the following interventions: chloroquine or hydroxychloroquine, amodiaquine and quinacrine, combinations of antimalarials, topical steroids, oral steroids, intralesional steroids, azathioprine, clofazimine, dapsone, gold, methotrexate, phenytoin, retinoids, thalidomide, vitamin E, sunscreens, surgery, ultraviolet light, and laser treatment. These review authors described benefits and harms qualitatively for each of the interventions. Jessop 2003 identified three RCTs for discoid lupus erythematosus in SLE that described the following interventions (Meinao 1996; Tsakonas 1991; Williams 1994): chloroquine or hydroxychloroquine. These three RCTs are also included in the current review.

Compared to this review, Jessop 2003 presented differences in study eligibility criteria (included observational studies and case reports instead of focusing only on RCTs). Jessop 2003 also showed differences in participant diagnostic eligibility criteria (included CLE without SLE as well as CLE with SLE). Our review and Jessop 2003 included three of the same RCTs for CLE in SLE, and many of the same intervention classes were identified.

Heath 2004 searched the National Library of Medicine for RCTs, non-randomised controlled studies, uncontrolled studies, and case reports for cutaneous and non-cutaneous disease in SLE in both human and relevant animal studies. The following interventions for SLE were found and reviewed for evidence, benefits, and harms: antimalarials, thalidomide, methotrexate, calcineurin inhibitors (tacrolimus, ciclosporin), mycophenolate mofetil, azathioprine, cyclophosphamide, intravenous immunoglobulin G, leflunomide, nucleoside analogues (cladribine, fludarabine, cytarabine), biologics (anti-interleukin (IL)-10, rituximab, abetimus sodium (LBJ 394), CM-T412). Heath 2004 identified five RCTs for cutaneous SLE for the following interventions: antimalarials (Meinao 1996; Tsakonas 1991; Williams 1994), methotrexate (Carneiro 1999), and oral ciclosporin A and oral and intravenous corticosteroids (Dammacco 2000). These same five RCTs were identified independently in the current review.

Compared to this review, Heath 2004 had differences in study eligibility criteria (included non-randomised observational studies and case reports) instead of focusing only on RCTs (as we did in our review). Heath 2004 also had differences in participant diagnostic eligibility criteria (included non-cutaneous disease in SLE and relevant animal studies), whereas our review focused only on CLE in SLE in humans. Our review and Heath 2004 included five of the same RCTs for CLE in SLE, and many of the same intervention classes were identified.

Heath 2004 and Jessop 2003 were conducted much earlier than our review (16 and 17 years earlier, respectively) and therefore did
not identify some of the more recent monoclonal and biological therapies for CLE in SLE. Also, these reviews focused mainly on Western Medical traditions and did not assess any TCM treatments and looked at no or few complementary and alterative therapies.

Fairley 2020 conducted an extensive systematic review of the literature from 1990 to March 2019 and included clinical trials, observational studies, or case series of CLE, with or without SLE. This review identified the following treatments: topical calcineurin inhibitors, sun protection, R-salbutamol cream, antimalarials, synthetic disease-modifying antirheumatic drugs (DMARDs), retinoids, Thalomid (thalidomide, Celpgene)/Revlimid (lenalidomide, Celpgene), biologic therapies, IV immune globulin, laser, and other therapies.

Fairley 2020 had differences in study eligibility criteria (non-randomised clinical trials, observational studies, or case series, rather than RCTs only). Fairley 2020 also had differences in participant diagnostic eligibility criteria (included CLE with SLE and CLE without SLE). In addition, Fairley 2020 focused on mainly on Western Medical traditions and looked at relatively few complementary and alterative therapies and no TCM treatments. Overall, Fairley 2020 searched fewer records (6637 compared with 9706 in our review), was limited to English language papers (compared with no language restrictions for our review), was smaller (7343 participants identified compared with 11,232 participants in our review), identified fewer intervention categories (11 compared with 22 in our review) over fewer years (from 1990 to March 2019 compared with as far back as 1946 (with MEDLINE/Ovid) to September 2020 in our review), and found fewer RCTs (only 22 in total for CLE with and without SLE compared with 61 for CLE in SLE alone in our review). We also included ongoing studies and unpublished studies, whereas Fairley 2020 included published studies only.

In terms of similarities, both reviews were conducted at a similar time and many of the same intervention classes were identified. Both reviews also had two review authors independently review abstracts, a detailed PRISMA diagram, and risk of bias analyses. Fairley 2020 extracted "data pertaining to treatment response" and noted "highly heterogenous results". These review authors were "unable to conduct meta-analysis due to heterogeneity of included studies in terms of study design and protocol, treatments, patient populations, and definitions of CLE subtypes where these were recorded" and therefore summarised the information narratively. In contrast, our review was able to conduct some quantitative and pooled data analyses, likely due to a more limited review scope (CLE in SLE only), although our analyses were also restricted due to many of the same issues with data heterogeneity. Of the 22 RCTs included in Fairley 2020, only 14 pertained to CLE in SLE: 13 of these had already been independently identified by our review (Bezerra 2005; Furie 2011; Furie 2015c; Furie 2016b; Islam 2012; Kuhn 2011; Navarra 2011; Stohl 2017; Szepeckiewicz 2013; Tzung 2007; Van Vollenhoven 2018; Wallace 2018; Yokogawa 2015). Of the 22 RCTs identified for Fairley 2020, 8 were CLE without SLE and therefore were excluded by our review, and 1 - Werth 2017c - was included in 1 - Studies awaiting classification as an RCT of potential interest, which we will evaluate in detail and will likely integrate into our review at the next update. Our review identified an additional 48 published RCTs for CLE in SLE that had not been identified in Fairley 2020.

Systematic reviews with more limited focus of interventions

The following systematic reviews had a more limited focus on interventions for CLE and SLE: Chassét 2017a; Chassét 2017b; Mok 2007; Sato 2001; Tzellos 2008.

Sato 2001 focused on methotrexate and did not identify any additional RCTs beyond Carneiro 1999.

Mok 2007 focused on mycophenolate mofetil for non-renal manifestations of SLE and did not identify any additional RCTs beyond those already independently identified in this review.

Tzellos 2008 focused on the interventions of topical tacrolimus and pimecrolimus and did not identify any additional RCTs beyond those already identified in this review.

Chassét 2017a focused on antimalarials for CLE and did not identify any additional RCTs beyond those already independently identified in this review.

Chassét 2017b focused on thalidomide for CLE and did not identify any additional RCTs beyond those already independently identified in this review.

Rirash 2017, from the Cochrane musculoskeletal group, systematically reviewed in detail the evidence for calcium channel blockers for primary and secondary Raynaud’s phenomenon.

Qualitative evidence-based reviews

The following reviews focused on the related topic of CLE in SLE; however they were not systematic reviews and/or did not contain any quantitative analyses: Callen 2004; Fett 2011; Kuhn 2010a; Kuhn 2010b; Walling 2009; Winkelmann 2013). These reviews did incorporate varying degrees of evidenced-based principles and identified many of the same RCTs described below.

Callen 2004 published a useful table of evidence, which cited one RCT for sunscreen (Stege 2000), one retrospective study for sunscreen (Herzinger 2004), one RCT for clofazimine (Bezerra 2005), and the same RCTs noted by Jessop 2009.


Kuhn published an extensive two-part update of therapeutic options: Kuhn 2010a; Kuhn 2010b. This qualitative evidence-based review cited the systematic review of Jessop 2003 and the following RCTs: Jemec 2009; Tzung 2007 (DLE only); McGrath 1996; Polderman 2001; Ruzicka 1992 (discoid and SLE only); and Bezerra 2005.

Fett 2011 reviewed and assessed evidence-based treatment options for both CLE and SLE. No additional RCTs beyond those already independently noted in this review were identified.

Winkelmann 2013 reviewed and assessed treatment options for cutaneous lupus erythematosus based on Oxford Centre for Evidence-Based medicine criteria. No interventions were found to meet Level 1 evidence, defined as systematic review of randomised trials or n-of-1 trials. Several interventions were found to meet Level 2 evidence, defined as "randomised trial" or "observational study with dramatic effect": − sunscreen (Kuhn 2011a), corticosteroids.
Interventions for cutaneous disease in systemic lupus erythematosus (Review)

(Roenigk 1980), tacrolimus (Kuhn 2011; Tzung 2007), pimecrolimus (Barikbin 2009; Sticherling 2007), R-salbutamol (Jemec 2009), hydroxychloroquine (Ruzicka 1992), chloroquine (Bezerra 2005), retinoids (Ruzicka 1992), and clofazimine (Bezerra 2005).

Chang 2016b reviewed therapeutic options for CLE including cutaneous disease in systemic lupus erythematosus. No additional RCTs beyond those already independently noted in this review were identified.

Kuhn 2017 presented European Consensus-Based (SZK) guidelines for treatment of cutaneous lupus erythematosus guided by the European Dermatology Forum (EDF) in co-operation with the European Academy of Dermatology and Venereology. No additional RCTs beyond those already noted in this review were identified.

Presto 2017 reviewed new biological therapies in CLE. No additional RCTs beyond those already independently noted in this review were identified.

Scope of the review

We recognise that one of the limitations of our review, in particular for clinicians, is that the scope is limited to only participants who had a diagnosis of "CLE with SLE" and we excluded "CLE without SLE" or "exclusion category 3" as described in Table 4. Details about each excluded study are given in Excluded studies.

Excluding the "CLE without SLE" group might be considered an unnecessarily narrow focus if the response of cutaneous lupus to treatment is sufficiently similar in people with and without a full diagnosis of SLE.

If we had included data from the 12 RCTs from "exclusion category 3", we would have had 12 additional studies involving participants with CLE without SLE. However, given the small number of studies per intervention and data heterogeneity, overall, inclusion of these data would still not permit meta-analysis to any meaningful degree.

More specifically, for hydroxychloroquine, a commonly used systemic treatment for CLE in clinical practice, pooling all the CLE RCT data (with and without SLE), would only increase the number of identified RCTs (Levy 2001; Tsakonas 1991; Williams 1994; Yokogawa 2015) from 5 to 6 with the addition of Ruzicka 1992, a comparison study of acitretin versus hydroxychloroquine. The impact on our conclusions is unlikely to be significant given the heterogeneity of data resulting in an inability to perform meta-analysis.

Our conclusions are dependent on the relatively few RCT studies that met our inclusion criteria. Fairley 2020, is a systematic review that included both RCT and non-RCT data for CLE (with and without SLE) (Agreements and disagreements with other studies or reviews). Of the 107 trials identified by Fairley 2020, only 22 trials were RCTs and 85 were non-controlled trials, observational studies or case series. We, in contrast, identified 61 RCTs for CLE with SLE alone in our review. Therefore, the broader focused review (Fairley 2020) did not yield more RCTs.

Our choice to focus on RCTs potentially misses some comparisons of interest. For example, with regard to hydroxychloroquine, Fairley 2020 identified a total of 15 hydroxychloroquine trials (one RCT [Yokogawa 2015] and 15 observation studies), whereas we identified 5 RCTs and 2 non-RCT trials using our inclusion criteria. In all, Fairley 2020 identified 22 studies for antimalarials (hydroxychloroquine, chloroquine and quinacrine) of which 2 were RCTs, 2 were non-controlled trials, 16 were observational studies and 3 were case series. With regard to methotrexate, we identified 3 RCTs whereas Fairley 2020 identified 1 RCT and 2 observational trials.

Overall, however, the conclusions of our narrower focused review and the broader focused review of Fairley 2020 ended up being similar. For example, for hydroxychloroquine, Fairley 2020 noted that there was "low to moderate evidence" of benefit from hydroxychloroquine with "about 50% response rates". Fairley 2020 also concluded that CLE subtype subgroup data was "limited". For methotrexate, Fairley 2020 noted that "limited evidence supports benefit, perhaps equivalent to chloroquine" and CLE subtype subgroup data was "limited". Our conclusions for the interventions of hydroxychloroquine and methotrexate are similar and we also found it was difficult to distinguish the subgroups in our review. So to summarise, despite the differences in scope, our conclusions were similar.

Other limitations that we acknowledge are as follows: methotrexate is currently not typically used for CLE and is being relatively highlighted in our review due to the positive results, although these come from only a small number of RCTs, as well as due to our more narrow scope (excluding CLE in the absence of a full SLE diagnosis): both factors appear to weigh the findings in favour of methotrexate. On the other hand, hydroxychloroquine is commonly used for CLE and is being relatively downplayed by our review, due to our focus on RCTs and given that the weight of the clinical evidence for hydroxychloroquine lies in the many non-RCT trials. Therefore clinicians should exercise caution when evaluating the available evidence for clinical decision making. We also note that the three types of CLE (acute, subacute and chronic) are not clearly distinguished in this review due to challenges with heterogeneous reporting in the included studies.

Understanding which interventions are of particular importance to clinicians, we will continue to monitor clinically important but excluded trials, especially those which include people without a full diagnosis of SLE (exclusion category 3) in the future. If future data are sufficiently homogeneous based on a sensitivity analysis, it may be possible to pool data for CLE (with and without SLE) in future updates of this review.

Authors' conclusions

Implications for practice

We emphasise that clinicians should use caution in translating the findings of this review into clinical practice. Available evidence consists mainly of small randomised controlled trials (RCTs) for many of the interventions, resulting in imprecision and considerable uncertainty. We found only limited-quality evidence, so we are unable to draw firm conclusions regarding the effects of interventions for cutaneous disease in systemic lupus erythematosus (SLE). The included studies assessed a range of interventions, and there were few opportunities to combine results in meta-analyses.

Key interventions with potential benefit compared with placebo derived from low- to moderate-quality quantitative evidence were
as follows: methotrexate, dehydroepiandrosterone (DHEA), and chloroquine (complete clinical clearance), and hydroxychloroquine (clinical flare).

Treatments with possible benefit compared with placebo derived from mainly low-quality evidence (narrative data) reported by study investigators were as follows: anifrolumab, baricitinib, belimumab, BIIB059, CC-220, cosmetic camouflage, nifdefipine, SM101, ustekinumab, and ultraviolet light (UVA)-1 phototherapy.

Treatments without demonstrated benefit compared with placebo were intravenous abatacept, oral fish oil, oral ginsenosides, subcutaneous lulizumab pegol, oral nicardipine, oral prednisone, repository corticotropin gel (subcutaneous injections), intravenous sirukumab, and oral zileuton.

Treatments with more possible harms than benefits included copper and bortezomib. Oral copper did not demonstrate efficacy and demonstrated some evidence of serious harms including six withdrawals from the study and three hospital admissions (one for stroke and two for chest infection) based on narrative reports from authors. Although bortezomib was reported to result in improved skin in one patient, a very high rate (87.5%) of severe side effects led to discontinuation of the medication in other patients (narrative report).

In terms of achieving complete clinical response, we found the following results.

- Methotrexate or chloroquine may increase this outcome when compared with placebo (both low-quality evidence).
- Little to no difference may be seen between ciclosporin versus azathioprine, or methotrexate versus chloroquine, in achieving this outcome (both low-quality evidence).

This outcome was not reported for the comparison hydroxychloroquine versus placebo.

In terms of achieving partial clinical response, we found the following results.

- When compared with placebo, hydroxychloroquine may increase this outcome, but the 95% confidence interval (CI) indicates that hydroxychloroquine may make no difference to or may decrease this outcome (low-quality evidence).

This outcome was not reported for the following comparisons: oral methotrexate versus placebo; oral chloroquine versus placebo; oral ciclosporin versus oral azathioprine; and oral methotrexate versus oral chloroquine.

In terms of reducing the number of clinical flares, we found the following results.

- Hydroxychloroquine probably increases this outcome when compared with placebo (moderate-quality evidence).
- There may be no difference between methotrexate and placebo in effects on this outcome, but the 95% CI indicates that there may be more or fewer flares with methotrexate (moderate-quality evidence).

This outcome was not reported for the following comparisons: oral chloroquine versus placebo; oral ciclosporin versus oral azathioprine; and oral methotrexate versus oral chloroquine.

We found limited data for adverse events, and reports were discrepant, but hydroxychloroquine, chloroquine, and methotrexate have well-documented adverse effects including gastrointestinal manifestations, liver problems, and retinopathy for hydroxychloroquine and chloroquine, and teratogenicity during pregnancy for methotrexate.

Studies awaiting classification and numerous ongoing studies may alter the conclusions of this review, especially given the fortunate development that more studies than ever before are reporting skin-specific outcomes such as the Cutaneous Lupus Disease Area and Severity Index (CLASI).

**Implications for research**

This review highlights that most RCTs for SLE have not reported skin-specific outcomes. Researchers are encouraged to collect and report skin-specific outcomes given the importance of such information to patients and clinicians. Studies have shown that skin disease is more important to participants than internal organ damage (Tebbe 1997). When possible, dermatologists should be included in future SLE research teams to help with the collection and analysis of meaningful skin-specific outcomes. The CS-COUSIN core outcome initiative is a resource that future SLE trial authors can consult to select and report uniform skin-specific outcome measures (CS-COUSIN 2019). The use of uniform skin-specific outcome measures, with aligned timing of outcome assessment, will increase the possibility that future systematic reviews and meta-analyses can pool and analyse meaningful and homogenous data.

Different general systemic lupus activity measures have been compared for their relevance to the skin, and Parodi 2000 concluded that the most reliable general SLE activity measurement instrument for the skin is the SLAM score (integument domain). However, none of the general SLE activity measurement instruments was found to be entirely satisfactory for the purposes of dermatologic research, and for this reason, a skin-specific disease activity index called the Cutaneous Lupus Area and Severity Index (CLASI) was developed (Albrecht 2007; Bonilla-Martinez 2008; Krathen 2008). Skin-specific composite outcome measures such as CLASI and dermatology-specific quality of life measures should be used more often in studies to provide more patient-centred data and because skin outcomes are extremely important to patients yet are relatively understudied. Wider use of standardised and validated dermatology quality of life (QoL) scores for trial participants diagnosed with this often disabling condition would provide data to aid treatment decisions. For example, dermatology QoL scores would help investigators to monitor change in dosage or drug or cessation of therapy.

Treatments may have effects of differing magnitude or direction for each of the different manifestations, requiring careful consideration and weighing of risks and benefits depending on individual preferences. Future studies need to take into account these potential complexities by measuring relevant outcome variables.

Systemic oral or intravenous steroids are often considered standard of care in SLE. More RCTs on the optimal use of systemic steroids and ideal combinations with steroid-sparing agents would be useful for clinicians in practice.
Although studies were performed in a wide range of countries around the world including multiple countries in North America, South America, Europe, Asia, and Australia, only three RCTs included participants in Africa (Clowse 2015; Merrill 2016; Merrill 2018), and two RCTs included participants in the Middle East (Merrill 2016; Merrill 2018). Only one RCT involved the paediatric population (Lima 2016).

In addition, virtually no studies have looked at CLE in SLE treatment and outcomes over much longer periods of time. Longer-term studies of CLE in SLE should be designed, so that the extent of relief from cutaneous symptoms from participants' perspectives (symptoms, quality of life) and safety and efficacy should be included in the design of such studies. We do recognise that long-term studies may be difficult to perform for reasons including expense and attrition, with fewer participants remaining in the study over long periods of time.

Future research studies do not necessarily need to compare interventions against placebo but could be head-to-head intervention trials that would help clinicians better understand the efficacy and trade-offs of different interventions.

It is known that cutaneous SLE disease subgroups are clinically heterogeneous and correspond to different prognoses and responses to treatment. For example, lupus-non-specific skin symptoms are associated with higher SLE disease severity than lupus-specific skin symptoms (Parodi 2000; Zecevic 2001). Therefore, combining data on subgroups of cutaneous SLE may not always be appropriate. Studies also need to be designed to detect possible differences in efficacy depending on population subsets of those with cutaneous lupus. Ideally as many details about the exact subsets of cutaneous SLE should be reported in clinical studies, namely, details about lupus-specific versus lupus-non-specific disease and specific types of skin involvement within these categories (such as oral ulcers versus alopecia) should be included to allow subgroup analysis.

In general, the quality of studies could be enhanced by improving reporting and following recommended experimental design in the areas of allocation, methods, blinding of assessors, and intention-to-treat analysis. Strand 2004 summarises some of the concepts related to the design of studies in SLE. It is also recommended that researchers perform a formal sample size calculation to ensure that trials are adequately powered that any meaningful effects can be detected and highlighted. Authors of SLE trials are encouraged to publish their data on CLE. If their typical specialty journals have word or space limitations, study authors could consider submitting the data to dermatology-oriented journals as a separate paper, because dissemination of this collected information would be valuable for dermatology researchers, clinicians, and patients. Finally, authors of negative studies should be encouraged to publish, so that data are available for clinical interest and for possible meta-analysis in the future.

ACKNOWLEDGEMENTS

We are grateful to Dr Carlos Cesar Cusmanich for his contribution to the protocol and review.

Cora W Hannon would also like to thank her advisor at the Harvard School of Public Health, Marcia A Testa, PhD, MPH. Many thanks to Jan Wang, NP, for help with translation of an article published in Chinese.

The results section of this review was checked using RevMan HAL v 4.0.

The Cochrane Skin editorial base wishes to thank Sue Jessop, Cochrane Dermatology Editor for this review; Victoria P Werth, clinical referee; Matthew Grainge, Statistical editor; Dolores Matthews who copy-edited the review; and Nicole Pitcher who wrote the plain language summary.
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Merrill 2010b

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Petri 2010


Petri 2013


Interventions for cutaneous disease in systemic lupus erythematosus (Review)
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Interventions for cutaneous disease in systemic lupus erythematosus (Review)
CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Andrade-Ortega 2009

Methods
This was a randomised parallel-group open and controlled trial

Participants

Inclusion criteria
- 19 participants with systemic lupus erythematosus (SLE) by American College of Rheumatology (ACR) criteria and cutaneous lupus erythematosus (CLE) (three with cutaneous vasculitis lesions)
- Sex: 18 women, 2 men
- Race: not specified (study from Mexico)
- Mean age (years): 35.7 ± 12.1 standard deviation (SD)

Exclusion criteria
- Pregnancy
- Breast-feeding
- Use of other immunosuppressant medication
- Active infection
- Hepatitis

Interventions

Intervention (n = 10)
A: rituximab 1 gram infusion over 4 hours (with premedication of hydroxyzine, paracetamol, and dexamethasone 8 mg intravenous (IV)) on days 1 and 15 of the study. Medication was re-administered if flaring after the sixth month. Total study duration was 12 months

Intervention group also received steroids (1 gram IV for 3 doses or 1 mg/kg/d with gradual taper) for 12 months

Control intervention (n = 9)

References to other published versions of this review

Hannon 2008b

* Indicates the major publication for the study
**Andrade-Ortega 2009** (Continued)

B: cyclophosphamide IV pulse (+ "chemoprotectant" medication Mesna at 80% of cyclophosphamide dose) each month for 6 months, then every 3 months until the end of the study (standard treatment)

Control group also received steroids (1 gram IV for 3 doses or 1 mg/kg/d with gradual taper) for 12 months

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Primary outcomes</th>
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<tbody>
<tr>
<td></td>
<td>None were reported</td>
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<td>Adverse events</td>
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<td>Multiple hospitals in Mexico</td>
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<tr>
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**Risk of bias**

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<th>Authors' judgement</th>
<th>Support for judgement</th>
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<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>A randomisation table was used</td>
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<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>No details about allocation concealment were given</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>High risk</td>
<td>This was an open study (not blinded)</td>
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<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>High risk</td>
<td>This was an open study (not blinded)</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Low risk</td>
<td>All participants were included in the analysis (no dropouts). Study authors did not report performing an intent-to-treat (ITT) analysis. We could not verify that ITT was performed by examining the data</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>The study protocol was not available. Primary outcomes were reported. Negative data were reported</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>Study authors presented a table with baseline characteristics of groups. There was no evidence of baseline imbalance between groups. Insufficient information is available to assess whether an important risk of other bias exists</td>
</tr>
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</table>

**Bezerra 2005**

**Study characteristics**

**Methods**

This was a parallel-group triple-blind randomised controlled trial

**Participants**

**Inclusion criteria**
• 33 outpatient participants with SLE by ACR criteria and cutaneous disease (9 with malar rash, 3 with subacute cutaneous lupus erythematosus (SCLE) annular type, 4 with SCLE psoriasiform, 8 with localised discoid lupus erythematosus (DLE), 18 with disseminated DLE)
• Sex: 31 female, 2 male
• Age: mean was 34.0 years in the clofazimine group and 34.4 years in the chloroquine group
• Race: 25 white, 8 mulatto

**Exclusion criteria**

• Use of same medications as trial in 3 months before the trial
• Pregnancy
• Lactation
• Lupus with neurological, renal, or haematological involvement
• Lupus requiring “aggressive treatment”

**Interventions**

**Intervention (n = 16)**

A: clofazimine 100 mg/d for 6 months

**Control intervention (n = 17)**

B: chloroquine 250 mg/d for 6 months

In addition, participants were on stable prednisone doses during the trial and sunscreen was applied twice a day

**Outcomes**

**Primary outcomes**

Complete rash clearance (total response = score 6) at baseline, 1, 2, 4, and 6 months

Partial rash clearance (good response = score 5 = greater than 50% response) at baseline, 1, 2, 4, and 6 months

**Secondary outcomes**

Systemic lupus erythematosus disease activity index (SLEDAI) (Mexican version) but skin-specific domains were not extractable from the article

Adverse events

**Funding source**

Clofazimine was donated by Health Secretary of State of Rio Grande do Norte. STIEFEL Pharmaceutical Company donated the sunscreen used in the study

**Location**

University Hospital of Universidade Federal do Rio Grande do Norte (UFRN), in Natal, Brazil

**Notes**

**Risk of bias**

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<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
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<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
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<td>Comment: insufficient information was given on the sequence generation method used</td>
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<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>No details about allocation concealment were given</td>
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</table>
**Cochrane Library**

**Cochrane Database of Systematic Reviews**

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**Bezerra 2005** (Continued)

| Blinding of participants and personnel (performance bias) | Low risk | Quote: “clofazimine and chloroquine were placed into identical standard packages, making it impossible to identify their contents”
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<td>All outcomes</td>
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| Blinding of outcome assessment (detection bias) | Low risk | Quote: “patients were examined by two observers who were blinded to the treatment group”
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<td>All outcomes</td>
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| Incomplete outcome data (attrition bias) | Low risk | Quote: “patients were withdrawn and analysed according to assigned protocol”
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<tr>
<td>All outcomes</td>
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</table>

| Selective reporting (reporting bias) | Unclear risk | Study protocol was not available. Study authors reported pre-specified outcomes regardless of statistical significance |

| Other bias | Unclear risk | Study authors presented a table of baseline demographics showing that no evidence of baseline imbalance among treatment groups. Information was insufficient to assess whether an important risk of other bias exists |

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**Bootsma 1995**

**Study characteristics**

**Methods**

This was a parallel-group open randomised controlled trial

**Participants**

**Inclusion criteria**

- 156 participants with SLE by ACR criteria and CLE (77 participants had malar rash, 38 had discoid lupus, 73 had photosensitivity, 26 had oral ulcers at baseline)
- 46 patients had a confirmed rise in double-stranded deoxyribonucleic acid (DNA) after randomisation and were divided into 2 groups (24 who received conventional treatment and 22 who received "early treatment"). The early treatment group at baseline included 12 participants with malar rash, 4 with discoid lupus, 9 with photosensitivity, and 8 with oral ulcers; the conventional treatment group at baseline included 12 participants with malar rash, 5 with discoid lupus, 12 with photosensitivity, and 7 with oral ulcers
- Sex: 133 female, 23 male
- Age: mean was 38.6 years, with range of 19.2 to 77.2 years
- Race: 131 white, 22 Asian, 3 black

**Exclusion criteria**

- Pregnant
- Contraindications to treatment with steroids

**Interventions**

**Intervention (n = 22)**
A: "early treatment" with prednisone and/or cytotoxic agents (IV cyclophosphamide or oral azathioprine) based on lab results of rise in anti-double-stranded DNA (rather than waiting for clinical signs of relapse) and monitored over 6 months

**Control intervention (n = 24)**

B: "later treatment based on clinical relapses only" (so called conventional treatment, initiated on appearance of clinical flare) of same prednisone and/or cytotoxic agent (IV cyclophosphamide or oral azathioprine) as interventional group was monitored over 6 months

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Primary outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>None were reported</td>
<td></td>
</tr>
</tbody>
</table>

**Secondary outcomes**

Adverse events: minor and severe adverse events were described

**Funding source**

Funding was provided by a grant from the Dutch League against Rheumatism

**Location**

3 university hospital centres in the Netherlands

**Notes**

**Risk of bias**

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Quote: &quot;within each of four strata, block randomisation was used&quot;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Comment: no details about the method of sequence generation were given</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Quote: &quot;randomisation was carried out by two independent people not informed about clinical data&quot;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Comment: most likely, allocation concealment was sufficient</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>High risk</td>
<td>Blinding was not discussed</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>High risk</td>
<td>Blinding was not discussed</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>Detailed tables of distribution of patients and reasons for withdrawal were provided. Intent-to-treat (ITT) analysis was not mentioned by study authors directly; however by examining the data, we were able to confirm that ITT was performed</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>Study protocol was not available. Pre-specified outcomes were reported regardless of statistical significance</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>Study authors presented a table of baseline demographics and characteristics of treatment groups, and there was no evidence of baseline imbalance. Information was insufficient to assess whether an important risk of other bias exists</td>
</tr>
</tbody>
</table>
### Carneiro 1999

#### Study characteristics

**Methods**

This was a parallel-group randomised placebo-controlled trial

**Participants**

**Inclusion criteria**
- 41 participants with SLE by ACR criteria and with CLE (28 with cutaneous discoid and/or malar rash at the beginning of the study)
- Sex: 39 female, 2 male
- Age: mean 32.2 years in methotrexate group, 30.2 years in placebo group
- Race: 19 white, 22 non-white

**Exclusion criteria**
- Creatinine ≥ 2.0 mg/dL
- Contraindications to use of methotrexate
- Recent use of antimalarials or immunosuppressive medications
- Pregnancy
- Nursing
- Life-threatening SLE
- Loss of renal function

**Interventions**

**Intervention (n = 20)**

A: methotrexate 15 to 20 mg per week (dosing based on weight - 15 mg for participants < 50 kg, 20 mg for participants > 50 kg) for 6 months

Participants were also on prednisone

**Control intervention (n = 21)**

B: placebo

Participants were also on prednisone

**Outcomes**

**Primary outcomes**

Discoid or malar rash present at 6 months (event = rash; non-event = clearance)

**Secondary outcomes**

Mean Systemic Lupus Erythematosus Activity Index (SLEDAI) scores (no standard deviation given in the study)

Adverse events: reported and listed in table and analysed

Mean prednisone doses (no standard deviation given)

**Funding source**

Funding source was not stated

**Location**

Rheumatology Clinic at Universidade Federal de Sao Paulo, Sao Paulo, Brazil

**Notes**

**Risk of bias**

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation</td>
<td>Unclear risk</td>
<td>Quote: &quot;patients entering study were numbered consecutively and random-ized into two groups&quot;</td>
</tr>
</tbody>
</table>
**Cochrane Database of Systematic Reviews**

### Carneiro 1999 (Continued)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Risk of Bias</th>
<th>Description</th>
</tr>
</thead>
</table>
| **Allocation concealment** (selection bias) | Unclear risk | Quote: "only the physician who presented the randomisation knew which drug corresponded to A or B"  
Comment: although not completely clear from information given by study authors, allocation concealment was likely sufficient |
| **Blinding of participants and personnel** (performance bias) | Low risk | Quote: "medications were dispensed by one staff member not involved in any other activities in the trial"  
Comment: methods used by study authors were probably sufficient to maintain blinding |
| **Blinding of outcome assessment** (detection bias) | Low risk | Quote: "rheumatologist who evaluated patients did not know which patients were taking methotrexate or placebo"  
Comment: methods used by study authors were probably sufficient to maintain blinding |
| **Incomplete outcome data** (attrition bias) | Unclear risk | Follow-up was complete in 37 of 41 participants (90%), with 4 of 41 participants (10%) lost to follow-up. Two placebo participants dropped out due to severe flare of disease requiring hospitalisation. In the methotrexate group, 1 patient dropped out due to pulmonary tuberculosis, and the other due to urticaria/dyspepsia. Intention-to-treat analysis was not stated and could not be confirmed as performed by examination of published data |
| **Selective reporting** (reporting bias) | Unclear risk | Study protocol was not available. Planned outcomes including those that were not statistically significant were reported in the results section |
| **Other bias** | Unclear risk | Study authors included a table of baseline characteristics of treatment groups, and there was no evidence of baseline imbalance. Information was insufficient to assess whether an important risk of other bias exists |

### Clowse 2015

#### Study characteristics

<table>
<thead>
<tr>
<th>Methods</th>
<th>This was a report of 2 phase 3 randomised, double-blind, parallel-group, multi-arm, placebo-controlled trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td><strong>Inclusion criteria</strong></td>
</tr>
</tbody>
</table>
| | • 1584 participants with SLE (by ACR criteria), of whom 793 were participants in the Embody 1TM trial and 791 in the Embody 2TM trial; Active skin involvement of at least 2B in the British Isles Lupus Assessment Group (BILAG) mucocutaneous domain was one of the criteria that permitted inclusion in this study; however details about exact number of participants with a diagnosis of cutaneous disease were not given  
• Sex: not given  
• Race: not given  
• Age: mean: not given; however patients were 18 years of age or older |
| | **Exclusion criteria** |
| | • "BILAG grade A" renal or central nervous system (CNS) domain scores |
| Interventions | **Intervention** |

---

**Interventions for cutaneous disease in systemic lupus erythematosus (Review)**  
Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
C: (n = 263) placebo plus SOC therapies

**Outcomes**

**Primary outcomes**
None were reported

**Secondary outcomes**
None were reported

**Funding source**
Commercial funding was provided by UCB Pharma, Monheim, Germany, and Brussels, Belgium

**Location**
This multi-centre study was conducted in North and South America, Europe, Australia, Asia, and Africa

**Notes**
NCT1262365 (Embody 1TM), NCT1261793 (Embody 2TM)

**Risk of bias**

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Randomisation was stated; however no details about methods were given</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>No details about the randomisation method were given, so it is not clear whether randomisation was centralised</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>Low risk</td>
<td>Study authors stated that this was a &quot;double blind&quot; study; however more details were not given</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Unclear risk</td>
<td>Details given in the study were insufficient to assess whether assessors were blinded</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Unclear risk</td>
<td>Details about withdrawals were given. The study completion rate was approximately 67% for both trials. Intent-to-treat analysis was performed by study authors. Missing data were imputed as &quot;worst possible outcome&quot;</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>High risk</td>
<td>Study protocol was not available. All primary outcomes at 48 weeks were reported. Study authors had stated that secondary outcomes included BILAG-based Combined Lupus Assessment (BICLA) response at various time points (12, 24, and 36 weeks); however these results were not reported</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>Study authors included a table of baseline characteristics, and no evidence of baseline imbalance was noted between treatment groups. Information was insufficient to assess whether an important risk of other bias exists</td>
</tr>
</tbody>
</table>
This was a multi-centre open prospective randomised parallel-group pilot study

**Inclusion criteria**
- 18 participants with SLE by ACR criteria and with CLE (9 participants with discoid erythema, 8 with malar rash, 1 with oral/nasopharyngeal ulcer)
- Sex: 14 women, 4 men
- Race: not stated
- Age: median age 30 years in treatment group, 29 years in placebo group

**Exclusion criteria**
- Very severe SLE
- Pregnant women
- Contraindications to ciclosporin
- Alcohol abuse
- Malabsorption

Intervention (n = 10)
A: intravenous 6-methylprednisolone (3 boluses (1 gram)) followed by oral cyclosporine A (< 5 mg/kg/d) plus oral prednisone 0.5 to 1 mg/kg/d reduced by 5 mg/d every 2 weeks for 12 months, with follow-up for 24 months

Control intervention (n = 8)
B: oral prednisone alone

Primary outcomes
Numbers of participants with resolution of SLE criteria

Secondary outcomes
Adverse events

Funding source
Funding was not stated

Location
Outpatient clinic in Italy

Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>No information was given, other than that the study was randomised</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>No details were given</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>High risk</td>
<td>This was an open study (no blinding)</td>
</tr>
</tbody>
</table>

**Interventions for cutaneous disease in systemic lupus erythematosus (Review)**
Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
### Dammacco 2000 (Continued)

<table>
<thead>
<tr>
<th>Blinding of outcome assessment (detection bias)</th>
<th>High risk</th>
<th>This was an open study (no blinding)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>Study authors accounted for all enrolled patients and gave reasons for withdrawals from the study. Study was completed by 12 of 18 participants (66%). Study authors did not state that they had performed an intention-to-treat (ITT) analysis. We were able to verify that ITT analysis was indeed performed by examining the data</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>Study protocol was not available. Planned outcomes from the methods section were reported in the results</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>Study authors provided a table of baseline data, and there was no evidence of imbalance between treatment groups. Information was insufficient to assess whether an important risk of other bias exists</td>
</tr>
</tbody>
</table>

### Duffy 2004

**Study characteristics**

<table>
<thead>
<tr>
<th>Methods</th>
<th>This was a parallel-group double-blind randomised double placebo-controlled trial with factorial design</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Participants</strong></td>
<td><strong>Inclusion criteria</strong></td>
</tr>
<tr>
<td></td>
<td>- 65 participants with SLE by ACR criteria started the study; out of 52 SLE participants who finished the study, the following had CLE: 30 with malar rash, 3 with discoid rash, 37 with photosensitivity, 32 with oral ulcers</td>
</tr>
<tr>
<td></td>
<td>- Sex: ratio 9:1 women:men</td>
</tr>
<tr>
<td></td>
<td>- Age: mean 46.6 years, range 22 to 76 years</td>
</tr>
<tr>
<td></td>
<td>- Race: 65 white, 0 non-white</td>
</tr>
<tr>
<td></td>
<td><strong>Exclusion criteria</strong></td>
</tr>
<tr>
<td></td>
<td>- Requiring ongoing treatment for life-threatening disease</td>
</tr>
<tr>
<td></td>
<td>- Needing more than 10 mg prednisone daily</td>
</tr>
<tr>
<td></td>
<td>- Recent vitamin usage</td>
</tr>
<tr>
<td></td>
<td>- Allergies to copper or fish</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Interventions</th>
<th><strong>Intervention</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A: (n = 13) fish oil and copper in the following forms: daily supplements for 24 weeks (6 months) of 3 × 1 gram of omega-3 Max eicosapentaenoic acid (EPA) fish oil capsules (containing 18% EPA of 180 mg and 12% docosahexaenoic acid (DHA) of 120 mg) and/or 3 mg copper per day (copper diglycinate amino acid complex)</td>
</tr>
<tr>
<td></td>
<td><strong>Control interventions</strong></td>
</tr>
<tr>
<td></td>
<td>B: (n = 14) fish oil and placebo</td>
</tr>
<tr>
<td></td>
<td>C: (n = 13) copper and placebo</td>
</tr>
<tr>
<td></td>
<td>D: (n = 12) placebo and placebo</td>
</tr>
</tbody>
</table>

**Outcomes**

**Primary outcomes**

None reported
### Duffy 2004 (Continued)

#### Secondary outcomes

- Systemic Lupus Activity Measure, Revised (SLAM-R) score integument domain (narrative data only)
- Adverse events (reported narrative information only)

#### Funding source

- Funding was not stated

#### Location

- Outpatient rheumatology clinics in Northern Ireland

#### Notes

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Quote: “patients were randomly assigned”</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Comment: no details about random sequence generation were given</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>No details about allocation concealment were given</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Low risk</td>
<td>Quote: “a visually identical placebo capsule... to conceal taste and odor”</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Comment: study authors reported that the study was &quot;double blind&quot;. Blinding was probably sufficient</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Unclear risk</td>
<td>Insufficient details were given by study authors to assess whether assessors were blinded</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>High risk</td>
<td>Study authors discussed some reasons for the 13 withdrawals from the study. However, minimal details were given, and there was no breakdown of data per treatment group. A per-protocol analysis was performed. Study authors analysed only the 52 of 65 participants who completed the study</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>Study protocol was not available. All planned outcome measures described in the methods section are reported, including SLAM-R, dietary assessment, and laboratory measurements. Results that were statistically insignificant were also reported</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>Study authors provided a table of baseline data, and there was no evidence of imbalance between groups. Information was insufficient to assess whether an important risk of other bias exists</td>
</tr>
</tbody>
</table>

### Duliege 2016

#### Study characteristics

- **Methods**: This was a phase 2, multi-centre, randomised, quadruple-blind, placebo-controlled parallel-group clinical trial

- **Inclusion criteria**
54 participants with SLE and/or DLE; at least 2 active discoid lesions secondary to SLE or DLE before study entry, each with a minimum erythema rating score ≥ 2. At least 1 of the active discoid lesions must have been present (by history) for ≥ 3 weeks before screening

- Sex: 44 women, 10 men
- Race: not stated
- Age (mean): 46.8 years (11.69 SD)

**Exclusion criteria**

- Congenital or acquired immunodeficiency including human immunodeficiency virus (HIV) infection, agammaglobulinemias, T-cell deficiencies or human T-cell leukaemia virus 1 (HTLV-1) infection at any time before the study
- Lymphoproliferative disease or previous total lymphoid irradiation
- Uncontrolled or poorly controlled hypertension
- History of psoriasis, eczema, or relevant atopy
- Exposure to excessive or chronic ultraviolet (UV) radiation (e.g. tanning beds, sunbathing, solarium, phototherapy) within 2 weeks before randomisations or during the study period

**Interventions**

**Intervention (n = 36)**
A: R932333 ointment 6% (60 mg/g) applied twice a day for 6 weeks

**Control Intervention (n = 18)**
B: placebo ointment applied twice a day for 6 weeks

**Outcomes**

**Primary outcomes**
Percentage of patients who achieved at least a 50% decrease from baseline in total combined erythema and scaling score for all treated lesions at week 4. A decrease is an improvement in measurement of erythema and in scaling of lesions

**Secondary outcomes**
Adverse events (minor and severe)

**Funding source**
This study was funded by Rigel Pharmaceuticals

**Location**
Outpatient clinics in USA and Canada

**Notes**
This study is NCT01597050. Trial website notes that the R333 (a topical Janus kinase/spleen tyrosine kinase (JAK/SYK) inhibitor for SLE) trial was completed; however due to negative results, the company halted clinical development of this compound

**Risk of bias**

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation</td>
<td>Unclear risk</td>
<td>Quote: This trial was &quot;randomized&quot;.</td>
</tr>
<tr>
<td>(selection bias)</td>
<td></td>
<td>Comment: No details were given about random sequence generation.</td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>Unclear risk</td>
<td>No details were given about allocation concealment.</td>
</tr>
<tr>
<td>(selection bias)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blinding of participants</td>
<td>Low risk</td>
<td>Quote: Authors stated that there was &quot;quadruple blinding: Participant, Care Provider, Investigator, Outcomes Assessor&quot;</td>
</tr>
<tr>
<td>and personnel (performance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>bias)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All outcomes</td>
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</tr>
</tbody>
</table>
### DUPlie2016 (Continued)

<table>
<thead>
<tr>
<th></th>
<th>Blinding of outcome assessment (detection bias)</th>
<th>Low risk</th>
<th>Quote: Authors stated that there was &quot;quadruple blinding: Participant, Care Provider, Investigator, Outcomes Assessor&quot;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>All outcomes</td>
<td>High risk</td>
<td>Quote: Authors state on <a href="http://www.clinicaltrials.gov">www.clinicaltrials.gov</a> web site that there were severe &quot;limitations of the study, such as early termination leading to small numbers of participants analysed and technical problems with measurement leading to unreliable or uninterpretable data.&quot;</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>High risk</td>
<td>The study protocol was not available. Data was collected on SLE and DLE patients however reported data was pooled, subsets were not reported.</td>
<td></td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>Significant technical issues were noted by authors. There was insufficient information to assess whether an important risk of other bias exists.</td>
<td></td>
</tr>
</tbody>
</table>

### Fortin 2008

#### Study characteristics

| Methods | This was a parallel-group, triple-blind, randomised, placebo-controlled trial |

#### Participants

**Inclusion criteria**

- 86 participants with SLE by ACR criteria and CLE in SLE (74 patients with integument domain SLAM scores) and SLE severity (by SLAM-R and by the Systemic Lupus International Collaborating Clinics American College of Rheumatology Damage index (SLICC-DI/ACR)) ranging from moderate to severe; SLE duration ranged from 5.7 years in the methotrexate group to 4.5 years in the placebo group; CLE severity (by SLAM integument scores) ranged from 39 in the methotrexate group to 35 in the placebo group; however CLE duration information was not reported
- Sex: 78 women, 8 men
- Race: 66 white, 20 non-white
- Age: 34 to 48.5 years

**Exclusion criteria**

- Treatment with azathioprine or cyclophosphamide during previous 4 weeks
- Total SLAM-R < 8
- Total SLICC-DI/ACR score > 15
- Concomitant disease of kidney, lungs
- Cancer
- HIV
- Pregnancy
- CNS lupus
- CNS renal disease

#### Interventions

**Intervention (n = 41)**

A: methotrexate starting at 7.5 mg per week, with maximum dose of folic acid 2.5 mg/d for 12 months and prednisone

**Control Intervention (n = 45)**

B: placebo and prednisone

#### Outcomes

**Primary outcomes**
### Secondary outcomes

Adverse events (reported number of participants with mucocutaneous adverse events)

<table>
<thead>
<tr>
<th>Funding source</th>
<th>Funding was provided by the Arthritis Society of Canada and Faulding Canada, Inc (now Mayne Pharma (Canasa) Inc.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location</td>
<td>Outpatient clinics at university hospitals, research centres, and institutes in multiple cities in Canada</td>
</tr>
<tr>
<td>Notes</td>
<td></td>
</tr>
</tbody>
</table>

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Quote: &quot;participants were assigned...using a stratified blocked randomization implemented through a customized Fortran program&quot;</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Quote: &quot;the pharmacist at central location was the only person aware of randomisation status&quot;</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Low risk</td>
<td>Study authors reported that this study was &quot;triple blind&quot;</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Low risk</td>
<td>Quote: &quot;an independent blinded assessor scored the SLAM-R and SLEDAI while the clinical investigator recorded adverse events&quot;</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>Detailed analysis of outcome data was performed. Study authors stated that they performed an intention-to-treat analysis (ITT). We verified that ITT was indeed performed by examining published data</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>Study protocol was not available. All outcome data from the methods section were reported in the results section even if results were statistically insignificant</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>Study authors presented baseline data in the form of a table, and there was no evidence of baseline imbalance between treatment groups. Study authors explored bias via detailed discussion of potential sources of bias, and design efforts that were made to minimise potential bias</td>
</tr>
</tbody>
</table>

---

**Fortin 2008**

None were reported

---

**Furie 2011**

*Study characteristics*

| Methods                                      | This was a parallel-group, randomised, placebo-controlled, multi-arm trial |
**Participants**

**Inclusion criteria**
- 819 participants with SLE by ACR and cutaneous disease (478 with mucocutaneous organ involvement)
- Sex: 764 women, 55 men
- Age: mean ± SD: placebo group 40.0 ± 11.9 years; belimumab low-dose group 40.0 ± 11.4 years; belimumab high-dose group 40.5 ± 11.1 years
- Race: 569 white, 250 non-white

**Exclusion criteria**
- Serious concomitant illness
- Severe active lupus nephritis
- CNS lupus with severe manifestations
- Pregnancy
- Prior biologics
- Certain prior immunosuppressant medications

**Interventions**

**Intervention**
- A: \( n = 271 \) low-dose belimumab (human IgG1κ monoclonal antibody) 1 mg/kg IV on days 0, 14, and 28, then monthly for 18 months
- B: \( n = 273 \) high-dose belimumab 10 mg/kg IV on days 0, 14, and 28, then monthly for 18 months

**Control intervention**
- C: \( n = 275 \) placebo IV

Also could continue new antimalarial or current medication to week 16 (4 months)

**Outcomes**

**Primary outcomes**
None were reported

**Secondary outcomes**
Adverse events

**Funding source**
Funding was provided by a US NIH grant, Human Genome Sciences (based in the USA), and GlaxoSmithKline (based in the UK)

**Location**
This multi-centre study was conducted in the USA, Spain, Austria, Czech Republic, Mexico, Germany, and Sweden

**Notes**
Study trial number was NCT01283139

**Risk of bias**

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Quote: “patients were randomly assigned”</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Comment: no details about the sequence generation method were given</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Quote: randomisation was done &quot;via a centralized interactive voice response system&quot;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Comment: allocation concealment was likely adequate</td>
</tr>
</tbody>
</table>
Furie 2011 (Continued)

Blinding of participants and personnel (performance bias)
All outcomes
Low risk
Quote: “all study site personnel and patients as well as sponsor and clinical research organization personnel were blinded to trial agent assignments”
Comment: blinding of participants and personnel was likely sufficient

Blinding of outcome assessment (detection bias)
All outcomes
Low risk
Quote: “all study site personnel and patients as well as sponsor and clinical research organization personnel were blinded to trial agent assignments”
Comment: blinding of assessors was likely sufficient

Incomplete outcome data (attrition bias)
All outcomes
Low risk
Study authors presented a detailed flow diagram that accounted for all withdrawals. Intent-to-treat analysis was “modified”. It included all randomised patients who received ≥ 1 dose of agent

Selective reporting (reporting bias)
Unclear risk
Study protocol was not available. All outcome data from the methods section were reported in the results, even those that were not statistically significant

Other bias
Unclear risk
Study authors presented a detailed table of the baseline characteristics of each treatment group. There was no evidence of baseline imbalance. Information was insufficient to assess whether an important risk of other bias exists

Furie 2015a

Study characteristics

Methods
This was a double-blind randomised placebo-controlled pilot study

Participants
Inclusion criteria
- 38 participants with SLE (by ACR criteria) and with arthritis and/or skin involvement; severity of SLE: moderate to (very) severe (defined by hybrid SLEDAI > 2 or BILAG A or B in mucocutaneous or musculoskeletal systems despite up to 30 mg prednisone daily for 1 month before treatment)
- Sex: not stated
- Race: not stated
- Mean age: not stated

Exclusion criteria
- Hybrid SLEDAI < 2

Interventions

A: (n = 13) Acthar gel (HP repository corticotropin) 80 units subcutaneous injection every other day plus daily prednisone for 8 weeks (2 months)

B: (n = 13) Acthar gel 40 units subcutaneous injection every day plus daily prednisone for 8 weeks (2 months)

Control intervention (n = 12)

C: placebo plus prednisone for 8 weeks (2 months)

Outcomes
Primary outcomes
None were reported

Secondary outcomes
Furie 2015a (Continued)

Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) (narrative only)

Funding source
Study was funded by Mallinckrodt Pharmaceuticals

Location
New York, United States

Notes
Study number was NCT02953821

Risk of bias

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<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
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<tbody>
<tr>
<td>Random sequence generation</td>
<td>Unclear risk</td>
<td>Randomisation was stated; however the method was not detailed</td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>Unclear risk</td>
<td>No details about allocation concealment were given</td>
</tr>
<tr>
<td>Blinding of participants and personnel</td>
<td>Low risk</td>
<td>Study authors stated that this was a double-blind study; however no further details were given</td>
</tr>
<tr>
<td>Blinding of outcome assessment</td>
<td>Unclear risk</td>
<td>Study authors did not give specific details about the assessor to verify whether the study was sufficiently blinded</td>
</tr>
<tr>
<td>Incomplete outcome data</td>
<td>Low risk</td>
<td>No dropouts or withdrawals were mentioned. All randomised participants were analysed. Study authors did not state that they had performed an intention-to-treat (ITT) analysis. We were able to verify that ITT analysis was indeed performed by examining the published study data</td>
</tr>
<tr>
<td>Selective reporting</td>
<td>Unclear risk</td>
<td>Study protocol was not available. Study authors reported non-statistically significant results despite considerable space restraints</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>No table was given for analysis of baseline characteristics or possible imbalance. Information was insufficient to assess whether an important risk of other bias exists</td>
</tr>
</tbody>
</table>

Furie 2015b

Study characteristics

Methods
This was a phase 2, randomised, placebo-controlled, multi-arm clinical trial

Participants

Inclusion criteria
- 546 participants with SLE (by ACR criteria); 91% had active "mucocutaneous" baseline involvement
- Sex: 546 female, 33 male
- Race: 108 Asian, 46 black, 137 white, 255 "other"
- Mean age: 37.1 years in the intervention group, 37.9 years in the placebo group

Exclusion criteria
- Severe lupus nephritis
- Severe CNS lupus
Furie 2015b (Continued)

- Severe vasculitis
- Infection
- Malignancy
- Prior immunosuppressant medications

**Interventions**

A: (n = 92) blisibimod 200 mg subcutaneously once each week and background medication (oral corticosteroid, antimalarial, and immunosuppressant) for up to 52 weeks

B: (n = 93) blisibimod 100 mg subcutaneously once each week and background medication (oral corticosteroid, antimalarial, and immunosuppressants) for up to 52 weeks

C: (n = 92) blisibimod 200 mg subcutaneously once every 4 weeks and background medication (oral corticosteroid, antimalarial, and immunosuppressants) for up to 52 weeks

**Control intervention (n = 269)**

D: placebo and background medication (oral corticosteroid, antimalarial, and immunosuppressant) for up to 52 weeks

**Outcomes**

**Primary outcomes**

None were reported

**Secondary outcomes of the trial**

Adverse events: severe

**Funding source**

Study was funded was funded by Anthera Pharmaceuticals

**Location**

Various outpatient centres in the United States, Brazil, India, and Peru

**Notes**

NCT01162681 (part of PEARL-SC trial) and NCT01395745 (CHABLIS-SC1)

**Risk of bias**

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
</table>
| Random sequence generation (selection bias) | Low risk | Quote: "interactive web response system"  
Comment: randomisation was likely sufficient |
| Allocation concealment (selection bias) | Low risk | Quote: "interactive web response system"  
Comment: allocation concealment implied that randomisation was done via a centralised system |
| Blinding of participants and personnel (performance bias)  
All outcomes | Low risk | Quote: "no subjects, investigators were unblinded during the trial"  
Comment: Blinding of participants and personnel was probably sufficient |
| Blinding of outcome assessment (detection bias)  
All outcomes | Low risk | Quote: "no direct participants were unblinded"  
Comment: Assessor blinding was probably sufficient |
| Incomplete outcome data (attrition bias)  
All outcomes | Low risk | Study authors gave very detailed information about withdrawals and other issues in a table and in narrative form. Study authors presented a detailed table |
### Furie 2015b

(Continued)

of their intention-to-treat (ITT) analysis; however this was a "modified intention-to-treat" analysis

<table>
<thead>
<tr>
<th>Selective reporting (reporting bias)</th>
<th>Unclear risk</th>
<th>Study protocol was not available. Negative results were presented, along with positive results, in a detailed table</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>Study authors presented a table of baseline characteristics, and no evidence of baseline imbalance was seen. Study authors acknowledged some risk of imbalance in some groups; however they did not perform formal analysis, and no gross imbalances were seen in presented data. Information was insufficient to assess whether an important risk of other bias exists</td>
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</table>

### Furie 2015c

#### Study characteristics

<table>
<thead>
<tr>
<th>Methods</th>
<th>This was a randomised, multi-arm, double-blind, placebo-controlled trial</th>
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<tbody>
<tr>
<td>Participants</td>
<td><strong>Inclusion criteria</strong></td>
</tr>
<tr>
<td></td>
<td>• 305 participants with SLE (by ACR criteria); exact details about number of these participants with active skin involvement were not given; however table referring to CLASI scores noted &quot;n = 77&quot;</td>
</tr>
<tr>
<td></td>
<td>• Sex: not stated</td>
</tr>
<tr>
<td></td>
<td>• Race: not stated</td>
</tr>
<tr>
<td></td>
<td>• Mean age: not given; however stated &quot;adults...&quot;</td>
</tr>
<tr>
<td></td>
<td><strong>Exclusion criteria</strong></td>
</tr>
<tr>
<td></td>
<td>• Not stated</td>
</tr>
<tr>
<td>Interventions</td>
<td><strong>Interventions</strong></td>
</tr>
<tr>
<td>A: (n = 17) anifrolumab 300 mg intravenous infusion every 4 weeks for 48 weeks plus standard of care followed over 12 months (365 days)</td>
<td></td>
</tr>
<tr>
<td>B: (n = 14) anifrolumab 1000 mg intravenous infusion every 4 weeks for 48 weeks plus standard of care followed over 12 months (365 days)</td>
<td></td>
</tr>
<tr>
<td><strong>Control intervention (n = 8)</strong></td>
<td></td>
</tr>
<tr>
<td>C: placebo every 4 weeks for 48 weeks plus standard of care followed over 12 months (365 days)</td>
<td></td>
</tr>
<tr>
<td>Outcomes</td>
<td><strong>Primary outcomes</strong></td>
</tr>
<tr>
<td>None were reported</td>
<td></td>
</tr>
<tr>
<td><strong>Secondary outcomes</strong></td>
<td></td>
</tr>
<tr>
<td>CLASI (narrative)</td>
<td></td>
</tr>
<tr>
<td>Adverse events (narrative)</td>
<td></td>
</tr>
<tr>
<td>Funding source</td>
<td>This study was funding by MedImmune</td>
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<tr>
<td>Location</td>
<td>Various sites around the United States and 1 site in the United Kingdom</td>
</tr>
<tr>
<td>Notes</td>
<td>NCT01438489; this study was called MUSE phase 2b</td>
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</table>
Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Randomisation was stated; however no details about methods were given</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>No specific details about randomisation were given, so we cannot assume that it was centralised</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>Low risk</td>
<td>Study authors reported that this was a double-blind study; however no further details were given</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Unclear risk</td>
<td>Study authors gave insufficient details regarding assessor blinding</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Unclear risk</td>
<td>For some outcomes, analysis was intent-to-treat. However for other outcomes, this is less clear. For example, of 305 randomised patients, for the outcome of CLASI, the starting n was only 77, and the final CLASI analysis included only a small subset of patients (n = 39) with CLASI baseline ≥ 10. No details about dropouts were given</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>High risk</td>
<td>Study protocol was not available. Some key data such as final CLASI scores are missing</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>There was no table of baseline characteristics, so could not assess risk of baseline imbalance between treatment groups. Information was insufficient to assess whether an important risk of other bias exists</td>
</tr>
</tbody>
</table>

Furie 2016a

Study characteristics

Methods
This was a phase 4, prospective, multi-centre, parallel-group, double-blind, placebo-controlled, randomised pilot trial

Participants

Inclusion criteria
- 38 participants with SLE (by ACR criteria) and active disease with arthritis and/or rash based on hybrid SLEDAI and BILAG score A or B in mucocutaneous or musculoskeletal domain
- Participants were required to have positive antibodies (antinuclear antibodies (ANAs), anti-double-stranded DNA (anti-dsDNA), anti-Smith or anti-cardiolipin) and persistent disease despite stable doses of prednisone or equivalent (7.5 mg to 30 mg per day) for 4 weeks before screening
- Sex: 90.9% to 100% female, depending on treatment group
- Race: 41 white, 18 black
- Mean age: 39.1 with SD of 9.1 years to 43.2 with SD of 7.2 years, depending on treatment group; all patients 18 years of age or older

Exclusion criteria
- Initiation of corticosteroids within 2 months before screening
- Active nephritis
- Other medications within specified time frame before screening
Interventions

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>A: (n = 13) repository corticotropin injection (RCI) 40 units a day for 4 weeks, then tapered to twice weekly for weeks 5 to 8 for 2 months</td>
<td>Unclear risk</td>
<td>Quote: this trial was &quot;randomized&quot;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Comment: no details about random sequence generation were given</td>
</tr>
<tr>
<td>B: (n = 13) repository corticotropin injection (RCI) 80 units every other day for 4 weeks, then tapered to twice weekly for weeks 5 to 8 for 2 months</td>
<td>Unclear risk</td>
<td>Study authors provided insufficient details about centralisation of randomisation</td>
</tr>
<tr>
<td>C: (n = 12) placebo gel injection (volume matched) for 2 months</td>
<td>Low risk</td>
<td>Quote: this trial was &quot;double-blind&quot; and there were &quot;volume-matched placebo groups&quot;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Comment: likely sufficient</td>
</tr>
</tbody>
</table>

Control intervention

C: (n = 12) placebo gel injection (volume matched) for 2 months

Study was followed by a second phase (44 weeks) open-label extension

Outcomes

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcomes</td>
<td>None were reported</td>
<td></td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td>CLASI</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hybrid SLEDAI (hSLEDAI) measuring resolution of rash or arthritis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>BILAG</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adverse events: minor and severe</td>
<td></td>
</tr>
</tbody>
</table>

Funding source

Mallinckrodt Pharmaceuticals funded the study

Location

20 outpatient sites in the USA

Notes

This study was NCT01753401

Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
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<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Quote: this trial was &quot;randomized&quot;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Comment: no details about random sequence generation were given</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Study authors provided insufficient details about centralisation of randomisation</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Low risk</td>
<td>Quote: this trial was &quot;double-blind&quot; and there were &quot;volume-matched placebo groups&quot;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Comment: likely sufficient</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Unclear risk</td>
<td>Blinding of assessors was not discussed</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>Quote: &quot;all results reported used the modified intention-to-treat (mITT) population, defined as all randomised patients who had received at least one dose of study medication and who had any post-baseline efficacy or safety data&quot;</td>
</tr>
</tbody>
</table>
Furie 2016a (Continued)

Comment: detailed table of "patient disposition was also given with reasons for withdrawals". Withdrawals were not excessive

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>Study protocol was not available. Planned outcomes were reported regardless of statistical significance</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>Study authors presented a table of baseline characteristics with no evidence of imbalance. Information was insufficient to assess whether an important risk of other bias exists</td>
</tr>
</tbody>
</table>

Furie 2016b

Study characteristics

Methods

This was a phase 1b, multi-centre, parallel-group, double-blind, placebo-controlled, randomised trial

Participants

Inclusion criteria

- 12 participants with SLE (by 1997 ACR criteria) and active CLE (acute, subacute, and/or chronic cutaneous forms)
- Sex: not stated
- Race: not stated
- Mean age: not given; all patients were "adult"

Exclusion criteria

- Not stated

Interventions

Intervention (n = 8)

A: single IV administration of BIIB059 at a dose of 20 mg/kg followed over 12 weeks

Control intervention (n = 4)

B: single IV administration of placebo followed over 12 weeks

Outcomes

Primary outcomes

None were reported

Secondary outcomes

CLASI

Adverse events: minor and severe

Funding source

This study was funded by Biogen of Cambridge, MA, USA

Location

Multiple outpatient sites in the USA

Notes

NCT02106897

Risk of bias

Bias                              | Authors' judgement | Support for judgement |
<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Quote: this study was &quot;randomized&quot;</td>
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</table>
### Furie 2016b (Continued)

<table>
<thead>
<tr>
<th></th>
<th>Comment: no details about the method of random sequence generation were given</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>Low risk</td>
</tr>
<tr>
<td></td>
<td>Comment: likely sufficient</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Unclear risk</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Low risk</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
</tr>
</tbody>
</table>

### Griffiths 2010

**Study characteristics**

**Methods** This was an open, parallel-group, multi-centre, randomised controlled trial

**Participants**

**Inclusion criteria**

- 89 participants with SLE by ACR criteria and cutaneous CLE (43 with malar rash, 11 with discoid, 35 with photosensitivity, 44 with oral ulcers)
- Sex: 82 women, 7 men
- Race: 59 white, 30 non-white
- Age range: 25 to 53 years

**Exclusion criteria**

- Hypertension
- Pregnant
- History of adverse events with ciclosporin or azathioprine

**Interventions**

**Intervention (n = 47)**

A: oral ciclosporin 1 mg/kg/d initial dose increased to target 2.5 mg/kg/d with maximum of 3.5 mg/kg/d and also treated with prednisolone, Calcichew D3 2 tablets daily as background prophylaxis for osteoporosis given to all participants, hydroxychloroquine (stable dose throughout study), NSAIDs

**Control intervention (n = 42)**

B: azathioprine also treated with prednisolone, Calcichew D3 2 tablets daily as background prophylaxis for osteoporosis given to all participants, hydroxychloroquine (stable dose throughout study), non-steroidal anti-inflammatory drugs (NSAIDs)
### Primary outcomes

- Presence of rash, lupus rash, malar rash, oral ulcers

### Secondary outcomes

- Adverse events: reported cutaneous adverse events

### Funding source

Study was funded by the Arthritis Research Campaign (ARC) UK, Grant Number ID14293. Ciclosporin was supplied by Novartis Pharmaceuticals. Calcichew D3 was supplied by Shire Pharmaceuticals.

### Location

Outpatient clinics from university hospitals and affiliated research centres at multiple locations in UK.

### Risk of bias

#### Bias

<table>
<thead>
<tr>
<th>Author's judgement</th>
<th>Support for judgement</th>
</tr>
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<tbody>
<tr>
<td><strong>Random sequence generation (selection bias)</strong></td>
<td>Low risk</td>
</tr>
<tr>
<td><strong>Allocation concealment (selection bias)</strong></td>
<td>Low risk</td>
</tr>
<tr>
<td><strong>Blinding of participants and personnel (performance bias)</strong>&lt;br&gt;<strong>All outcomes</strong></td>
<td>High risk</td>
</tr>
<tr>
<td><strong>Blinding of outcome assessment (detection bias)</strong>&lt;br&gt;<strong>All outcomes</strong></td>
<td>High risk</td>
</tr>
<tr>
<td><strong>Incomplete outcome data (attrition bias)</strong>&lt;br&gt;<strong>All outcomes</strong></td>
<td>Low risk</td>
</tr>
<tr>
<td><strong>Selective reporting (reporting bias)</strong></td>
<td>Unclear risk</td>
</tr>
<tr>
<td><strong>Other bias</strong></td>
<td>Unclear risk</td>
</tr>
</tbody>
</table>

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**Griffiths 2010 (Continued)**

**Study characteristics**
This was a parallel-group, randomised controlled trial

**Inclusion criteria**

- 40 participants with SLE by ACR and CLE
- Sex: 35 women, 5 men
- Race: 37 white, 3 non-white
- Age range: 21 to 70 years

**Exclusion criteria**

- No use of non-steroidal anti-inflammatory drugs (NSAIDs) in the 3 days before the start of the trial
- Active liver, cardiac, renal, neurological, endocrine, or haematological disease
- Use of immunosuppressant or certain other medications

**Intervention (n = 15)**

A: zileuton (N-(1-benzo-[b]-thien-2-ylethyl)-N-hydroxyurea), a selective 5-lipoxygenase (leukotriene) inhibitor, 600 mg orally 4 times per day for 8 weeks

**Control intervention (n = 15)**

B: placebo

**Primary outcomes**

None were reported

**Secondary outcomes**

Skin (integument) domain of SLAM score (oral ulcers, cutaneous rash, vasculitis, alopecia) at 8 weeks

Adverse events: reported and noted with table that lists details

Other outcomes: severity of malar rash

**Funding source**

Funding was provided through a grant from Abbott Laboratories

**Location**

Outpatient clinic at Ohio State University, in Columbus, Ohio, USA

**Risk of bias**

**Bias** | **Authors' judgement** | **Support for judgement**
---|---|---
Random sequence generation (selection bias) | Low risk | Quote: "a randomisation scheme was generated by the clinical statistics department at Abbott Laboratories"
Comment: random sequence generation was probably sufficient

Allocation concealment (selection bias) | Low risk | Quote: "treatment designation was recorded in sealed double blind labels provided with study drug and in sealed envelopes stored in the clinical statistics department"
Comment: allocation concealment was probably sufficient

Blinding of participants and personnel (performance bias) | Low risk | Quote: "neither the patients, nor the investigator...had knowledge of the study drug assignment before or during the course of the study"
**Hackshaw 1995 (Continued)**

<table>
<thead>
<tr>
<th>Bias Type</th>
<th>Risk</th>
<th>Description</th>
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<tbody>
<tr>
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<td>Quote: “the zileuton capsules were identical appearing to the placebo capsules”</td>
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<tr>
<td>Comment: Blinding was probably sufficient</td>
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</tr>
<tr>
<td>------------------------------------------------</td>
<td>--------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low</td>
<td>Two participants in the zileuton group were lost to follow-up, with a total of 38 of 40 participants (95%) completing the study. Study authors did not state that they had performed an intention-to-treat (ITT) analysis. We could not verify that ITT had indeed been performed for all data</td>
</tr>
<tr>
<td>Comment: Blinding was probably sufficient</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>High</td>
<td>Study protocol was not available. All planned outcome measures were reported, except the secondary outcomes of severity of malar rash and assessment of fatigue. Negative results were also reported</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear</td>
<td>There was no evidence of baseline imbalance between treatment groups. Information was insufficient to assess whether an important risk of other bias exists</td>
</tr>
</tbody>
</table>

**Ishii 2015**

**Study characteristics**

**Methods**

This was a parallel-group randomised placebo-controlled trial

**Participants**

**Inclusion criteria**

- 14 participants with SLE (by ACR criteria) and CLE (1 participant was reported to have active skin involvement that improved with the intervention)
- Sex: not stated
- Race: not stated (trial in Japan)
- Mean age: not stated

**Exclusion criteria**

- Not discussed

**Interventions**

**Intervention (n = 8)**

A: bortezomib 1.3 mg/m² twice weekly for 8 doses plus oral prednisone 10 mg/d or greater for 4 weeks (1 month)

**Control intervention (n = 6)**

B: placebo plus oral prednisone 10 mg/d or greater for 4 weeks (1 month)

**Outcomes**

**Primary outcomes**

Partial clearance of cutaneous manifestations: "improvement"

**Secondary outcomes**

Adverse events
### Ishii 2015 (Continued)

**Funding source**  
One study author had commercial findings from numerous sources. Remaining authors disclosed no commercial funding

**Location**  
Outpatient clinics in various cities in Japan

**Notes**

#### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Randomisation was stated; however method was not detailed</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>No details about allocation concealment were given</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>High risk</td>
<td>Blinding was not mentioned</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>High risk</td>
<td>Blinding was not mentioned</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>High risk</td>
<td>7/8 patients in the treatment group withdrew due to side effects; 2/6 in the placebo group withdrew</td>
</tr>
<tr>
<td>Study authors used “last observation carried forward” (LOCF) analysis due to high attrition rate; this may have introduced bias</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>Study protocol was not available. Study authors reported negative results</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>Provided data were insufficient to assess baseline imbalance between treatment groups. Information was insufficient to assess whether an important risk of other bias exists</td>
</tr>
</tbody>
</table>

### Islam 2012

#### Study characteristics

**Methods**  
This was a parallel-group, randomised, controlled, open-label trial

**Participants**

**Inclusion criteria**
- 41 participants with SLE with 4 withdrawals, leading to 37 participants completing the study
- Demographic information for the 4 withdrawals not available
- Sex: 36 women, 1 man
- Race: not stated
- Mean age for methotrexate group: 24.0 ± 4.5 years (SD); for chloroquine group: 24.9 ± 7.0 years SD

**Exclusion criteria**
- Pregnancy
Islam 2012 (Continued)

- Lactation
- Involvement of any other systems
- Eye problems
- Raised alanine aminotransferase (ALT)/creatinine
- Recent prednisone > 20 mg/d
- Antimalarial medications in past 4 months

Interventions

**Intervention (n = 6)**
A: oral methotrexate 10 mg each week for 24 weeks (6 months) and continuation of dose of fixed oral prednisone taken for at least 2 months before the study at doses not exceeding 10 mg each day; increasing the dose was not permitted

**Control intervention (n = 19)**
B: oral chloroquine 150 mg each day for 24 weeks (6 months) and continuation of dose of fixed oral prednisone taken for at least 2 months before the study at doses not exceeding 10 mg each day; increasing the dose was not permitted

Outcomes

**Primary outcomes**
Clearance (disappearance) of skin rash of any type (subacute cutaneous lupus erythematosus, chronic discoid lupus erythematosus, "butterfly rash" scored as "present" or "absent")

**Secondary outcomes**
Adverse events (severe and minor events reported)

Funding source
No funding was received from industry or government

Location
Lupus clinic at a tertiary care clinic, in Dhaka, Bangladesh

Notes

**Risk of bias**

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Quote: &quot;the patients were randomly allocated to either methotrexate or chloroquine groups. Randomization was performed following a random number table without considering their presentation. We followed their vertical series on odd and even numbers&quot;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Comment: random sequence generation was likely sufficient</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Methods of allocation concealment were not mentioned</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>High risk</td>
<td>This was an open-label study</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>High risk</td>
<td>This was an open-label study</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Unclear risk</td>
<td>Reasons for withdrawal were stated. There were 2 withdrawals from each group. Intent-to-treat analysis was not performed by study authors. We verified that analysis by authors was per-protocol. We were able to perform an in-</td>
</tr>
</tbody>
</table>
Islam 2012 (Continued)
tent-to-treat analysis for some outcomes relevant to this review by using some of the authors’ published data

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>Study protocol was not available. Negative results were reported</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>Study authors presented a table of baseline data; there was no evidence of baseline imbalance. Information was insufficient to assess whether an important risk of other bias exists</td>
</tr>
</tbody>
</table>

Kahan 1985

Study characteristics

Methods
This was a randomised controlled cross-over trial

Participants
Inclusion criteria
- 30 total participants (5 with SLE and Raynaud’s phenomenon)
- Sex: 5 women, 0 men
- Race: not stated
- Mean age: 40.4 years

Exclusion criteria
- Not stated

Interventions
Intervention (n = 5)
A: nifedipine 20 mg 3 times per day for 1 week

Control intervention (n = 5)
B: placebo 3 times per day for 1 week

Outcomes
Primary outcomes
None were reported

Secondary outcomes
Mean number of digital vasospastic events per week

Adverse events (narrative form)

Funding source
Funding source was not stated

Location
Outpatient clinics in cardiology and rheumatology at a single university site in France

Notes
Data for SLE were pooled with those for rheumatoid arthritis. We were unable to extract data specific for SLE

Risk of bias

Bias
Random sequence generation (selection bias) Unclear risk No method of randomisation was stated
### Allocation concealment (selection bias)

<table>
<thead>
<tr>
<th>Study</th>
<th>Risk</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kahan 1985</td>
<td>Unclear risk</td>
<td>No details about allocation concealment were given</td>
</tr>
</tbody>
</table>

### Blinding of participants and personnel (performance bias)

<table>
<thead>
<tr>
<th>Study</th>
<th>Risk</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kahan 1985</td>
<td>Low risk</td>
<td>Study authors stated that this was a double-blind study; however no other details were given</td>
</tr>
</tbody>
</table>

### Blinding of outcome assessment (detection bias)

<table>
<thead>
<tr>
<th>Study</th>
<th>Risk</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kahan 1985</td>
<td>Unclear risk</td>
<td>Study authors did not give specific details about assessor blinding</td>
</tr>
</tbody>
</table>

### Incomplete outcome data (attrition bias)

<table>
<thead>
<tr>
<th>Study</th>
<th>Risk</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kahan 1985</td>
<td>Low risk</td>
<td>No outcome data were omitted from analysis (100% of presented data were analysed)</td>
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</table>

### Selective reporting (reporting bias)

<table>
<thead>
<tr>
<th>Study</th>
<th>Risk</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kahan 1985</td>
<td>High risk</td>
<td>Study protocol was not available. Study authors did not report key data such as sample size for each treatment group or negative results</td>
</tr>
</tbody>
</table>

### Other bias

<table>
<thead>
<tr>
<th>Study</th>
<th>Risk</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kahan 1985</td>
<td>Unclear risk</td>
<td>Study authors did not present enough details to determine if there was a baseline imbalance between treatment groups. Information was insufficient to assess whether an important risk of other bias exists</td>
</tr>
</tbody>
</table>

### Study characteristics

**Methods**

This was a parallel-group, multi-arm, randomised, double-blind, placebo-controlled multi-centre phase 2b trial

**Participants**

**Inclusion criteria**

- 431 participants with SLE (by ACR criteria) with reported mean CLASI activity scores of 8.4 ± 8.5 SD for placebo group and similar among 3 treatment groups
- Sex: 398 female, 33 male
- Race: 253 white; 65 Asian; 33 black; 20 American Indian/Alaskan native; 60 other
- Mean age: 38.4 years ± 12.3 (S.D.) for the placebo group (N=108); 39.9 years ± 11.4 (S.D.) for the sifalimumab 200 mg treatment group (N=108); 40.0 years ± 11.3 (S.D.) for the sifalimumab 600 mg treatment group (N=108); and 39.4 years ± 12.1 (S.D.) for the sifalimumab 1200 mg treatment group (N=107). Age range for participants was 18 to 75 years.

**Exclusion criteria**

- Active or severe lupus nephritis
- Neuropsychiatric SLE

**Interventions**

**Interventions**

A: (n = 33) sifalimumab 200 mg intravenous infusion once per month plus standard of care for 52 weeks (12 months)

B: (n = 33) sifalimumab 600 mg intravenous infusion once per month plus standard of care for 52 weeks (12 months)

C: (n = 26) sifalimumab 1200 mg intravenous infusion once per month plus standard of care for 52 weeks (12 months)
**Khamashta 2016** *(Continued)*

**Control intervention (n = 17)**

D: placebo once per month plus standard of care for 52 weeks (12 months)

### Outcomes

<table>
<thead>
<tr>
<th>Type of Outcome</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcomes</strong></td>
<td>None were reported</td>
</tr>
<tr>
<td><strong>Secondary outcomes</strong></td>
<td>CLASI</td>
</tr>
<tr>
<td></td>
<td>Adverse events</td>
</tr>
</tbody>
</table>

### Funding source

Study was funded by MedImmune

### Location

This multi-centre study was conducted at 107 sites in 20 countries in North, Central, and South America, Western and Eastern Europe, South Africa, and Asia

### Notes

NCT01283139

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Quote: &quot;patients were randomised by an interactive voice and web management system&quot;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Comment: random sequence generation was likely sufficient</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Quote: the randomisation was &quot;centralised&quot;; it was supervised by an &quot;independent external adjudication group who approved the randomization&quot;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Comment: allocation concealment was likely sufficient</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>Low risk</td>
<td>Study authors reported that this was a &quot;double-blind&quot; study</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Unclear risk</td>
<td>No specific details about blinding of assessors were given</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Low risk</td>
<td>Few details about the dropouts were given. No flow table was provided. On analysis of data, many outcome points had complete data. (100% completion rates for certain data)</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>High risk</td>
<td>Study protocol was not available. Most data were analysed for multiple endpoints. However for some outcomes, minimal data were available. For example, for the CLASI outcome, analysis was conducted only for a subset of 127 of the 431 randomised.</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>Study authors provided baseline data in a table, and there was no evidence of baseline imbalance between treatment groups. Information was insufficient to assess whether an important risk of other bias exists.</td>
</tr>
</tbody>
</table>
Study characteristics

Methods
This was a split-body randomised, double-blind, vehicle-controlled trial

Participants

Inclusion criteria
- 30 participants (only 3/30 met SLE criteria for SLE-2 with DLE, and 1 with ACLE); each participant had at least 2 skin lesions
- Sex: 18 women, 12 men
- Race: not stated
- Mean age: 45.2 ± 10.35 SD years

Exclusion criteria
- Systemic medications 6 months before the beginning of the study
- Pregnancy
- Lactation
- Sensitivity to tacrolimus

Interventions

Intervention (split body) (n = 30)
Group 1: (tube A: tacrolimus 0.1% ointment applied to first of the 2 lesions on the same participant for 12 weeks; tube B: vehicle comprised petrolatum, paraffin, propylene carbonate, bleached wax, rigid paraffin applied twice daily to the second of 2 lesions on same participant)

Group 2: (tube A: vehicle comprising petrolatum, paraffin, propylene carbonate, bleached wax, rigid paraffin applied twice daily to the first of 2 lesions on the same participant; tube B: tacrolimus 0.1% ointment applied to second of the 2 lesions on same participant for 12 weeks)

Outcomes

Primary outcomes
Clinical evaluation of 4 criteria individually and as composite score: (1) erythema, (2) hypertrophy/desquamation, (3) oedema, (4) dysesthesia

Difference between baseline scores and scores on days 14, 28, 56, and 84 of the study

Secondary outcomes
Adverse events (narrative information)

Funding source
Funding sources were Astellas Pharma GmbH and Heisenberg Scholarship from the German Research Foundation

Location
Outpatient dermatology clinics at 3 university hospitals and affiliated clinics in Germany

Notes

Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Quote: &quot;randomisation was compiled with the computer program RANCODE version 3.6 by the Coordination Centre for Clinic Trials (KKS)&quot;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Comment: random sequence generation was likely adequate</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Allocation concealment is assumed to be adequate as there was central randomisation</td>
</tr>
</tbody>
</table>
### Kuhn 2011 (Continued)

<table>
<thead>
<tr>
<th>Bias</th>
<th>Risk</th>
<th>Description</th>
</tr>
</thead>
</table>
| Blinding of participants and personnel (performance bias) | Low risk | Quote: "patients and physicians were blinded"
Comment: study authors described that active and placebo were produced by 1 company and labelling was done in the pharmacy according to Good Clinical Practice (GCP) guidelines. Further details were not given; however blinding was likely adequate |
| Blinding of outcome assessment (detection bias) | Unclear risk | Insufficient details regarding blinding of assessors were given |
| Incomplete outcome data (attrition bias) | Low risk | Study authors accounted for all data. Two patients did not complete the study for unknown reasons. Analysis was both intent-to-treat and per-protocol |
| Selective reporting (reporting bias) | High risk | Study protocol was not available. Some basic data were not presented clearly in the main text. For example, sample size for each treatment group was listed in a table that was published separately from the main article |
| Other bias | Unclear risk | A table with baseline data was presented by study authors. There was no evidence of baseline imbalance between treatment groups. Information was insufficient to assess whether an important risk of other bias exists |

### Lanna 2019

#### Study characteristics

<table>
<thead>
<tr>
<th>Methods</th>
<th>This was a randomised, controlled, open, parallel-group clinical trial with 2 arms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td><strong>Inclusion criteria</strong></td>
</tr>
<tr>
<td></td>
<td>• 43 participants with SLE (diagnosed by ACR 1997 or SLICC 2012 criteria) and over 18 years of age with &quot;sequelae of cutaneous lupus manifestations on their face&quot;</td>
</tr>
<tr>
<td></td>
<td>• Sex: all women</td>
</tr>
<tr>
<td></td>
<td>• Age: mean ± SD: 45.0 years (range 37.3 to 55.7 years) in the cosmetic camouflage intervention group; 50.0 years (range 43.0 to 55.0 years) in the control group</td>
</tr>
<tr>
<td></td>
<td>• Race: not stated</td>
</tr>
<tr>
<td></td>
<td><strong>Exclusion criteria</strong></td>
</tr>
<tr>
<td></td>
<td>• SLEDAI 2000 (2k) modified &gt; 4</td>
</tr>
<tr>
<td></td>
<td>• Lack of understanding of questionnaires</td>
</tr>
<tr>
<td></td>
<td>• Psychological and/or psychiatric treatment initiation or modification during the study</td>
</tr>
<tr>
<td>Interventions</td>
<td><strong>Intervention</strong></td>
</tr>
<tr>
<td></td>
<td>A: (n = 28) patients were trained in cosmetic camouflage use for the &quot;scars of cutaneous manifestations of the disease&quot; (in 2 sessions 3 months apart over 6 months) and were instructed to use makeup daily</td>
</tr>
<tr>
<td></td>
<td><strong>Control intervention (n = 15)</strong></td>
</tr>
<tr>
<td></td>
<td>B: &quot;no training in cosmetic camouflage&quot;</td>
</tr>
<tr>
<td>Outcomes</td>
<td><strong>Primary outcomes</strong></td>
</tr>
<tr>
<td></td>
<td>None were reported</td>
</tr>
<tr>
<td></td>
<td><strong>Secondary outcomes</strong></td>
</tr>
</tbody>
</table>
**Risk of bias**

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Quote: this was a &quot;randomized&quot; trial</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>It is unclear if randomisation was centralised</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>High risk</td>
<td>Quote: it was not stated whether this was a blinded trial</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Unclear risk</td>
<td>It is unclear whether assessors were blinded</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>High risk</td>
<td>Quote: study authors stated that analysis was &quot;per-protocol&quot;</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>No protocol was available</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>Some baseline characteristics were presented. Minimal information about baseline characteristics was available to assess for imbalance. Information was insufficient to assess whether an important risk of other bias exists</td>
</tr>
</tbody>
</table>

---

**Levy 2001**

**Study characteristics**

| Methods | This was a parallel-group randomised controlled trial |

**Inclusion criteria**

- 20 pregnant female participants diagnosed with SLE by ACR criteria and with cutaneous disease (biopsy-proven DLE) were enrolled between 8 and 18 weeks of pregnancy
- Children (female and male) born to study participants were also studied and compared (exposure to placebo versus exposure to hydroxychloroquine) for up to 3 years after birth
- Sex: female 20, male 0 (all female)
Levy 2001 (Continued)

- Age: mean 29 ± 3 years in the hydroxychloroquine group, 29 ± 4 years in the placebo group
- Race: 9 white, 11 "non-white"

**Exclusion criteria**
- Previous severe CNS or renal involvement with lupus

### Interventions

**Intervention (n = 10)**

A: hydroxychloroquine (doses not stated) and prednisone during pregnancy (8 to 12 weeks) through 12 weeks postpartum (total of 10 months)

**Control intervention (n = 10)**

B: placebo and prednisone during pregnancy (8 to 12 weeks) through 12 weeks postpartum (total of 10 months)

### Outcomes

**Primary outcomes**

Reported % of participants with partial improvement (conversion of data was required) as skin (1) better or (2) worse or (3) no change

**Secondary outcomes**

"Systemic lupus flare"

Adverse events (for participants and to offspring of participants): reported and qualitatively analysed, such as toxaemia of pregnancy

Prednisone average dose at 18 weeks and at delivery

### Funding source

Sanofi-Winthrop Laboratory of Brazil provided "no cost" coded capsules of HCQ and placebo. Otherwise per study authors, Sanofi-Winthrop Laboratory of Brazil did not finance this study

### Location

Hospital Universitario Pedro Ernesto, UERJ, Division of Rheumatology, Rio de Janeiro, Brazil

### Notes

Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Randomisation was stated, but information on the method used was insufficient</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Study states that participants were “sequentially included”, or that consecutive participants were enrolled in the study. However it is unclear what happened after enrolment</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Unclear risk</td>
<td>Quote: &quot;HCQ or identical placebo capsules were dispensed&quot; Comment: the study had &quot;double&quot; blinding per study authors. It does appear from text that investigators were indeed blinded. However, it is not clear from text if pregnant participants were truly fully blinded. So the conclusion is that blinding may have been sufficient</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Unclear risk</td>
<td>Quote: &quot;a skilled pediatrician was blinded&quot; Comment: at least 1 assessor was blinded; however it is not clear from the text whether other assessors (obstetricians) were blinded as well</td>
</tr>
</tbody>
</table>
Levy 2001 (Continued)

Incomplete outcome data (attrition bias) All outcomes Low risk Follow-up was complete, with no participants lost to follow-up. Study authors did not state that they had performed an intention-to-treat (ITT) analysis. We could not confirm that ITT was performed by examination of published data

Selective reporting (reporting bias) High risk Study protocol was not available. Some negative data were presented. Some data and graphs may have been omitted

Other bias Unclear risk There was no evidence of baseline imbalance; however minimal data were presented. Information was insufficient to assess whether an important risk of other bias exists

Lima 2016

Study characteristics

Methods This was a parallel-group, randomised, double-blind, placebo-controlled study

Participants

Inclusion criteria
- 45 participants with SLE (by ACR criteria), with SLE onset before age 16, maximum age 25; of these participants, 11 had active skin involvement
- Sex: 45 female, 0 male
- Race: 32 Caucasian; 13 non-Caucasian
- Mean age: 18.5 ± 3.5 years in the intervention group; 19.3 ± 3.3 years in the placebo group

Exclusion criteria
- SLEDAI > 12
- Other autoimmune disease
- Infection
- Renal impairment
- Liver disease
- Certain other medications recently

Interventions

Intervention (n = 22)
A: oral cholecalciferol 50,000 IU each week plus stable doses of standard therapy (glucocorticoids, hydroxychloroquine, or immunosuppressives) for 6 months

Control intervention (n = 23)
B: oral placebo each week plus stable doses of standard therapy (glucocorticoids, hydroxychloroquine, or immunosuppressives) for 6 months

Outcomes

Primary outcomes
None were reported

Secondary outcomes
SLEDAI (narrative only)
Mild and severe adverse events

Funding source Support was provided through government grants. No commercial sources were declared

Location Hospital das Clinicas da Universidade de Sao Paulo, Brazil, from July 2012 to August 2013
### Lima 2016 (Continued)

#### Notes

NCT01892748

#### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Randomisation was stated; however no details about methods were given</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Insufficient details about method of allocation concealment were given. It is unclear whether randomisation was centralised</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>Low risk</td>
<td>Study was double-blinded to patients and physicians. Tablets for intervention and placebo were &quot;identical&quot;</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Unclear risk</td>
<td>Details about blinding of assessors were insufficient</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Unclear risk</td>
<td>There were 5 withdrawals from the study due to &quot;personal reasons and loss to follow-up&quot;. Analysis was not intention-to-treat, but rather &quot;as treated&quot;</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>Study protocol was not available. Main outcomes were reported</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>Study authors presented a table of baseline characteristics; no statistical difference between treatment groups was detected. Information was insufficient to assess whether an important risk of other bias exists</td>
</tr>
</tbody>
</table>

#### McGrath 1996

#### Study characteristics

**Methods**

This was a randomised, 2-phase, cross-over controlled trial

**Participants**

**Inclusion criteria**

- 26 participants with SLE by ACR criteria and CLE (26 with malar rash, 9 with hair loss, 9 with livedo reticularis, 8 with mucosal ulcers, 7 with Raynaud’s phenomenon, 2 with discoid rash)
- Sex: 26 women, 0 men
- Race: 19 white, 7 non-white
- Age: mean 40.23 years, range 23 to 66 years

**Exclusion criteria**

- Not discussed in detail

**Interventions**

**Interventions (cross-over design)**

A: (n = 14) phase 1 (part 1): ultraviolet A1, 340 to 400 nanometers (NM) irradiation therapy at doses of 60 kj/m²5 times per week for 3 weeks; phase 1 (part 2): visible light placebo for 3 weeks

B: (n = 12) phase 1 (part 1): exposure to visible light placebo for 3 weeks. Phase 1 (part 2): ultraviolet A1 (340 to 400 NM) irradiation therapy at doses of 60 kj/m²3 times per week for 3 weeks
A and B combined: phase 2 extended 12-week unblinded treatment (same for all patients) of ultraviolet A1 (340 to 400 NM) irradiation therapy at doses of 60 kJ/m²3 times per week for 6 weeks, twice a week for 3 weeks, then once a week for 3 weeks

### Outcomes

#### Primary outcomes
None were reported

#### Secondary outcomes
Reported narrative (not quantitative)
Adverse events (narrative information - not quantitative)

### Funding source
Funding source was a US NIH grant

### Location
University dermatology clinic in New Orleans, Louisiana, USA

### Notes
Study used a bench canopy (fan-cooled sun bed) ALISUN "1000 Combi" (ALISUN company, Eindhoven, The Netherlands) with TL/10R lamps (Philips International, Eindhoven, The Netherlands) at 87 W/m² with duration 11.5 minutes at spectrum 340 to 450 NM with peak at 365 NM. UVasun filters (MUTZHAS Co., Munich, Germany) eliminated UVB and UVA2 emission

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
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</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>The word &quot;random&quot; was used by study authors; however the method used was unclear</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>The method of allocation concealment was not stated</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>Unclear risk</td>
<td>Quote: &quot;neither the physician nor the patient was aware of the irradiation source being used&quot;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Comment: blinding was likely sufficient</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Unclear risk</td>
<td>It is unclear whether assessors were blinded</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Unclear risk</td>
<td>In the initial phase, only 1 patient did not complete the study due to developing a sensitising rash. In all, 25 of 26 participants completed the study. Intention-to-treat analysis was not performed. Study authors analysed the data for only 25 of 26 participants who completed the study (per-protocol analysis)</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>Study protocol was not available. We were unable to assess whether all planned outcomes were reported. Study authors did publish results regardless of their statistical significance</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>Study authors did not publish comparative data for treatment groups, so we were unable to assess risk of baseline imbalance. Information was insufficient to assess whether an important risk of other bias exists</td>
</tr>
</tbody>
</table>
Meinao 1996

**Study characteristics**

**Methods**
This was a parallel-group randomised controlled trial.

**Participants**

- **Inclusion criteria**
  - 24 participants had SLE and 4 had skin lesions at the start of the study (2 in the chloroquine group and 2 in the placebo/prednisone group); details about types of skin lesions were not given.
  - Sex: 21 women, 2 men.
  - Age: mean 31 years in the chloroquine group; mean 30 years in the placebo/prednisone group.
  - Race: 9 white, 7 "non-white".

- **Exclusion criteria**
  - Life-threatening manifestations of lupus.

**Interventions**

- **Intervention (n = 12)**
  - A: chloroquine 250 mg/d for 12 months and prednisone (no higher than 0.5 mg/kg/d).

- **Control intervention (n = 12)**
  - B: placebo and prednisone (no higher than 0.5 mg/kg/d) for 12 months.

**Outcomes**

- **Primary outcomes**
  - Percentage of participants with presence of skin findings.

- **Secondary outcomes**
  - Adverse events.

**Funding source**
Funding source was not mentioned.

**Location**
Outpatient clinic at Universidade Federal de Sao Paulo, Sao Paulo, Brazil.

**Notes**

**Risk of bias**

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
</table>
| Random sequence generation (selection bias) | Unclear risk | Quote: "patients were randomly allocated into two groups"
| | | Comment: no details about sequence generation were given |
| Allocation concealment (selection bias) | Unclear risk | Method of allocation concealment was unclear |
| Blinding of participants and personnel (performance bias) All outcomes | Unclear risk | Study authors stated that the study was double-blind, but further details were not given |
| Blinding of outcome assessment (detection bias) All outcomes | Unclear risk | Insufficient details about blinding of assessors were given |
| Incomplete outcome data (attrition bias) | Low risk | In all, 23 of 24 participants completed the study. One placebo patient dropped out due to severe dyspepsia. Study authors did not state that they had per- |

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*Interventions for cutaneous disease in systemic lupus erythematosus (Review)*
Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
### Meinao 1996 (Continued)

All outcomes

formed an intention-to-treat (ITT) analysis. We were able to verify by examination of published data that an ITT analysis was indeed performed

<table>
<thead>
<tr>
<th>Bias</th>
<th>Risk</th>
<th>Evidence</th>
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<tbody>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>Study protocol was not available. Results were reported regardless of their statistical significance</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>Study authors presented a table with baseline characteristics of treatment groups, and there was no evidence of imbalance. Information was insufficient to assess whether an important risk of other bias exists</td>
</tr>
</tbody>
</table>

### Merrill 2010a

### Study characteristics

<table>
<thead>
<tr>
<th>Methods</th>
<th>This was a parallel-group, multi-centre, exploratory, phase 2b, double-blind, randomised, placebo-controlled trial</th>
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<tbody>
<tr>
<td>Participants</td>
<td><strong>Inclusion criteria</strong></td>
</tr>
<tr>
<td></td>
<td>• 257 participants with SLE; of these patients, 39 had BILAG A mucocutaneous domain, 146 had BILAG B mucocutaneous domain, 8 had BILAG A vasculitis domain, 30 had BILAG B vasculitis domain</td>
</tr>
<tr>
<td></td>
<td>• Sex: 234 women, 23 men</td>
</tr>
<tr>
<td></td>
<td>• Race: 143 white, 114 non-white</td>
</tr>
<tr>
<td></td>
<td>• Mean age ± SD: 40.5 ± 12.8 years in the placebo group; 40.2 ± 11.4 years in the rituximab group</td>
</tr>
<tr>
<td></td>
<td><strong>Exclusion criteria</strong></td>
</tr>
<tr>
<td></td>
<td>• Concomitant illness that required prednisone or cyclophosphamide</td>
</tr>
<tr>
<td></td>
<td>• History of cancer</td>
</tr>
<tr>
<td></td>
<td>• Organ-threatening SLE such as lupus nephritis or CNS disease</td>
</tr>
<tr>
<td></td>
<td>• Pregnancy</td>
</tr>
<tr>
<td>Interventions</td>
<td><strong>Intervention (n = 169)</strong></td>
</tr>
<tr>
<td></td>
<td>A: rituximab 1000 mg IV (total of 2 doses) given 14 days apart and prednisone plus a baseline immunosuppressant (azathioprine, mycophenolate mofetil, methotrexate) with assessments on days 1, 15, 168, and 182 and followed for a total of 12 months</td>
</tr>
<tr>
<td></td>
<td><strong>Control intervention (n = 88)</strong></td>
</tr>
<tr>
<td></td>
<td>B: placebo and prednisone plus a baseline immunosuppressant (azathioprine, mycophenolate mofetil, methotrexate) with assessments on days 1, 15, 168, and 182 and followed for a total of 12 months</td>
</tr>
<tr>
<td>Outcomes</td>
<td><strong>Primary outcomes</strong></td>
</tr>
<tr>
<td></td>
<td>None were reported</td>
</tr>
<tr>
<td></td>
<td><strong>Secondary outcomes</strong></td>
</tr>
<tr>
<td></td>
<td>Reported in a narrative manner</td>
</tr>
<tr>
<td></td>
<td>Adverse events (reported in a narrative manner (not quantitatively))</td>
</tr>
<tr>
<td>Funding source</td>
<td>Funding was from Genentech</td>
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<tr>
<td>Location</td>
<td>55 centres at various outpatient clinics in North America</td>
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</table>
### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Randomisation was stated, but no details were given. Randomisation was done at a 2:1 ratio</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Details about allocation concealment were not given</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Low risk</td>
<td>This study was double-blind</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Unclear risk</td>
<td>Insufficient details about blinding of assessors were given</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>Study authors included a flow chart table of reasons for withdrawal. Study authors did not state that they had performed an intention-to-treat (ITT) analysis. We were able to verify that an ITT analysis was indeed performed by examining published study data</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>High risk</td>
<td>Study protocol was not available. Most data were reported. Some data were omitted. For example, for sub-analyses, study authors are quoted as follows: “there were no differences in the endpoint in prespecified subgroup analysis except in the African-American/Hispanic group which comprised approximately one third of the patients in the study”</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>Study authors provided a baseline demographic table. No significant differences were noted between treatment groups at baseline. Information was insufficient to assess whether an important risk of other bias exists</td>
</tr>
</tbody>
</table>

### Study characteristics

#### Methods

This was a parallel-group, randomised, triple-blind, placebo-controlled trial

#### Participants

**Inclusion criteria**

- 185 participants with SLE (60 with active discoid lesions)
- Sex: 159 women, 16 men
- Race: 113 white, 62 non-white
- Mean age: 38.6 ± 12.14 SD years

**Exclusion criteria**

- Lupus nephritis
- CNS lupus
- Concomitant disease that required systemic steroids
- Pregnancy
Merrill 2010b (Continued)

- Breast-feeding

Interventions

**Intervention (n = 41)**

A: abatacept 0.9% IV infusion (10 mg/kg) on days 1, 15, and 29, then each 4 weeks up to day 337 in study of 12 months, as well as prednisone 30 mg/d or equivalent for 1 month plus background treatments of azathioprine, antimalarial agents, ciclosporin, methotrexate, mycophenolate acid, tacrolimus, corticosteroids, NSAIDs, proteinuria therapies, and statins

**Control intervention (n = 19)**

B: normal saline IV infusion on days 1, 15, and 29, then each 4 weeks up to day 337, as well as prednisone 30 mg/d or equivalent for 1 month plus background treatments of azathioprine, antimalarial agents, ciclosporin, methotrexate, mycophenolate acid, tacrolimus, corticosteroids, NSAIDs, proteinuria therapies, and statins

Outcomes

**Primary outcomes**

None were reported

**Secondary outcomes**

Reported flare in discoid lesions (new BILAG A or B)

New BILAG A over past year

Reported flare in physician-based assessment of discoid lesions

Adverse events

Funding source

Funding was provided by Bristol-Myers Squibb, Princeton, NJ, and UCB Pharma

Location

Outpatient clinics at multiple university centres and research institutes in the USA, Mexico, Belgium, Canada, UK, South Korea, and Australia

Notes

**Risk of bias**

<table>
<thead>
<tr>
<th>Bias</th>
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</tr>
</thead>
<tbody>
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<td>Unclear risk</td>
<td>Randomisation was stated but no details about methods were given</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>No details about allocation concealment were given</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>Low risk</td>
<td>Study authors stated that this was a double-blind trial. Minimal details on preparation of intravenous solutions were given</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Unclear risk</td>
<td>Quote: there was &quot;a blinded analysis of BILAG prior to unblinding...&quot; Comment: at least part of the assessment was blinded; however further details were not given</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Low risk</td>
<td>A detailed accounting of outcome data was given. Study authors even discussed differences in enrolment versus randomisation. Intention-to-treat (ITT) analysis was stated as performed by study authors. We were able to verify that ITT was performed by examining published data</td>
</tr>
</tbody>
</table>
Merrill 2010b (Continued)

<table>
<thead>
<tr>
<th>Selective reporting (reporting bias)</th>
<th>Unclear risk</th>
<th>Study protocol was not available. Planned primary and secondary outcomes were reported, as were statistically insignificant results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>Study authors had some issues with the definition of flares in the computer system. Correction was careful and appears to be valid. Randomisation was stratified by the confounders of primary manifestation and by BILAG. There was no evidence of baseline imbalance. Information was insufficient to assess whether an important risk of other bias exists</td>
</tr>
</tbody>
</table>

Merrill 2011

**Study characteristics**

**Methods**

This was a phase 1, double-blind, multi-arm, randomised, placebo-controlled trial

**Participants**

**Inclusion criteria**

- 51 participants with SLE; 46 had active mucocutaneous involvement
- Sex: 47 women, 4 men
- Race: 40 white, 11 non-white
- Mean age ± SD: 48 years ± 10 SD in the placebo group with range of 36 of 65 years; 44 years ± 11 SD in the intervention groups with range of 23 to 80 years

**Exclusion criteria**

- Recent immunosuppressive agents
- Infection
- Active central nervous system (CNS) lupus
- Cardiac, liver, or renal disease

**Interventions**

**Interventions**

A: (n = 6) sifalimumab (anti-tumour necrosis factor (TNF)-α monoclonal antibody) 0.3 mg/kg single intravenous dose for 84 days

B: (n = 6) sifalimumab (anti-TNF-α monoclonal antibody) 1 mg/kg single intravenous dose for 84 days

C: (n = 6) sifalimumab (anti-TNF-α monoclonal antibody) 3 mg/kg single intravenous dose for 84 days

D: (n = 7) sifalimumab (anti-TNF-α monoclonal antibody) 10 mg/kg single intravenous dose for 84 days

E: (n = 8) sifalimumab (anti-TNF-α monoclonal antibody) 30 mg/kg single intravenous dose for 84 days

**Control intervention (n = 17)**

F: placebo for 84 days (approximately 3 months)

This study also had a second phase (open-label) with 18 patients (3 of whom had been part of the first blinded part of the study, together with 15 new participants)

**Outcomes**

**Primary outcomes**

None were reported

**Secondary outcomes**

Reported outcome of flares in lupus
### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Study was randomised 2:1, and no further details were given</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>No details about allocation concealment were given</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Low risk</td>
<td>Study authors reported that this was a double-blind study (first phase) followed by an open-label study (unblinded in the second phase)</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Unclear risk</td>
<td>Details given about blinding of assessors were insufficient</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Unclear risk</td>
<td>There was 1 dropout before medication administration. Study authors did not state that they had performed an intention-to-treat (ITT) analysis. We could not verify that an ITT analysis was indeed performed by examining published study data</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>High risk</td>
<td>Study protocol was not available. Some data were missing. For example, fewer patients with photographs for skin lesion comparison were discussed in the results than initially planned. Study authors did report at least some statistically insignificant results</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>Study authors provided a table of baseline characteristics, and there was no evidence of baseline imbalance between treatment groups. Information was insufficient to assess whether an important risk of other bias exists</td>
</tr>
</tbody>
</table>

### Study characteristics

**Methods**

This was a phase 3, multi-centre, parallel-group, double-blind, placebo-controlled, randomised trial

**Participants**

**Inclusion criteria**

- 1124 participants with SLE (by 1997 ACR criteria) and moderate to severe activity (by Safety of Estrogens in Lupus Erythematosus National Assessment - SLE Disease Activity Index ≥ 6 at baseline)
- Sex: female 91.9% to 92.8% of patients, depending on treatment group
- Race: white (majority), indigenous American, Asian, Black/African American, multiple races
- Mean age: approximately 42 years with SD of 12, range 18 to 83 years

**Exclusion criteria**
### Interventions

- **Interventions**
  A: (n = 372) subcutaneous tabalumab starting with a loading dose (240 mg) at week 0 and followed by 120 mg every 2 weeks (120 Q2W) for 12 months plus standard of care
  B: (n = 376) 120 mg every 4 weeks (120 Q4W) (administered by alternating 120 mg tabalumab injections and placebo Q2W) plus standard of care

- **Control intervention (n = 376)**
  C: subcutaneous placebo every 2 weeks for 12 months plus standard of care

### Outcomes

- **Primary outcomes**
  None were reported

- **Secondary outcomes**
  SLEDAI mucocutaneous domain improvement (% of patients)

- **Adverse events: minor and severe**

### Funding source

Funding for the study was provided by Eli Lilly

### Location

This multi-centre study was located in numerous countries around the world (USA, Canada, Mexico, Central America, South America, Europe, Africa, Middle East, Asia)

### Notes

This trial (NCT01205438) was called ILLUMINATE-2

### Risk of bias

<table>
<thead>
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<td></td>
<td>Comment: no details about the method of random sequence generation were given</td>
</tr>
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<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>It is unclear whether randomisation was centralised</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>Low risk</td>
<td>Quote: this was a &quot;double-blind&quot; trial</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Comment: blinding of participants and personnel was likely sufficient</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Unclear risk</td>
<td>It is unclear whether assessors were blinded</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Low risk</td>
<td>Study authors presented a detailed table of withdrawals. Withdrawals comprised 20.7% to 23.4% of each group. Analysis was intent-to-treat</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>No protocol was available</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Quote: &quot;although key secondary endpoints were not met, numerous other secondary endpoints significantly improved&quot;</td>
</tr>
</tbody>
</table>
Merrill 2016 (Continued)

Other bias | Unclear risk
---|---

Study authors presented a detailed table of baseline characteristics. There was no evidence of baseline imbalance. Information was insufficient to assess whether an important risk of other bias exists.

Merrill 2018

**Study characteristics**

<table>
<thead>
<tr>
<th>Methods</th>
<th>This was a phase 2, multi-centre, multiple-group, double-blind, placebo-controlled, randomised trial</th>
</tr>
</thead>
</table>

### Participants

**Inclusion criteria**
- 349 participants with SLE (by 1982 and 1997 ACR criteria) and moderate to severe activity (participants were required to have elevated serum antinuclear antibodies, as well as BILAG “A” (severe) or “B” (moderate) arthritis and/or cutaneous manifestations, and SLEDAI ≥ 6 (at least 4 from clinical features)
- Sex: not stated
- Race: not stated
- Mean age: not stated

**Exclusion criteria**
- Normal serum antinuclear antibodies
- No minimum criteria of BILAG “A” (severe) or “B” (moderate) arthritis and/or cutaneous manifestations, and SLEDAI ≥ 6 (at least 4 from clinical features)
- Maximum dose of corticosteroids exceeds 30 mg/d of prednisone or equivalent at screening and exceeds 10 mg/d at day 1

### Interventions

**Interventions**
- A: (n = 69) subcutaneous lulizumab pegol (lulizumab) 12.5 mg weekly for 6 months plus standard of care
- B: (n = 68) subcutaneous lulizumab pegol (lulizumab) 12.5 mg every other week for 6 months plus standard of care
- C: (n = 68) subcutaneous lulizumab pegol (lulizumab) 5 mg every other week for 6 months plus standard of care
- D: (n = 70) subcutaneous lulizumab pegol (lulizumab) 1.25 mg every other week for 6 months plus standard of care
- **Control intervention (n = 71)**
  E: subcutaneous placebo weekly for 6 months (24 weeks) plus standard of care

### Outcomes

**Primary outcomes**
- None were reported

**Secondary outcomes**
- CLASI change from baseline
- CLASI-20
- CLASI-50
Merrill 2018 (Continued)

Adverse events: minor and severe

Funding source
Funding for the study was provided by Bristol Myers Squibb

Location
This international multi-centre study was performed in the USA, Argentina, Brazil, Canada, Chile, Colombia, France, Germany, Hungary, Italy, Japan, Korea, Lebanon, Mexico, Netherlands, Peru, Poland, Romania, Russian Federation, South Africa, Spain, and Taiwan

Notes
NCT02265744

Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
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<td>Quote: this was a &quot;randomized&quot; trial</td>
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<td></td>
<td>Comment: no details about the method of random sequence generation were given</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>It is unclear whether randomisation was centralised</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Unclear risk</td>
<td>Quote: this was a &quot;double-blind&quot; trial</td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
<td>Comment: blinding of participants and personnel was likely sufficient</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Unclear risk</td>
<td>It is unclear whether assessors were blinded</td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
<td>Study authors presented a detailed table of withdrawals. Withdrawals comprised 4.2% of the placebo group and 7.4% to 13.2% of each treatment group. Analysis was not intent-to-treat. Data were presented only for 346/349. The 3 missing participants were not discussed</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Unclear risk</td>
<td>A protocol was available at <a href="https://clinicaltrials.gov/ct2/show/study/NCT02265744">https://clinicaltrials.gov/ct2/show/study/NCT02265744</a></td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
<td>Comment: planned endpoints were reported regardless of statistical significance. Available published data are minimal compared with the long protocol</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>No table of baseline characteristics was presented. No information about baseline characteristics were given to assess for imbalance. Information was insufficient to assess whether an important risk of other bias exists</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>No table of baseline characteristics was presented. No information about baseline characteristics were given to assess for imbalance. Information was insufficient to assess whether an important risk of other bias exists</td>
</tr>
</tbody>
</table>

Navarra 2011

Study characteristics

Methods
This was a multi-arm, triple-blind, randomised, placebo-controlled trial

Participants

Inclusion criteria

- 867 participants with SLE by ACR criteria and CLE (513 participants with baseline BILAG mucocutaneous domain findings and 709 participants with SELENA/SLEDAI baseline mucocutaneous domain findings)
Navarra 2011 (Continued)

- Sex: 821 women, 46 men
- Race: 229 white, 638 non-white
- Mean age ± SD: 35.0 years ± 10.6 SD for low-dose intervention group; 35.4 years ± 10.8 SD for high-dose intervention group; 36.2 years ± 11.8 SD for placebo group

**Exclusion criteria**

- Severe lupus nephritis
- CNS lupus
- Pregnancy
- Previous B-lymphocyte target drug
- IV cyclophosphamide
- Prednisone > 100 mg/d

### Interventions

#### Interventions

**A** (n = 288) belimumab 1 mg/kg intravenous dose during 1 hour infusion on days 0, 14, and 28, then each month for 48 weeks

and continued standard of care (with changes not permitted after 16 weeks for immunosuppressant agents and 24 weeks for antimalarials)

**B** (n = 290) belimumab 10 mg/kg intravenous dose during 1 hour infusion on days 0, 14, and 28, then each month for 48 weeks

and continued standard of care (with changes not permitted after 16 weeks for immunosuppressant agents and 24 weeks for antimalarials)

**Control intervention** (n = 287)

C: placebo intravenous dose during 1 hour infusion days 0, 14, and 28, then each month for 48 weeks and continued standard of care (with changes not permitted after 16 weeks for immunosuppressant agents and 24 weeks for antimalarials)

### Outcomes

#### Primary outcomes

None were reported

#### Secondary outcomes

BILAG, SELENA/SLEDAI mucocutaneous domains (narrative data only - no quantitative data)

### Adverse events

#### Funding source

Funding was provided by Human Genome Sciences and Glaxo-Smith Kline

#### Location

Outpatient clinics at 90 centres in 13 countries in Latin America, Asia, Pacific and Eastern Europe, Australia, Hong Kong, India, Korea, Philippines, Taiwan, Argentina, Brazil, Chile, Colombia, Peru, Romania, Russia

#### Notes

This was called the BLISS-S2 Trial; trial number NCT00424476

### Risk of bias

#### Bias

<table>
<thead>
<tr>
<th><strong>Bias</strong></th>
<th><strong>Authors' judgement</strong></th>
<th><strong>Support for judgement</strong></th>
</tr>
</thead>
</table>
| Random sequence generation (selection bias) | Low risk               | Quote: "patients...assigned to treatment by use of a central stratified voice response system, with central randomisation list"
|                            |                        | Comment: random sequence generation was likely sufficient because randomisation list was used |
### Navarra 2011 (Continued)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Risk</th>
<th>Description</th>
</tr>
</thead>
</table>
| **Allocation concealment** (selection bias) | Low risk | Quote: "central randomisation list provided by Human Genome Sciences"  
Comment: allocation concealment was likely sufficient because allocation was centralised |
| **Blinding of participants and personnel** (performance bias) | Low risk | Quote: "patients, investigators, study coordinators, and sponsors were masked"; "an unmasked pharmacist used unmarked infusion bags"  
Comment: blinding was likely sufficient for participants and personnel |
| **Blinding of outcome assessment** (detection bias) | Unclear risk | It is unclear whether all assessors were masked because specific details were not given |
| **Incomplete outcome data** (attrition bias) | Low risk | Study authors used a modified intention-to-treat analysis. They excluded 2 patients who had never received any study treatment |
| **Selective reporting** (reporting bias) | Unclear risk | Study protocol was not available. Study authors reported outcomes regardless of statistical significance |
| **Other bias** | Unclear risk | Study authors provided detailed information in tabular form showing no evidence of baseline imbalance. Information was insufficient to assess whether an important risk of other bias exists |

### Ordi-Ros 2017

**Study characteristics**

**Methods**
This was a multi-centre, superiority, open-label, randomised, controlled trial.

**Participants**
- **Inclusion criteria**
  - 240 participants with active SLE (by ACR criteria)
  - Sex: not stated
  - Race: not stated
  - Mean age: not given; all patients were 18 years of age or older
- **Exclusion criteria**
  - Not stated in abstract

**Interventions**
- **Intervention (n = 120)**
  - A: oral enteric-coated mycophenolate sodium (target dose: 1440 mg/d) for 24 months, in addition to prednisone and/or antimalarials
- **Control intervention (n = 120)**
  - B: oral azathioprine (target dose: 2 mg/kg/d) for 24 months, in addition to prednisone and/or antimalarials

**Outcomes**
- **Primary outcomes**
  - None were reported
- **Secondary outcomes**
### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
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<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Quote: this was a &quot;randomized&quot; trial</td>
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<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Comment: no details about method of random sequence generation were given</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>High risk</td>
<td>Quote: this was an &quot;open-label&quot; study</td>
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<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Unclear risk</td>
<td>Comment: there was no blinding</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Unclear risk</td>
<td>We were unable to assess information about withdrawals or intention-to-treat analysis</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>Study protocol was not available. Planned outcomes from the methods section were reported in the results</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>We were unable to assess information about baseline imbalance. Information was insufficient to assess whether an important risk of other bias exists</td>
</tr>
</tbody>
</table>

### Pena-Rossi 2009

**Study characteristics**

**Methods**

This was a parallel-group, multi-arm, double-blind, randomised, placebo-controlled, sequential dose-escalating, exploratory phase 1b study

**Participants**

**Inclusion criteria**

- 24 participants with SLE; at baseline, 16 had photosensitivity, 14 malar rash, 4 oral ulcers, and 10 discoid lupus
- Sex: 22 women, 2 men

---

Funding source: Funding source was not stated

Location: Multiple centres in Spain

Notes: Trial number was NCT01112215
### Exclusion criteria

- Immunosuppressant drugs 8 weeks before study of prednisone > 20 mg/d or hydroxychloroquine > 400 mg/d
- Change in dose regimen 4 weeks before the study
- Previous therapy with another biological agent
- Severe renal disease
- Severe CNS lupus disease
- Infection
- Pregnancy
- Breast-feeding

| Interventions | A: (n = 5) atacicept (recombinant fusion protein) intravenous 3 mg/kg single dose followed for 6 weeks  
B: (n = 5) atacicept (recombinant fusion protein) intravenous 9 mg/kg single dose followed for 6 weeks  
C: (n = 5) atacicept (recombinant fusion protein) intravenous 18 mg/kg single dose followed for 6 weeks  
D: (n = 5) atacicept (recombinant fusion protein) intravenous 9 mg/kg multiple doses (2 doses) followed for 9 weeks  
E: placebo |
|---|---|

### Primary outcomes

None were reported

### Secondary outcomes

Adverse events

### Funding source

Funding was provided by Merck-Serono (Geneva, Switzerland) and ZymoGenetics (Seattle, WA, USA)

### Location

3 centres in Russia

### Notes

Protocol number was 25842

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
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<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Study was randomised 5:1, but the randomisation method was not stated</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>No details about allocation concealment were given</td>
</tr>
</tbody>
</table>
| Blinding of participants and personnel (performance bias) All outcomes | Low risk | Study authors reported that this study was double-blind. They stated that they used "matching" placebo but gave no additional details  
Comment: blinding was likely sufficient |
**Pena-Rossi 2009** (Continued)

<table>
<thead>
<tr>
<th>Blinding of outcome assessment (detection bias)</th>
<th>Unclear risk</th>
<th>Insufficient details about blinding of assessors were given</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>No withdrawals from the study were reported, and all data presented in the study were analysed</td>
</tr>
<tr>
<td>All outcomes</td>
<td>Low risk</td>
<td>Study protocol was available. All planned outcome measures, including statistically insignificant results, were reported</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>Study authors presented baseline data, and there was no evidence of baseline treatment group imbalance. Information was insufficient to assess whether an important risk of other bias exists</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>Study authors presented baseline data, and there was no evidence of baseline treatment group imbalance. Information was insufficient to assess whether an important risk of other bias exists</td>
</tr>
</tbody>
</table>

**Petri 2004**

**Study characteristics**

<table>
<thead>
<tr>
<th>Methods</th>
<th>This was a parallel-group, randomised, double-blind, placebo-controlled trial</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inclusion criteria</strong></td>
</tr>
<tr>
<td>- 381 women with active SLE</td>
</tr>
<tr>
<td>- Race: 283 white, 98 black</td>
</tr>
<tr>
<td>- Mean age: 43.8 years for placebo, 44.4 years for prasterone</td>
</tr>
<tr>
<td><strong>Exclusion criteria</strong></td>
</tr>
<tr>
<td>- Immunosuppressive medications</td>
</tr>
<tr>
<td>- Severe renal or CNS involvement</td>
</tr>
<tr>
<td>- Breast-feeding</td>
</tr>
<tr>
<td>- Liver disease</td>
</tr>
<tr>
<td>- Infection</td>
</tr>
<tr>
<td>- Pregnancy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intervention (n = 189)</strong></td>
</tr>
<tr>
<td>A: oral prasterone (dehydroepiandrosterone, or DHEA) 200 mg daily plus standard SLE treatments for up to 12 months</td>
</tr>
<tr>
<td>Standard SLE treatments were stable unchanged dosages before the study and during the protocol period, such as prednisone (&lt; 10 mg/d), antimalarials, and immunosuppressive agents</td>
</tr>
<tr>
<td><strong>Control intervention (n = 192)</strong></td>
</tr>
<tr>
<td>B: placebo plus standard SLE treatments for up to 12 months</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcomes</strong></td>
</tr>
<tr>
<td>Percentage of participants with rash, acne, stomatitis (mucosal ulcers), alopecia</td>
</tr>
<tr>
<td><strong>Secondary outcomes</strong></td>
</tr>
<tr>
<td>Reported time to SLE flare</td>
</tr>
<tr>
<td>Mean changes in individual scoring instruments</td>
</tr>
</tbody>
</table>
Petri 2004 (Continued)

Adverse events (analysed with table)

Funding source
Funding was provided by Genelabs Technologies, Inc., Redwood City, California, USA

Location
This multi-centre study was conducted at 27 centres in USA and Sweden

Notes

Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Quote: “predetermined randomisation codes assigned”</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Comment: randomisation method for participants was likely sufficient</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Randomisation codes were “predetermined randomisation codes” assigned to participants, so allocation concealment was likely sufficient and was unlikely to have been foreseen</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>Low risk</td>
<td>Quote: “capsules containing placebo were identical to those containing prasterone”</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Comment: blinding for investigators and participants was likely sufficient</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Unclear risk</td>
<td>Details about blinding of assessors were not given</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>In the placebo group of 192 participants, 142 (74%) completed the study and 50 (26%) discontinued the placebo early. Of the early discontinuations (withdrawals), 9 (4.7%) were due to lack of efficacy, 11 (5.7%) to an adverse event, and 30 (15.6%) to other reasons. In the prasterone group of 189 participants, 124 (65.6%) completed the study and 65 (34.4%) discontinued the study early. Of the early discontinuations (withdrawals), 11 (5.8%) were due to lack of efficacy, 27 (14.3%) to an adverse event, and 27 (14.3%) to other reasons. There were no meaningful differences in withdrawals between the 2 groups, except for withdrawals due to adverse events ($P = 0.005$). Per study authors, the differences in withdrawals were primarily reflected by androgenic adverse events (acne or hirsutism) in the prasterone group, a majority of which were mild. Study authors stated that they performed an intention-to-treat (ITT) analysis. We confirmed that an ITT analysis was performed by examining published data</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>Study protocol was not available. All planned primary and secondary outcomes were reported in results, regardless of statistical significance</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>Study authors presented a table of baseline characteristics of study patients (by treatment group). There was no evidence of baseline imbalance. Information was insufficient to assess whether an important risk of other bias exists</td>
</tr>
</tbody>
</table>

Petri 2010

Study characteristics

Methods
This was a parallel-group, randomised, controlled trial
### Participants

**Inclusion criteria**
- 51 participants with SLE; 11 had “other” organ involvement that may include skin involvement
- Any patients enrolled in the study as a result of cutaneous disease were required to have failed hydroxychloroquine/quinacrine as well as immunosuppression
- Sex: 42 women, 5 men
- Race: 15 white, 35 non-white
- Age range: 27 participants between 18 and 39 years; 20 between 40 and 59 years

**Exclusion criteria of the trial**
- Musculoskeletal lupus

### Interventions

**Intervention (n = 24)**
A: high-dose intravenous cyclophosphamide 50 mg/kg daily for 4 days without stem cell rescue (1 cycle only) monitored for 24 months

**Control intervention (n = 27)**
B: monthly dosing with IV cyclophosphamide at 750 mg/m² body mass index for 6 months, then each 3 months for 24 months

### Outcomes

**Primary outcomes**
Narrative information (not quantitative)

**Secondary outcomes**
Adverse events

### Funding source
Funding source was the US National Institute of Arthritis and Musculoskeletal and Skin Diseases

### Location
2 university clinics in Baltimore, Maryland, USA

### Notes

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Randomisation was stated, but no details on methods used were given</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Allocation concealment was not specifically discussed by study authors</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>High risk</td>
<td>This study included no blinding</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>High risk</td>
<td>This study included no blinding</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Unclear risk</td>
<td>Three withdrawals occurred before medication was given. One patient withdrew due to suicide. No intention-to-treat analysis was performed. Studt authors did not analyse data on 4 dropouts</td>
</tr>
</tbody>
</table>
### Selective reporting (reporting bias)

<table>
<thead>
<tr>
<th>Risk</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unclear</td>
<td>Study protocol was not available. Important outcomes including negative results were reported</td>
</tr>
</tbody>
</table>

### Other bias

<table>
<thead>
<tr>
<th>Risk</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unclear</td>
<td>Results show no evidence of baseline imbalance. Any confounders were most likely accounted for by randomisation. Information was insufficient to assess whether an important risk of other bias exists</td>
</tr>
</tbody>
</table>

---

### Study characteristics

#### Methods

This was a double-blind, placebo-controlled, randomised, multi-arm sequential dose escalation trial.

#### Participants

**Inclusion criteria**

- 161 participants with SLE (15 had BILAG A scores for mucocutaneous domain and 90 had BILAG B scores for mucocutaneous domain at baseline)
- Sex: 154 women, 7 men
- Race: 116 white, 40 black, 4 Asian, 1 other
- Mean age: 44.8 years ± 10.9 SD for placebo group, 42.2 years ± 11.3 SD for combined intervention group

**Exclusion criteria**

- Active illness other than SLE
- Infection
- Certain prior medications

#### Interventions

**Interventions**

A: (n = 26) intravenous sifalimumab 0.3 mg/kg administered over ≥ 60 minutes every 2 weeks for 26 weeks (6.5 months) for a total of 14 doses. Participants were monitored for an additional 24 weeks post treatment (total time of study approximately 54 weeks - 12.5 months). Stable doses of prednisone, antimalarials, or immunosuppressives with 2 courses of burst oral steroids allowed during day 0 to day 126

B: (n = 25) intravenous sifalimumab 1 mg/kg administered over ≥ 60 minutes every 2 weeks for 26 weeks (6.5 months) for a total of 14 doses and monitored afterwards for a total of 12.5 months. Stable doses of prednisone, antimalarials, or immunosuppressives with 2 courses of burst oral steroids allowed during day 0 to day 126

C: (n = 27) intravenous sifalimumab 3 mg/kg administered over ≥ 60 minutes every 2 weeks for 26 weeks (6.5 months) for a total of 14 doses and monitored afterwards for a total of 12.5 months. Stable doses of prednisone, antimalarials, or immunosuppressives with 2 courses of burst oral steroids allowed during day 0 to day 126

D: (n = 43) intravenous sifalimumab 10 mg/kg administered over ≥ 60 minutes every 2 weeks for 26 weeks (6.5 months) for a total of 14 doses and monitored afterwards for a total of 12.5 months. Stable doses of prednisone, antimalarials, or immunosuppressives with 2 courses of burst oral steroids allowed during day 0 to day 126

**Control intervention (n = 40)**

E: placebo and stable doses of prednisone, antimalarials, or immunosuppressives with 2 courses of burst oral steroids allowed during day 0 to day 126

#### Outcomes

**Primary outcomes**

None were reported
Petri 2013 (Continued)

**Secondary outcomes**

Adverse events

---

**Funding source**

Funding was provided by MedImmune, LLC

**Location**

Multiple centres in USA, Canada, Argentina, Brazil, and Chile

**Notes**

Sifalimumab was formerly known as MEDI-545

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**Risk of bias**

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Quote: “the randomization list was generated by United BioSource Corporation” Comment: random sequence generation was likely sufficient</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Quote: &quot;treatment was assigned using a central interactive voice response system&quot; Comment: allocation concealment was likely sufficient</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>Low risk</td>
<td>Quote: &quot;subjects and clinical site staff were blinded to treatment allocation&quot; Comment: blinding of participants and personnel was likely sufficient</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Unclear risk</td>
<td>Insufficient details about blinding of assessors were given</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Low risk</td>
<td>Study authors accounted for and described reasons for withdrawal in a text and flow diagram. Study authors stated that they performed an intention-to-treat (ITT) analysis. We verified that they indeed performed an ITT analysis by examining published data. Study authors also reported that they used a modified intent-to-treat analysis</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>Study protocol was not available. All planned outcome measures regarding statistically insignificant outcomes were reported</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>Study authors note that bias may have been introduced by cohorts that had variable enrolment based on country and site. They also note that heterogeneous baseline characteristics of the study population made comparisons between groups difficult. Information was insufficient to assess whether an important risk of other bias exists</td>
</tr>
</tbody>
</table>

---

**Polderman 2001**

**Study characteristics**

**Methods**

This was a randomised double-blind placebo-controlled cross-over study

**Participants**

Inclusion criteria

- 11 participants with “mild/moderate” SLE
Polderman 2001 (Continued)

- All 11 participants were evaluated for the SLAM integument domain
- Sex: 10 women, 1 man
- Race: 9 “white” and 2 “dark skin colour”
- Mean age 38.1 years, age range 18 to 56 years, median 35 years

**Exclusion criteria**
- None mentioned

**Interventions**

**Intervention (cross-over design)**

A: (n = 9)

Phase 1: ultraviolet A-1 (long wave cold light) therapy with irradiation to total body of 6 J/cm² 5 days a week for 3 weeks; washout period 9 weeks

Phase 2: placebo (TL light tubes with blue plastic) with equivalent exposure times of 3 minutes 20 seconds for 3 weeks, followed by a washout period of 9 weeks

B: (n = 2)

Phase 1: placebo (TL light tubes with blue plastic) with equivalent exposure times of 3 minutes 20 seconds for 3 weeks, followed by washout period of 9 weeks

Phase 2: ultraviolet A-1 (long wave cold light) therapy with irradiation to total body of 6 J/cm² 5 days a week for 3 weeks; washout period 9 weeks

**Outcomes**

**Primary outcomes**

None were reported

**Secondary outcomes**

Reported SLAM integument domain with incomplete quantitative data

Adverse events (narrative form)

**Funding source**

Funding was provided by the Dutch League against Rheumatism

**Location**

Dermatology and Rheumatology outpatient clinic in the Netherlands

**Notes**

Machine used was the Photomed 250,000 (Photomed Medizintechnik GmbH Vertrieb Deutschland, Gehrden, Germany) with filter system to eliminate infrared

**Risk of bias**

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
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<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Patients were randomly allocated by an &quot;independent person&quot;. Study authors did not describe the method of randomisation</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Allocation concealment was not described in detail</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Low risk</td>
<td>Quote: “both the doctor and the patients were blinded to the treatment”</td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
<td>Comment: blinding was likely sufficient</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Unclear risk</td>
<td>Insufficient details about blinding of assessors were given</td>
</tr>
</tbody>
</table>
### Polderman 2001 (Continued)

| Incomplete outcome data (attrition bias) | Low risk | No loss to follow-up was reported. All published data were analysed |
| Selective reporting (reporting bias) | Unclear risk | Study protocol was not available. All outcomes mentioned in the methods were reported in the results, including negative results |
| Other bias | Unclear risk | Study authors attempted to control for "washout" effects. There was no evidence of baseline imbalance. Information was insufficient to assess whether an important risk of other bias exists |

### Rupp 1987

#### Study characteristics

**Methods**
This was a randomised prospective double-blind cross-over study

**Participants**

**Inclusion criteria**

- 15 participants with connective tissue disease-related Raynaud’s phenomenon (6 with SLE, 8 with other systemic sclerosis, 1 with rheumatoid arthritis)
- Sex: 13 women, 2 men
- Race: not stated
- Mean age: 42.5 years
- This was one-half of a larger study of 30 patients that also included 15 patients with primary Raynaud’s disease; data on the 2 types of Raynaud’s (Raynaud’s disease versus Raynaud’s phenomenon) were analysed separately

**Exclusion criteria**

- Sensitivity to calcium channel blockers
- Coronary disease
- Atherosclerotic disease
- Vascular disease
- Digital amputations
- Pregnancy
- Breast-feeding
- Occupational Raynaud’s

**Interventions**

**Intervention (n = 15)**

A: oral nicardipine 3 times a day for 4 weeks (1 month)

**Control intervention (n = 15)**

B: placebo for 4 weeks (1 month) (a single treatment group crossed over to placebo after 1 month of treatment, for a total trial duration of 2 months)

**Outcomes**

**Primary outcomes**

None were reported

**Secondary outcomes**

Decreased number of "flares" in disease, as defined by the number of Raynaud’s attacks/d
### Rupp 1987 (Continued)

- **Decreased severity of Raynaud’s attacks**
- **Adverse events (minor and severe)**

<table>
<thead>
<tr>
<th><strong>Funding source</strong></th>
<th>Funding was provided by Syntex Laboratories and University of Iowa CRC Grant RR59</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Location</strong></td>
<td>University Hospital and Clinics in Iowa, USA</td>
</tr>
</tbody>
</table>

**Notes**

#### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Study authors stated that the trial was randomised; however no details about the method of random sequence generation were given</td>
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<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>No details about the method of allocation concealment were given</td>
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<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Low risk</td>
<td>This was a double-blind study. Capsules and placebos were noted to be &quot;indistinguishable&quot;</td>
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<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Unclear risk</td>
<td>Insufficient details about blinding of assessors were given</td>
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<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>All SLE patients completed the study. Withdrawals from other arms of the study were fully accounted for. One patient withdrew due to headache</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>Study protocol was not available. All planned outcomes appear to have been reported regardless of statistical significance</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>Study authors reported baseline characteristics of treatment groups; there was no evidence of baseline imbalance. Information was insufficient to assess whether an important risk of other bias exists</td>
</tr>
</tbody>
</table>

### Stohl 2017

#### Study characteristics

**Methods**

This was a 52-week randomised, double-blind, placebo-controlled study of the efficacy and safety of subcutaneous belimumab in systemic lupus erythematosus

**Participants**

- **Inclusion criteria**
  - 839 participants with SLE (by ACR criteria) with CLE
  - Sex: most patients were female (93.7% receiving belimumab, 95.7% receiving placebo)
  - Race: in the placebo group, 80 people were Hispanic/Latino compared with 160 in the treatment group; in the placebo group, 200 people were "not Hispanic or Latino", and 396 were "not Hispanic or Latino" in the treatment group
  - Mean age: 38.6 years (38.1 years in the belimumab group, 39.6 years in the placebo group)
### Exclusion criteria
- Not stated

### Interventions

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A: (n = 556)</td>
<td>belimumab 200 mg SC weekly by prefilled syringe for 52 weeks</td>
</tr>
<tr>
<td>B: (n = 280)</td>
<td>placebo SC weekly by prefilled syringe in addition to standard SLE therapy for 52 weeks</td>
</tr>
</tbody>
</table>

### Control Intervention

- B: (n = 280) placebo SC weekly by prefilled syringe in addition to standard SLE therapy for 52 weeks

### Outcomes

#### Primary outcomes
None were reported

#### Secondary outcomes
- SRI mucocutaneous domain
- Adverse events (minor and severe)

### Funding source
Study was funded by GlaxoSmithKline PLC (GSK)

### Location
- 177 sites in 30 countries in North, Central, and South America; Eastern and Western Europe; Australia; and Asia between November 2011 and February 2015

### Notes
Study was known as the “BLISS-SC study” (BLISS-SC ID BEL112341; ClinicalTrials.gov ID NCT01484496)

### Risk of bias

<table>
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<tr>
<th>Bias</th>
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<th>Support for judgement</th>
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<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Unclear risk</td>
<td>No information about blinding of assessors was given</td>
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<tr>
<td>All outcomes</td>
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<td></td>
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<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
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<tr>
<td>All outcomes</td>
<td></td>
<td>Comment: detailed information about withdrawals from the study was given</td>
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</table>
Stohl 2017 (Continued)

<table>
<thead>
<tr>
<th>Source: Stohl 2017</th>
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<tbody>
<tr>
<td>Selective reporting (reporting bias)</td>
</tr>
<tr>
<td>Study protocol was not available. Outcomes were reported regardless of statistical significance</td>
</tr>
<tr>
<td>Other bias</td>
</tr>
<tr>
<td>A table of baseline characteristics was presented with no evidence of baseline imbalance. Information was insufficient to assess whether an important risk of other bias exists</td>
</tr>
</tbody>
</table>

Szepietowski 2013

Study characteristics

Methods

This was an international phase 1, randomised, double-blind, placebo-controlled, multiple-interventional, dose-ascending study that was completed in 2 parts

Participants

**Inclusion criteria (part A-CLE)**

- 33 participants randomised
- Sex: 21 females, 12 males
- Race: 31 white, 2 Asian
- Average age: 53 years, range 29 to 69 years
- Included 31 participants with CLE (histologically confirmed). CLE participants were defined as participants with SCLE, discoid lupus, or lupus erythematosus (LE) tumidus. However, it is not clear how many of these patients (if any) also met criteria for SLE by ACR, so only data from part B could be included for analysis

**Inclusion criteria (part B-SLE with CLE)**

- 23 participants screened
- SLE patients defined as diagnosed according to ACR criteria and with active disease by SELENA-SLEDAI
- 15 SLE participants randomised (15 experimental, 5 placebo) and CLE evaluated by CLASI at baseline
- Demographics for 15 SLE participants were reported
- Sex: 13 females, 2 males
- Race: 9 white, 6 Asian
- Average age: 42 years, age range from 19 to 58 years

**Exclusion criteria**

- Recent bacterial or viral infection
- Recent use of certain medications

Interventions

**Interventions (part A)**

A: (n = 7) intravenous sirukumab (a human anti-interleukin-6 monoclonal antibody) 1 mg/kg every 2 weeks for 4 infusions (infusions over 6 weeks with total monitoring over 5 months) and other medications such as prednisone, antimalarials, non-steroidal anti-inflammatory drugs (NSAIDs)

B: (n = 7) intravenous sirukumab 4 mg/kg every 2 weeks for 4 infusions (infusions over 6 weeks with total monitoring over 5 months) and other medications such as prednisone, antimalarials, non-steroidal anti-inflammatory drugs (NSAIDs)

C: (n = 7) intravenous sirukumab 10 mg/kg every 2 weeks for 4 infusions (infusions over 6 weeks with total monitoring over 5 months) and other medications such as prednisone, antimalarials, non-steroidal anti-inflammatory drugs (NSAIDs)

**Control intervention (part A) (n = 8)**
D: placebo intravenous infusions every 2 weeks for a total of 4 doses (infusions over 6 weeks with total monitoring over 5 months) and other medications such as prednisone, antimalarials, non-steroidal anti-inflammatory drugs (NSAIDs)

**Intervention (part B) (n = 10)**

E: intravenous sirukumab (a human anti-interleukin-6 monoclonal antibody) 10 mg/kg every 2 weeks for 4 infusions (infusions over 6 weeks with total monitoring over 5 months) and other medications such as prednisone, antimalarials, non-steroidal anti-inflammatory drugs (NSAIDs)

**Control intervention (part B) (n = 5)**

F: placebo infusions over 6 weeks with total monitoring over 5 months and other medications such as prednisone, antimalarials, non-steroidal anti-inflammatory drugs (NSAIDs)

### Outcomes

**Primary outcomes**

None were reported

**Secondary outcomes**

- CLASI
- Dermatology Life Quality Index (DLQI)
- BILAG global (but not skin domains)
- SELENA-SLEDAI global (but not skin domains)

Adverse events: minor and severe

### Funding source

Funding was via Janssen Research and Development (Centocor Research and Development), a division of Johnson and Johnson

### Location

Germany, Sweden, Netherlands, Poland, Thailand, and USA

### Notes

Trial registration number was NCT01802740. Study comprises 2 reports, 1 of which reports data from an earlier conference abstract (Szepietowski 2011)

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
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</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Randomisation was stated, but details of random sequence generation were not given</td>
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<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Study authors did not describe methods used for allocation concealment</td>
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<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>Low risk</td>
<td>This was a double-blind study</td>
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<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Unclear risk</td>
<td>Insufficient details about blinding of assessors were given</td>
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<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>All randomised patients were treated. Study authors provided a detailed report on reasons for withdrawal. There were no withdrawals in part A. In part B, only 2 of 15 patients withdrew due to neutropenia or thrombocytopenia. Study authors did not state that they had performed an intention-to-treat (ITT)</td>
</tr>
</tbody>
</table>
Szepestowski 2013 (Continued)

analysis. We were able to verify that an ITT analysis was indeed performed by examining published study data

<table>
<thead>
<tr>
<th>Selective reporting (reporting bias)</th>
<th>Unclear risk</th>
<th>Study protocol was not available. All outcome measures from aims of study were reported in the results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>Study authors provided a table of baseline characteristics of treatment groups with no evidence of significant baseline imbalance. Information was insufficient to assess whether an important risk of other bias exists</td>
</tr>
</tbody>
</table>

Tillmanns 2014

Study characteristics

Methods

This was a phase 2a, randomised, double-blind, placebo-controlled, multi-arm, parallel-group study

Participants

**Inclusion criteria**

- 51 participants with SLE (by ACR criteria) and also specifically lupus nephritis; of these participants, 26 (50%) had active skin involvement
- Sex: not stated
- Race: not stated
- Mean age: not stated

**Exclusion criteria**

- No information given

Interventions

**Interventions**

A: (n = 22) SM101 (human soluble non-glycosylated version of the Fcγ receptor IIB) at 6 mg/kg dose infusion once per week for 4 weeks plus standard therapy (corticosteroids, mycophenolate mofetil, or azathioprine and adjuvant), then monitored for 6 months

B: (n = 18) SM101 at dose 12 mg/kg infusion once per week for 4 weeks plus standard therapy (corticosteroids, mycophenolate mofetil, or azathioprine and adjuvant), then monitored for 6 months

**Control intervention (n = 11)**

C: placebo once per week for 4 weeks plus standard therapy (corticosteroids, mycophenolate mofetil, or azathioprine and adjuvant), then monitored for 6 months

Outcomes

**Primary outcomes**

None were reported

**Secondary outcomes**

BILAG (narrative data)

Adverse events: severe (narrative)

Funding source

Funding was from commercial source of SuppreMol, GmbH, Martinsied, Germany

Location

8 European countries and Australia

Notes
### Tillmanns 2014 (Continued)

#### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Quote: &quot;a stratified randomization scheme with variable block size was used&quot;</td>
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<tr>
<td></td>
<td></td>
<td>Comment: random sequence generation was likely sufficient</td>
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<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>The method of allocation concealment was not stated, so it is not clear</td>
</tr>
<tr>
<td></td>
<td></td>
<td>whether randomisation was centralised</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>Low risk</td>
<td>Study authors reported that the study was double-blind; however minimal details were given</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Unclear risk</td>
<td>Insufficient details about blinding of assessors were given</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Low risk</td>
<td>No withdrawals from the study were reported. There was a 100% completion rate, and all published data were analysed. Study authors did not specifically state that they performed intent-to-treat (ITT) analysis. However, we confirmed that study authors performed ITT by examining published data</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>High risk</td>
<td>Study protocol was not available. Minimal information (for aims and results) was reported, so this study is at high risk for selective reporting</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>No baseline information was provided for treatment groups, so it is unclear whether any baseline imbalance was present. Information was insufficient to assess whether an important risk of other bias exists</td>
</tr>
</tbody>
</table>

### Tsakonas 1991

#### Study characteristics

**Methods**

This was a parallel-group randomised placebo-controlled discontinuation trial

**Participants**

**Inclusion criteria**

- 47 participants with SLE
- Sex: 46 women, 1 man
- Race: not stated
- Age mean ± SD: 45 ± 13.9 years in the hydroxychloroquine group; 44 ± 15.7 years in the placebo group

**Exclusion criteria**

- Daily hydroxychloroquine > 6.5 mg/kg
- Younger than 16 years of age
- Retinopathy
- Coexisting illness
- Severe SLE

**Interventions**

**Intervention (n = 25)**

A: continued hydroxychloroquine 100 mg to 400 mg daily
Tsakonas 1991 (Continued)

### Control intervention (n = 22)
B: placebo (stopped hydroxychloroquine) for 6 months

### Outcomes

#### Primary outcomes
None were reported

#### Secondary outcomes
Relative risk of clinical flare-up in 6 months as reported

### Adverse events

### Funding source
Funding was provided by the Arthritis Society of Canada and the Lupus Society of Canada. Medication was supplied by Winthrop Laboratories and Sterling Drug Canada

### Location
Outpatient clinics and hospitals in Canada

### Notes
Study was also described in the follow-up report - Tsakonas 1998

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
</table>
| Random sequence generation (selection bias) | Low risk           | Quote: "the schedule of randomisation was based on a table of random numbers in blocks of four. Distinct randomisation at each centre was according to whether or not receiving treatment with prednisone"  
Comment: random sequence generation was likely sufficient |
| Allocation concealment (selection bias) | Low risk           | Quote: "sealed unique numbered, opaque envelope" was used  
Comment: allocation concealment was likely sufficient |
| Blinding of participants and personnel (performance bias) All outcomes | Low risk | Quote: "the active and placebo medications were identical in appearance"  
Comment: study authors made efforts to maintain and assess success of blinding. At the end of the trial, study authors asked physicians and patients to guess whether they had received active medication or placebo. These results were compared with the actual medication received and were evaluated using the kappa statistic. No evidence of unblinding was found |
| Blinding of outcome assessment (detection bias) All outcomes | Unclear risk | It is unclear whether there was blinding of assessors because they were not specifically mentioned |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | Incomplete outcome data were discussed in detail. Study authors did not state that they had performed an intention-to-treat (ITT) analysis. We were able to verify that an ITT analysis was indeed performed by examining published study data |
| Selective reporting (reporting bias) | Unclear risk | Study protocol was not available. Planned outcome data were reported regardless of statistical significance |
| Other bias | Unclear risk | Study authors presented baseline characteristics of treatment groups, and there was no evidence of baseline imbalance. Information was insufficient to assess whether an important risk of other bias exists |
### Study characteristics

#### Methods

This was a parallel-group prospective randomised double-blind placebo-controlled trial.

#### Participants

**Inclusion criteria**
- 180 participants with SLE (by ACR criteria) screened
- 154 qualified for study and entered observational phase
- 41 patients developed serologic flare with clinical stability during study period of 18 months; 21 were randomised to prednisone and 20 to placebo
- Intervention group characteristics were as follows:
  - Sex: 19 female, 2 male
  - Race: 11 Hispanic, 3 African American, 4 Asian, 3 white
  - Age: mean 35.7 ± 13 years
- Placebo group characteristics were as follows:
  - Sex: 18 female, 2 male
  - Race: 8 Hispanic, 6 African American, 3 Asian, 3 white
  - Age: mean 34.1 ± 13.3 years

**Exclusion criteria**
- Unstable SLE disease (SLEDAI > 12)
- Active infection
- Uncontrolled diabetes
- Hypertension
- Pregnancy

#### Interventions

**Intervention (n = 21)**

A: prednisone 30 mg daily for 2 weeks, then 20 mg for 1 week, then 10 mg for 1 week for each flare for up to 18 months

**Control intervention (n = 20)**

B: placebo for each flare for 18 months

#### Outcomes

**Primary outcomes**

None were reported

**Secondary outcomes**

Flares in skin disease

Adverse events: minor and severe

#### Funding source

Funding was received from the US National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) and the National Institutes of Health (NIH)

#### Location

Multiple academic hospitals in the area of New York, USA

#### Notes

Risk of bias

#### Bias

Authors' judgement | Support for judgement

---

*Interventions for cutaneous disease in systemic lupus erythematosus (Review)*

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### Tseng 2006 (Continued)

<table>
<thead>
<tr>
<th>Random sequence generation (selection bias)</th>
<th>Unclear risk</th>
<th>Randomisation was stated; however no details on methods used were given by study authors</th>
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<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Details about allocation concealment were not given</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Low risk</td>
<td>Study authors reported that the study was double-blinded</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Unclear risk</td>
<td>Insufficient details given about blinding of assessors were given</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>A summary flow chart with details was prepared. Study authors did not state that they had performed an intention-to-treat (ITT) analysis. We were able to verify that an ITT analysis was indeed performed by examining published study data</td>
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<td>Unclear risk</td>
<td>Study protocol was not available. All primary and secondary outcomes listed in the methods were reported in the results</td>
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<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>Study authors provided a table with information about baseline groups, and there was no evidence of baseline imbalance. Information was insufficient to assess whether an important risk of other bias exists</td>
</tr>
</tbody>
</table>

### Tzung 2007

#### Study characteristics

**Methods**

This was a randomised double-blind bilateral split-body (face) comparison study

**Participants**

**Inclusion criteria**

- 20 participants with SLE; in the end, only 18 patients were included in the study
- Of the included patients, 13 had the malar rash of SLE, 4 had SLE, and 1 had SCLE
- Sex: 11 women, 7 men
- Race: not stated
- Mean age ± SD: 33.0 years ± 9.8 SD

**Exclusion criteria**

- Not described

**Interventions**

**Intervention (n = 18)**

A: topical tacrolimus 0.1% ointment twice daily plus micro dermabrasion for 2 months

**Control intervention (n = 18)**

B: clobetasol propionate 0.05% ointment twice daily plus micro dermabrasion for 2 months

**Outcomes**

**Primary outcomes**

Continuous outcome data based on rating scale for presence of erythema, desquamation, induration, and telangiectasias
### Secondary outcomes

Adverse events (not reported separately from primary outcomes)

<table>
<thead>
<tr>
<th>Funding source</th>
<th>Funding source was not stated</th>
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<tr>
<td>Location</td>
<td>Dermatology general hospital/university-affiliated clinic in Taiwan</td>
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</table>

**Risk of bias**

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
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</thead>
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<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>This study was randomised; however the method was not stated</td>
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<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Study authors did not describe methods for allocation concealment</td>
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<tr>
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</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>High risk</td>
<td>Study authors reported that 18 of 20 completed the study; however they did not discuss reasons for the 2 dropouts. Intention-to-treat analysis was not performed. Study authors performed analysis on only 18 of 20</td>
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<tr>
<td>Selective reporting (reporting bias)</td>
<td>High risk</td>
<td>Study protocol was not available. Minimal data were presented</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>Data regarding baseline groups were presented by study authors, and randomised groups had no evidence of baseline imbalance. Information was insufficient to assess whether an important risk of other bias exists</td>
</tr>
</tbody>
</table>

**Van Vollenhoven 1995**

**Study characteristics**

**Methods**

This was a parallel-group, double-blind, placebo-controlled, randomised trial

**Participants**

**Inclusion criteria**

- 28 participants with mild to moderate SLE; 6 had a malar rash, 9 had alopecia, 5 had mucosal ulcers
- Sex: 28 women, zero men
- Race: 20 Caucasian, 6 African American; 2 other
- Mean age ± SEM (years): 34.9 ± 2.6 years in intervention group, 39.6 ± 2.0 years in placebo group

**Exclusion criteria**

- Severe renal disease
Interventions for cutaneous disease in systemic lupus erythematosus (Review)

Van Vollenhoven 1995 (Continued)

- Requiring high-dose corticosteroids or cyclophosphamide

Interventions

**Intervention (n = 14)**

A: dehydroepiandrosterone (DHEA) 200 mg orally once daily for 3 months

**Control intervention (n = 14)**

B: placebo for 3 months

Outcomes

**Primary outcomes**

None were reported

**Secondary outcomes**

Adverse events

Funding source

Study was supported in part by grants from Northern California Arthritis Foundation, Bay Area Lupus Foundation, and National Lupus Erythematosus Foundation

Location

Outpatient clinic of Stanford University Medical Center, in Stanford, California, USA

Notes

Risk of bias

<table>
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<td>Unclear risk</td>
<td>Randomisation was stated as performed, but details about random sequence generation were not given</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>No details about allocation concealment were given</td>
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</tbody>
</table>
| Blinding of participants and personnel (performance bias) All outcomes | Low risk           | Quote: "patients were given capsules containing DHEA or identical placebo capsules to be taken once per day by month"
                                                                 | Comment: study authors reported that this was a double-blind study. Study authors considered and discussed the strength of blinding. A formal assessment was made, and study authors reported that no differences were found |
| Blinding of outcome assessment (detection bias) All outcomes | Unclear risk       | Insufficient details about blinding of assessors were given                           |
| Incomplete outcome data (attrition bias) All outcomes | Unclear risk       | Details about 2 patients (1 from the placebo group and 1 from the intervention group) who were lost to follow-up early in the study were not given. Study authors did note that discontinuations from the study were not due to adverse reactions. Study authors did not state whether they had performed an intention-to-treat (ITT) analysis. We were able to verify that an ITT analysis was indeed performed by examining published study data |
| Selective reporting (reporting bias) | Unclear risk       | Study protocol was not available. Outcomes reported appear to be complete. Negative results were also reported |
| Other bias                          | Unclear risk       | Study authors provided a table with baseline characteristics of treatment groups. No baseline imbalance was noted. Information was insufficient to assess whether an important risk of other bias exists |
### Study characteristics

**Methods**

This is a phase 2a, efficacy and safety, multi-centre, randomised, double-blind, placebo-controlled study.

**Participants**

**Inclusion criteria**

- 102 participants with SLE (by Systemic Lupus International Collaborating Clinics Classification Criteria)
- Sex: 93 women, 9 men
- Race: 70 white, 7 black, 14 Asian, 11 other
- Mean age ± SEM (years): 40.0 ± 12 years in intervention group, 42.9 ± 11.3 years in placebo group

**Exclusion criteria**

- Severe renal disease
- Confounding inflammatory disease (rheumatoid arthritis, psoriasis)
- Unstable SLE
- Active CNS SLE

**Interventions**

**Intervention (n = 60)**

A: ustekinumab IV loading dose by weight as follows: 260 mg (for weight 35 to 55 kg) or 390 mg (for weight 56 to 85 kg) or 520 mg (for weight > 85 kg), then 90 mg SC each 8 weeks plus concomitant medication for 6 months

**Control intervention (n = 42)**

C: placebo Infusion first dose plus concomitant medication followed by placebo SC plus concomitant medication every 8 weeks for 6 months

**Outcomes**

**Primary outcomes**

None were reported

**Secondary outcomes**

CLASI (≥ 50% improvement from baseline CLASI activity score)

Adverse events (minor and severe)

**Funding source**

Funding was received from Janssen Research & Development, LLC

**Location**

44 private practices and academic centres in Argentina, Australia, Germany, Hungary, Mexico, Poland, Spain, Taiwan, and USA

**Notes**

Study number was NCT02349061

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
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<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Quote: &quot;dynamic central randomisation was performed using an interactive web response system with stratification&quot;</td>
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<tr>
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<td>Comment: randomisation method was adequate</td>
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</table>
Van Vollenhoven 2018 (Continued)

Allocation concealment (selection bias) | Low risk | Quote: "randomisation codes were kept within the interactive web response system so patients and investigators remained masked to treatment allocation. The funder was masked to treatment allocation up to the week-24 database lock"
Comment: allocation concealment was adequate

Blinding of participants and personnel (performance bias) | Low risk | Study was "double-blind"

Blinding of outcome assessment (detection bias) | Low risk | Quote: "the interim analysis was performed by an unmasked statistical support team and reported to the data monitoring committee as well as a funder representative who was independent from the masked study team"
Comment: blinding was likely adequate given separation of teams

Incomplete outcome data (attrition bias) | Low risk | Detailed patient flow diagram was provided with detailed reasons for withdrawal from both groups. An acceptable percentage of both groups finished the study. Data analysis was stated as "modified intention-to-treat"

Selective reporting (reporting bias) | Unclear risk | Study protocol was not available. Planned outcomes were reported regardless of statistical significance

Other bias | Unclear risk | Study authors provided a detailed table of baseline characteristics with no evidence of imbalance. Information was insufficient to assess whether an important risk of other bias exists

Wallace 2009

Study characteristics

Methods
This was a multi-arm, parallel-group, phase 2, randomised, double-blind, placebo-controlled, dose-ranging study

Participants

Inclusion criteria
- 449 participants with SLE
- Sex: 418 women, 31 men
- Race: 315 white, 134 non-white
- Mean age ± SD: 42.2 years ± 10.9 SD in placebo group, 42.1 years ± 11.3 SD in intervention groups

Exclusion criteria (key)
- Active lupus nephritis or CNS disease
- Pregnancy
- Certain prior drugs

Interventions

Interventions
A: (n = 114) belimumab 1 mg/kg intravenous dose during 2 hour infusion on days 0, 14, and 28, then each 28 days for 52 weeks and continued standard of care

B: (n = 111) belimumab 4 mg/kg intravenous dose during 2 hour infusion on days 0, 14, and 28, then each 28 days for 52 weeks and continued standard of care
### Wallace 2009 (Continued)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Primary outcomes</th>
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<tbody>
<tr>
<td></td>
<td>None were reported</td>
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</table>

#### Secondary outcomes

- Adverse events

### Funding source

- Funding was provided by Human Genome Sciences and by a US National Institutes of Health (NIH) grant

### Location

- 59 sites in the United States and Canada

### Notes

- Trial registry number was NCT00071487

### Risk of bias

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<td>Study authors reported that this was a double-blind study</td>
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<tr>
<td>Blinding of outcome assessment</td>
<td>Unclear risk</td>
<td>Insufficient details about blinding of assessors were given</td>
</tr>
<tr>
<td>Incomplete outcome data</td>
<td>Low risk</td>
<td>A detailed flow diagram shows patient disposition. A modified intention-to-treat analysis was performed. Study authors did not analyse patients who were not treated with medication. They did analyse all patients who had received at least 1 treatment</td>
</tr>
<tr>
<td>Selective reporting</td>
<td>Unclear risk</td>
<td>Study protocol was not available. All outcome data as stated in the aims are reported in the results. Negative results were also reported</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>A detailed table including baseline data shows no evidence of baseline imbalance. Information was insufficient to assess whether an important risk of other bias exists</td>
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</table>

### Wallace 2013

#### Study characteristics

*Interventions for cutaneous disease in systemic lupus erythematosus (Review)*
**Wallace 2013 (Continued)**

### Methods

This was a phase 2b, randomised, double-blind, placebo-controlled, multi-centre study.

### Participants

**Inclusion criteria**
- 227 participants with SLE (by ACR criteria); 9 to 16 in each treatment arm group had CLE
- Sex: 86% to 100% in each treatment arm were female
- Race: white patients ranged from 69.2% to 86.6% of participants in each treatment arm; other races represented were black, Asian, and Native American and mixed race
- Mean age: 38 to 41 years; all patients were 18 years of age or older

**Exclusion criteria**
- Active severe neuropsychiatric or renal manifestations of SLE (except mononeuritis multiplex of > 4 weeks); pregnancy or lactation in females; active infection (including HIV or human T-cell lymphotropic virus type 1) or history of chronic infection; agammaglobulinemia; T-cell deficiencies; antiphospholipid antibody syndrome or use of oral anticoagulants or antiplatelet agents; malignancy (except treated non-melanoma skin cancers); significant haematologic abnormalities not attributed to SLE; vaccination during the study (except tetanus); and recent treatment with investigational monoclonal antibodies. Use of cyclophosphamide, cyclosporine, pimecrolimus, sirolimus, or tacrolimus was prohibited.

### Interventions

**Interventions**

- **A**: (n = 39) epratuzumab IV 200 mg cumulative dose (100 mg every other week (EOW)) over 3 months
- **B**: (n = 38) epratuzumab IV 800 mg cumulative dose (400 mg EOW) over 3 months
- **C**: (n = 37) epratuzumab IV 2400 mg cumulative dose (600 mg weekly) over 3 months
- **D**: (n = 37) epratuzumab IV 2400 mg cumulative dose (1200 mg EOW) over 3 months
- **E**: (n = 38) epratuzumab IV 3600 mg cumulative dose (1800 mg EOW) over 3 months

**Control intervention (n = 38)**

- B: IV placebo at same dosing intervals over 3 months

### Outcomes

**Primary outcomes**

None were reported

**Secondary outcomes**

- BILAG
- Adverse events: minor and severe

### Funding source

Study was funded by UCB Pharma

### Location

Trial was conducted between January 2008 and August 2009 at 47 centres in Belgium, Brazil, Hong Kong, Hungary, India, Lithuania, Poland, Spain, Ukraine, UK, and USA

### Notes

EMBLEM study (NCT00624351) and continuation study SLE0008 (NCT00660881)

Other associated trials include ClinicalTrials.gov NCT00383513; ClinicalTrials.gov NCT01408576

### Risk of bias

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<td>Unclear risk</td>
<td>Quote: this trial was &quot;randomized&quot;</td>
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</tbody>
</table>

**Interventions for cutaneous disease in systemic lupus erythematosus (Review)**

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
Wallace 2013 (Continued)

<table>
<thead>
<tr>
<th>Bias Type</th>
<th>Risk Type</th>
<th>Comment and Details</th>
</tr>
</thead>
</table>
| Allocation concealment (selection bias)       | Low risk        | Quote: “randomisation was via an interactive voice response system and was stratified”  
Comment: randomisation was centralised and was likely sufficient |
| Blinding of participants and personnel (performance bias) All outcomes | Low risk        | Quote: “all patients, investigators...were blinded to treatment. Placebo IV treatment was provided in vials that were identical in number and appearance to epratuzumab”  
Comment: blinding was likely sufficient |
| Blinding of outcome assessment (detection bias) All outcomes | Low risk        | Quote: “all...study staff were blinded to treatment with the exception of an independent data safety monitoring board”  
Comment: blinding was likely sufficient |
| Incomplete outcome data (attrition bias)      | Unclear risk    | Quote: “the intention-to-treat (ITT) analysis included all randomised patients”  
Comment: study authors presented a detailed table of reasons for withdrawal. We were able to verify that an ITT analysis was indeed performed by examining published study data |
| Selective reporting (reporting bias)          | Unclear risk    | Study protocol was not available. Planned outcomes were reported regardless of statistical significance |
| Other bias                                    | Unclear risk    | Study authors presented a detailed table of baseline characteristics with no evidence of imbalance between groups. Information was insufficient to assess whether an important risk of other bias exists& & & |

Wallace 2014

Study characteristics

Methods

These were 2 multi-centre, parallel-group, double-blind, placebo-controlled, randomised trials

Participants

**Inclusion criteria**

- 90 participants with SLE (by ACR criteria). Out of the 90 participants, 73 had CLE. Out of the 73 participants with CLE, 18 had severe CLE (defined by mucocutaneous BILAG A scores) and 55 had moderate CLE (defined by mucocutaneous BILAG B scores)
- Sex: not stated
- Race: not stated
- Mean age: not given; all patients were 18 years of age or older

**Exclusion criteria**

- “Patients were excluded for pregnancy, previous B-cell-targeted therapy, prior malignancy, active infection, allergy to murine or human antibodies, receipt of experimental therapy or any therapy with human or murine antibodies within 3 months, thrombosis, spontaneous or induced abortion, stillbirth or live birth within 4 weeks, or antiphospholipid antibodies plus a history of thromboembolic events. For ALLEVIATE-2, patients were also excluded if they had any BILAG A score”

Interventions

**Interventions**
### Interventions for cutaneous disease in systemic lupus erythematosus (Review)

Wallace 2014 (Continued)

A: (n = 42) epratuzumab at dose of 360 mg/m² intravenously in 12-week cycles for up to 48 weeks (4 infusions, at weeks 0, 1, 2, and 3, for cycle 1; 2 infusions, at weeks 0 and 1, for subsequent cycles), totaling 10 doses

B: (n = 11) epratuzumab at dose of 720 mg/m² intravenously in 12-week cycles for up to 48 weeks (4 infusions, at weeks 0, 1, 2, and 3, for cycle 1; 2 infusions, at weeks 0 and 1, for subsequent cycles), totaling 10 doses

**Control intervention (n = 37)**

B: IV placebo was administered intravenously in 12-week cycles for up to 48 weeks (4 infusions, at weeks 0, 1, 2, and 3, for cycle 1; 2 infusions, at weeks 0 and 1, for subsequent cycles), totaling 10 doses

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Primary outcomes</th>
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<tbody>
<tr>
<td></td>
<td>None were reported</td>
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</tbody>
</table>

**Secondary outcomes**

Change in BILAG from baseline (mucocutaneous domain)

Adverse events: minor and severe

**Funding source**

Funding was received from UCB Pharma

**Location**

ALLEVIA TÈ-1 was conducted at 16 sites in 6 countries (Belgium, Hungary, The Netherlands, Spain, UK, USA); ALLEVIA TÈ-2 at 28 sites in 6 countries (Belgium, Italy, The Netherlands, Spain, UK, USA)

**Notes**

ALLEVIA TÈ-1 (NCT00111306), ALLEVIA TÈ-2 (NCT00383214), open-label extension (SL0006). Trials were stopped early at 12 weeks due to medication shortage. Data were reported at 12 weeks

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
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<th>Support for judgement</th>
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<td></td>
<td>Comment: no details about the method of random sequence generation were given</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>It is unclear whether randomisation was centralised</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>Low risk</td>
<td>Quote: the trials were &quot;double-blind&quot;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Comment: blinding was likely sufficient</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Low risk</td>
<td>Quote: &quot;BILAG outcome was centrally graded by an independent, blinded reviewer&quot;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Comment: blinding was likely sufficient</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Low risk</td>
<td>Quote: &quot;the base population for all analyses was the intention to treat (ITT) (all randomised patients) population&quot;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Comment: a detailed table of withdrawals was presented by study authors</td>
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<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>Study protocol was not available. Planned outcomes were reported regardless of statistical significance</td>
</tr>
</tbody>
</table>
Wallace 2014 (Continued)

Other bias  Unclear risk  Study authors provided a detailed table of baseline characteristics without evidence of imbalance between groups. Information was insufficient to assess whether an important risk of other bias exists.

Wallace 2018

Study characteristics

Methods  This was a multi-centre, parallel-group, double-blind, placebo-controlled, randomised trial.

Participants

Inclusion criteria
• 314 participants with SLE (by ACR criteria) and "rash or arthritis"
• Sex: not stated
• Race: not stated
• Mean age: not given; all patients were 18 years of age or older

Exclusion criteria
• Not stated

Interventions

Interventions
A: (n = 105) IV baricitinib 2 mg once daily for 6 months and stable background SLE therapy
B: (n = 104) IV baricitinib 4 mg once daily for 6 months and stable background SLE therapy

Control intervention (n = 105)
C: oral placebo and stable background SLE therapy

Outcomes

Primary outcomes
Complete clearance of rash (pooled with arthritis)

Secondary outcomes
Adverse events: minor and severe

Funding source
Study was funded by Eli Lilly, Indianapolis, Indiana, USA

Location
Outpatient clinics in the USA, Mexico, Japan, England, Italy, and Germany

Notes
This was study NCT02708095

Risk of bias

<table>
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<td>Unclear risk</td>
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<td>Comment: No details about the method of random sequence generation were given</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>No information about centralisation of randomisation was given</td>
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### Wallace 2018 (Continued)

<table>
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<th>Risk of Bias</th>
<th>Description</th>
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<tr>
<td><strong>Blinding of participants and personnel (performance bias)</strong></td>
<td>All outcomes</td>
<td>Low risk</td>
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<tr>
<td><strong>Blinding of outcome assessment (detection bias)</strong></td>
<td>All outcomes</td>
<td>Unclear risk</td>
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<tr>
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<tr>
<td><strong>Selective reporting (reporting bias)</strong></td>
<td></td>
<td>Unclear risk</td>
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<tr>
<td><strong>Other bias</strong></td>
<td></td>
<td>Unclear risk</td>
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</table>

### Walton 1991

#### Study characteristics

**Methods**
This was a randomised double-blind placebo-controlled cross-over trial

**Participants**

**Inclusion criteria**
- 27 participants with SLE (subsets of skin disease were not stated)
- Sex: 25 women, 2 men
- Race: not stated
- Age range: 21 to 68 years at start of study

**Exclusion criteria (main)**
- Severe illness
- Clinically inactive SLE
- Major renal disease, already receiving special diet

**Interventions**

**Intervention (n = 8)**
A: "fish oil 1 gram oil (MaxEPA, Marfleet Refining Hull) and low-fat diet and "combined A, D capsules BPC"

**Control intervention (n = 9)**
B: placebo oil capsule and low-fat diet and "combined A, D capsules BPC"

This was a cross-over study with 2 phases: first phase: 12 weeks of intervention followed by 2 weeks of low-fat diet only; second phase (cross-over): low-fat diet only for 2 weeks followed by 12 weeks of intervention

**Outcomes**

**Primary outcomes**
Reported narrative information on rash, mouth ulcers for 1 patient only

**Secondary outcomes**
Walton 1991 (Continued)

<table>
<thead>
<tr>
<th>Adverse events</th>
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<tbody>
<tr>
<td><strong>Funding source</strong></td>
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<td><strong>Location</strong></td>
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**Risk of bias**

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<th>Support for judgement</th>
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<tr>
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<td>Study authors stated that the trial was randomised, but methods of random sequence generation were not stated</td>
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<tr>
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<td>Unclear risk</td>
<td>No details about allocation concealment were given</td>
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<tr>
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<td>Low risk</td>
<td>Quote: “capsules were allocated in a double blind manner so that neither the patients nor the doctors assessing the patients were aware of which capsules were being taken”</td>
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<td>Quote: “the control capsules were identical in appearance to the fish oil and contained peppermint flavored oil”</td>
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<td></td>
<td>Comment: blinding was likely sufficient</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Low risk</td>
<td>Quote: “only the dietician knew the allocation but she did not participate in the assessment of disease activity”</td>
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<tr>
<td></td>
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<td>Comment: this implies indirectly that all assessors were blinded</td>
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<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Low risk</td>
<td>Study authors reported that 18 of 27 completed the study. Detailed information about dropouts was given. In all, 10 dropouts were not able to comply with diet</td>
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<tr>
<td>Selective reporting (reporting bias)</td>
<td>High risk</td>
<td>Study protocol was not available. Detailed data about individual patients including dropouts were given. Some data do appear to be missing. For example, blood results that were recorded at each visit were not reported</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>Study authors did not present enough information to assess any baseline imbalance. Information was insufficient to assess whether an important risk of other bias exists</td>
</tr>
</tbody>
</table>

Werth 2017a

**Study characteristics**

| Methods | This was a randomised, double-blind, placebo-controlled, phase 2a dose escalation study of CC-220 |

**Inclusion criteria**

- 42 participants with SLE (by ACR criteria) and history of SLE for ≥ 6 months and CLE (CLASI scores at baseline)
- Severity of SLE: baseline Safety of Estrogens in Lupus Erythematosus National Assessment-Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) score ≥ 4
Werth 2017a (Continued)

- Sex: 39 female, 3 male
- Race: 64% white, 31% black or African American
- Mean age: 47.2 years

**Exclusion criteria**
- Not stated

**Interventions**

| Interventions | A: (n = not stated) oral CC-220 at dose of 0.3 mg every other day for 6 months | B: (n = not stated) oral CC-220 at dose of 0.3 mg each day for 6 months | C: (n = not stated) oral CC-220 at doses of 0.6/0.3 mg alternating each day for 6 months | D: (n = not stated) oral CC-220 at dose of 0.6 mg each day for 6 months |

**Control intervention (n = not stated)**
- B: oral placebo for 6 months

**Outcomes**

- **Primary outcomes**
  - None were reported

- **Secondary outcomes**
  - CLASI
  - Adverse events: severe

**Funding source**
- This study was sponsored by Celgene Corporation

**Location**
- This multi-centre study was conducted in the USA

**Notes**

**Risk of bias**

<table>
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<tr>
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<td>Comment: no details about the method of random sequence generation were given</td>
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<td>Low risk</td>
<td>Quote: this study was &quot;double-blinded&quot;</td>
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<tr>
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<td></td>
<td>Comment: blinding was likely sufficient</td>
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<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Unclear risk</td>
<td>No information about blinding of assessors was given</td>
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<tr>
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<td>Low risk</td>
<td>Quote: &quot;seventy-nine percent of subjects completed the study&quot;</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>Study protocol was not available. Published outcomes from study were reported divided among multiple publications. For the most part, despite significant space limitations for reporting of data in some publications, outcomes planned in the methods section were reported in the results section. Outcomes were reported regardless of statistical significance</td>
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<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>No table of baseline characteristics was presented, so we were not able to assess for baseline imbalance. Information was insufficient to assess whether an important risk of other bias exists</td>
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</table>

### Westberg 1990

**Study characteristics**

**Methods**

This was a cross-over, randomised, double-blind, placebo-controlled trial

**Participants**

**Inclusion criteria**

- 18 participants with SLE
- At baseline, 4 patients had skin findings, 3 with ++ and 1 with + rated severity (rating scale ranged from 0 to ++, with +++ as most severe rating)
- Sex: 15 women, 2 men
- Race: not stated
- Mean age: 44.2 years ± 6.6 SD

**Exclusion criteria**

- No clinical signs of SLE

**Interventions**

**Interventions (cross-over design)**

A: (n = 10) phase 1: 0.2 gram Max eicosapentaenoic acid (EPA)/kg body weight corresponding to 10 to 15 grams of fish oil daily (10 to 15 capsules per day in the form of 1 gram (MaxEPA) capsules) for 6 months, followed by washout period of 3 months; phase 2: olive oil for 6 months

B: (n = 10) phase 1: olive oil for 6 months followed by washout period for 3 months; phase 2: 0.2 gram MaxEPA/kg body weight corresponding to 10 to 15 grams of fish oil daily (10 to 15 capsules per day in the form of 1 gram (MaxEPA) capsules) for 6 months

**Outcomes**

**Primary outcomes**

None were reported

**Secondary outcomes**

None were reported

**Funding source**

Funding source was not stated

**Location**

University clinic in Sweden

**Notes**

**Risk of bias**

Comment: information about study withdrawals was given. Analysis was intent-to-treat
### Westberg 1990 (Continued)

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation</td>
<td>Unclear risk</td>
<td>Quote: &quot;after a run-in period, the patients were randomized&quot;</td>
</tr>
<tr>
<td>(selection bias)</td>
<td></td>
<td>Comment: the method of random sequence generation was not stated</td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>Unclear risk</td>
<td>Quote: &quot;randomized using numbered cards in an envelope&quot;</td>
</tr>
<tr>
<td>(selection bias)</td>
<td></td>
<td>Comment: it is not clear whether the allocation was sufficiently concealed (e.g. it is not stated if envelopes were opaque)</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>Low risk</td>
<td>Quote: &quot;MaxEPA and control substance were supplied in identical capsules&quot;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Comment: study authors reported that this was a double-blind study. Two patients admitted to have discovered the substance used in the study; however this issue was taken into account and does not seem to have affected behaviour during the study</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Unclear risk</td>
<td>Insufficient details about blinding of assessors were given</td>
</tr>
<tr>
<td>Incomplete outcome data</td>
<td>Unclear risk</td>
<td>Study authors noted that 3 patients dropped out due to the large number of pills they were required to swallow (10 to 15 per day). An intention-to-treat analysis was not performed. Study authors performed a &quot;per-protocol&quot; analysis</td>
</tr>
<tr>
<td>(attrition bias)</td>
<td></td>
<td>Study protocol was not available. Most planned outcomes were reported, but data on percentage and number of patients with clinical improvement (oral ulcers, hair loss, skin issues) were missing. Researchers did report some negative results</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>High risk</td>
<td>Study authors reported that 3 patients dropped out due to the large number of pills they were required to swallow (10 to 15 per day). An intention-to-treat analysis was not performed. Study authors performed a &quot;per-protocol&quot; analysis</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>No baseline data were presented, so we were unable to assess baseline risk. Information was insufficient to assess whether an important risk of other bias exists</td>
</tr>
</tbody>
</table>

### Williams 1994

#### Study characteristics

**Methods**

This was a parallel-group, double-blind, randomised, controlled trial

**Participants**

**Inclusion criteria**

- 71 participants with SLE
- Sex: 66 women, 5 men
- Race: 31 white, 41 non-white
- Mean age: 41 years for hydroxychloroquine group, 43 years for placebo group

**Exclusion criteria**

- Central CNS disease
- Lupus nephritis
- High-dose prednisone
- Eye conditions

**Interventions**

**Intervention (n = 40)**
### Williams 1994 (Continued)

**A**: 200 mg hydroxychloroquine twice per day for 12 months and continued prednisone and non-steroidal anti-inflammatory agents (NSAIDs)

**Control intervention (n = 31)**

B: placebo and continued prednisone and non-steroidal anti-inflammatory agents (NSAIDs)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th><strong>Primary outcomes</strong></th>
<th>Narrative data only (no quantitative)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Secondary outcomes</strong></td>
<td>Adverse events</td>
</tr>
</tbody>
</table>

**Funding source**
Funding was provided by the US National Institutes of Health

**Location**
Multiple university medical centre-affiliated clinics in the USA

**Notes**

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Quote: “patients...were randomly assigned with each clinic using a random number table”</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Comment: random sequence generation method was likely sufficient</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Study authors did not mention any methods of allocation concealment</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>Unclear risk</td>
<td>Study authors reported that this was a double-blind study</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Unclear risk</td>
<td>Insufficient details about blinding of assessors were provided</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Low risk</td>
<td>All recruited patients were enrolled. There were 29 withdrawals from the study, and only 2 were due to adverse events. An intention-to-treat analysis was mentioned and was performed to the extent that this was possible</td>
</tr>
<tr>
<td>Selective reporting (reporting bias) All outcomes</td>
<td>High risk</td>
<td>Study protocol was not available. Some planned outcomes may not have been reported. Minimal negative results were presented</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>Study authors provided a table with information about baseline characteristics compared to 1 endpoint only. No baseline imbalances were detected. Information was insufficient to assess whether an important risk of other bias exists</td>
</tr>
</tbody>
</table>

### Wright 2008

**Study characteristics**

*Interventions for cutaneous disease in systemic lupus erythematosus (Review)*

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
Methods

This was a randomised triple-blind placebo-controlled parallel trial

Participants

**Inclusion criteria**

- 60 participants with SLE
- Sex: 159 women, 4 men
- Race: not stated
- Mean age: \(48.5 \pm 9.1\) SD years for fish oil group, \(47.6 \pm 9.6\) SD years for placebo group

**Exclusion criteria**

- Diabetes mellitus
- Hypertension
- Pregnancy
- Breast-feeding
- Pulmonary disease
- Hepatitis
- Renal disease
- Heart disease
- Prednisone > 10 mg daily

Interventions

**Intervention (n = 30)**

A: low-dose \(\omega-3\)-polyunsaturated fatty acids in form of 4 Omacaor capsules per day, providing 1.8 grams eicosapentaenoic acid (EPA) and 1.2 grams docosahexaenoic acid (DHA) for 6 months

**Control intervention (n = 30)**

B: placebo

Outcomes

**Primary outcomes**

None were reported

**Secondary outcomes**

Integument domain SLAM score
Integument domain BILAG score

Adverse events

Funding source

Funding was provided by a Wellcome Trust Clinical Research Fellowship and a research grant from Lupus UK

Location

Outpatient clinics of various university and research centres in Northern Ireland

Notes

**Risk of bias**

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Quote: &quot;randomisation occurred off-site by an independent body&quot; (Victoria Pharmaceuticals, Belfast, Northern Ireland)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Comment: no details on random sequence generation method were given</td>
</tr>
</tbody>
</table>
Allocation concealment (selection bias) | Low risk | Allocation concealment by “randomisation off site by an independent body” (pharmaceutical company). It is likely that allocation was sufficiently concealed (central allocation)

Blinding of participants and personnel (performance bias) | Low risk | Quote: "the placebo was identical"
Comment: study authors stated that the study was "double-blind". Blinding was likely sufficient

Blinding of outcome assessment (detection bias) | Low risk | Quote: "all clinical assessments were performed by the same researcher...who was blinded"
Comment: blinding was likely sufficient

Incomplete outcome data (attrition bias) | Low risk | Study authors discussed detailed reasons for dropouts. They stated that they performed an intention-to-treat analysis. We also verified that ITT was performed by examining published data

Selective reporting (reporting bias) | Unclear risk | Study protocol was not available. All planned outcome measures were reported in the results section. Negative results were also presented

Other bias | Unclear risk | Baseline characteristics were described in a table, and no imbalance was noted between randomised groups. Information was insufficient to assess whether an important risk of other bias exists

Wright 2008 (Continued)

Yahya 2013

Study characteristics

Methods | This was an open-label, single-centre, randomised, controlled, parallel pilot study

Participants | **Inclusion criteria**
- 14 participants with SLE (by ACR criteria) and no renal involvement (18 patients were screened, with 15 enrolled and randomised; 1 patient with Sjogren’s was later excluded after randomisation); 6 of these participants had active skin involvement (50%) defined as malar rash, discoid, or vasculitic lesions at the beginning of the study: 3 patients from the mycophenolate group, 3 from the control group
- Sex: 10 female, 4 male
- Race: 6 Chinese, 5 Indian, 3 Malayan
- Mean age: 36.9 ± 15.5 years, median 30 years, range 18 to 63 years

**Exclusion criteria**
- No need for change in therapy
- Recent biological therapy
- Active lupus nephritis
- Pregnancy
- Lactation
- Allergy to mycophenolate

Interventions | **Intervention (n = 8)**
A: mycophenolate sodium 360 mg orally twice daily initially, escalated to 720 mg twice weekly at week 4 if no contraindications for 16 weeks (4 months) plus other treatments such as prednisolone, hydroxychloroquine
Control intervention (n = 6)
B: "dapsone" or "azathioprine" as indicated for 16 weeks (4 months) plus other treatments such as prednisolone, hydroxychloroquine

Outcomes

Primary outcomes
Partial clearance

Secondary outcomes
Adverse events: minor and severe

Funding source
Novartis supplied funding, medications, and other healthcare staff who were involved in the study. Study authors declared that they had no direct affiliations with Novartis

Location
Single centre (SLE outpatient or rheumatology ward) at University Malaya Medical Center, Malaysia

Notes

Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Quote: &quot;randomisation was done by a computer generated program which was provided by a random number generation service&quot;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Comment: random sequence generation was likely sufficient</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Quote: &quot;this [randomisation] program was made available by the <a href="http://www.random.org">www.random.org</a> web site&quot;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Comment: it is implied from information above that method was centralised and therefore was likely sufficient</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>High risk</td>
<td>No blinding is described because this was an open-label study</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>High risk</td>
<td>No blinding is described because this was an open-label study</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Low risk</td>
<td>Details about patient participation were given in table form. 18 participants were screened, with 15 then enrolled and randomised. 1 patient with Sjogren’s disease was later excluded (after randomisation) for a total of 14 patients analysed. 2 participants in the control group were lost to follow-up. Participants were described in detail. The intention-to-treat (ITT) analysis was not specifically mentioned by study authors. However we verified that ITT analysis was indeed performed by examining published data</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>Study protocol was not available. Planned primary and secondary outcome data were reported. Negative data were also reported</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>Study authors provided baseline characteristics of randomised treatment groups and noted that &quot;there was no statistically significant differences between the two treatment groups in baseline characteristics&quot;. Information was insufficient to assess whether an important risk of other bias exists</td>
</tr>
</tbody>
</table>
Yokogawa 2015

Study characteristics

Methods
This was a multi-centre, parallel-group, double-blind, placebo-controlled, randomised trial

Participants

Inclusion criteria
- 103 participants with cutaneous lupus erythematosus (CLE); of these participants, 56 of 96, or 58%, had SLE (by ACR criteria) and 42% had purely CLE without SLE
- Sex: not stated
- Race: not stated
- Mean age: not given; all patients were 18 years of age or older

Exclusion criteria
- CLASI < 4
- Fluctuation of CLASI ≥ 20% in screening period
- Prednisolone > 15 mg/d
- Pain VAS or fatigue VAS of 0

Interventions

Intervention (n = 72)
A: oral hydroxychloroquine (doses not stated) for 4 months

Control intervention (n = 24)
B: oral placebo for 4 months

Outcomes

Primary outcomes
Partial improvement by SkindeX29 (7-point scale for global assessment by patient)
Partial improvement by "central photo evaluation" (5-point scale)
Partial improvement by global assessment (7-point scale) by investigator

Secondary outcomes
CLASI

Adverse events: severe (narrative)

Funding source
Funding for this study was received from Sanofi KK

Location
Outpatient clinic in Tokyo, Japan

Notes
NCT01551069

Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Randomisation was stated; however details about the method were not given</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Insufficient information was given to determine whether randomisation was centralised</td>
</tr>
</tbody>
</table>

Interventions for cutaneous disease in systemic lupus erythematosus (Review)

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### Yokogawa 2015 (Continued)

<table>
<thead>
<tr>
<th>Bias Type</th>
<th>Risk</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>Low risk</td>
<td>Study authors reported that this was a double-blind study</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Unclear risk</td>
<td>Insufficient details about any blinding of assessors were given</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>High risk</td>
<td>Seven withdrawals (or dropouts) from the study were reported; however details were not given. Intention-to-treat analysis was not performed. Analysis was &quot;as treated&quot;</td>
</tr>
<tr>
<td>Selective reporting (reporting bias) All outcomes</td>
<td>High risk</td>
<td>Study protocol was not available. It is not possible to assess whether all planned outcomes were reported. No negative data were reported</td>
</tr>
<tr>
<td>Other bias All outcomes</td>
<td>Unclear risk</td>
<td>Study authors did not provide data on baseline characteristics, so it is not possible to compare treatment groups for baseline imbalance. Information was insufficient to assess whether an important risk of other bias exists</td>
</tr>
</tbody>
</table>

### You 2010

#### Study characteristics

<table>
<thead>
<tr>
<th>Methods</th>
<th>This was a prospective randomised double-blind placebo-controlled trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td><strong>Inclusion criteria</strong></td>
</tr>
<tr>
<td></td>
<td>- 60 participants with SLE by ACR criteria and CLE (21 with face erythema, 10 with aphtha, 11 with erythema of hands, 31 with alopecia)</td>
</tr>
<tr>
<td></td>
<td>- Sex: 55 female; sex of other 5 not stated</td>
</tr>
<tr>
<td></td>
<td>- Race: not stated</td>
</tr>
<tr>
<td></td>
<td>- Age range: 21 to 60 years in treatment group, 19 to 50 years in control group</td>
</tr>
<tr>
<td></td>
<td><strong>Exclusion criteria</strong></td>
</tr>
<tr>
<td></td>
<td>- Unknown because translation was not available</td>
</tr>
<tr>
<td>Interventions</td>
<td><strong>Intervention (n = 30)</strong></td>
</tr>
<tr>
<td></td>
<td>A: ginsenosides (GS) capsule of 50 mg and prednisone for 3 months</td>
</tr>
<tr>
<td></td>
<td><strong>Control intervention (n = 30)</strong></td>
</tr>
<tr>
<td></td>
<td>B: placebo and prednisone for 3 months</td>
</tr>
<tr>
<td>Outcomes</td>
<td><strong>Primary outcomes</strong></td>
</tr>
<tr>
<td></td>
<td>Presence of face erythema, aphtha, erythema of hands, alopecia, and oedema before and after treatment</td>
</tr>
<tr>
<td></td>
<td><strong>Secondary outcomes</strong></td>
</tr>
<tr>
<td></td>
<td>None were reported</td>
</tr>
<tr>
<td>Funding source</td>
<td>Funding source was not stated</td>
</tr>
</tbody>
</table>
### You 2010 (Continued)

**Location**
Outpatient clinic at Military Medical University in Shanghai, China

**Notes**

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>The method of randomisation was a randomising digital table</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>No details about allocation concealment were given</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Low risk</td>
<td>Study authors stated that the study was double-blind; however minimal details on process were given</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Unclear risk</td>
<td>Insufficient details regarding blinding of assessors were given</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>Study authors provided a detailed table that accounted for study data. The intent-to-treat analysis was not stated as performed by study authors. From data, we could verify that only a per-protocol analysis had been done. However, for the purposes of this review, we were able to perform the intention-to-treat (ITT) analysis, given the detailed information published by study authors</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>Study protocol was not available. Most outcomes appear to have been reported. Study authors also reported some negative results</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>Study authors provided a table of baseline characteristics of treatment groups, and there was no evidence of significant baseline imbalance between groups. Information was insufficient to assess whether an important risk of other bias exists</td>
</tr>
</tbody>
</table>

### Zhong 2013

**Study characteristics**

**Methods**
This was a parallel-group, pilot prospective, double-blinded, randomised, controlled study

**Participants**

**Inclusion criteria**
- 84 participants (with mild to moderate systemic lupus erythematosus with baseline skin findings in 24 of 42 in the Zi Sen Qing group and in 21 of 42 in the hydroxychloroquine group
- Sex: 39 women, 3 men in the Zi Sen Qing group; 38 women, 4 men in the hydroxychloroquine group
- Race: all Asian (Chinese)
- Mean age: 32.7 ± 13.6 SD years for Zi Sen Qing group, 34.8 ± 14.3 SD years for hydroxychloroquine group

**Exclusion criteria**
- Serious concomitant illness
- Severe lupus nephritis
- CNS lupus
Interventions

**Intervention (n = 42)**

A: Chinese Herbal Medicine (Zi Sen Qing) herbal formula sachet of 10 grams of granules in 200 millilitres of hot water twice daily for 12 weeks (3 months = short term) and prednisone.

Zi Sen Qing has the following ingredients: *Radix astragali*, *Rehmannia glutinosa* Libosch, *Fructus cornus*, *Paeonia lactiflora*, *Herba hedyotis diffusa*, and *Cortex moutan radicis*

**Control intervention (n = 42)**

B: hydroxychloroquine 100 mg twice per day for 12 weeks and prednisone

**Outcomes**

**Primary outcomes**

None were reported

**Secondary outcomes**

Short-term reduction in flares

Short-term study-specific "Chinese medicine syndrome (CMS)" score that included as part of the 7-part scoring system 3 items that were cutaneous: short-term lupus-specific "red skin rash with flat or raised erythema"; short-term lupus-non-specific "dry mouth and oral ulcers"; and "hair loss"; the other 4 parts of the score were musculoskeletal symptoms, fatigue, dry eyes, and tinnitus

Adverse events: short-term minor and short-term severe

**Funding source**

Funding was provided by the Bureau of Health, Shanghai Government

**Location**

Outpatient rheumatology specialty clinics at the School of Medicine, Longhua Hospital, Shanghai, China, from 1 March 2006 to 31 January 2009

**Notes**

Project number for the study was 2004X001A

**Risk of bias**

**Bias** | **Authors' judgement** | **Support for judgement**
--- | --- | ---
Random sequence generation (selection bias) | Low risk | Quote: “a random sequence was prepared by staff at the GCP center...with no connection to the study”
Comment: random sequence generation was likely sufficient

Allocation concealment (selection bias) | Low risk | Quote: “randomisation codes were kept in sealed, opaque envelopes labelled with consecutive random numbers and kept in a location far away from the clinical setting”
Quote: “emergency envelopes were kept by the principal investigator”
Comment: allocation concealment was probably adequate

Blinding of participants and personnel (performance bias) | Unclear risk | Quote: “to maintain blinding, investigators were not allowed to ask participants about the types of interventions and participants were instructed not to reveal their interventions”
Comment: investigators were blinded; however participants were not blinded
Zhong 2013 (Continued)

<table>
<thead>
<tr>
<th>Characteristics of excluded studies [ordered by study ID]</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACLE: acute cutaneous lupus erythematosus.</td>
</tr>
<tr>
<td>ACR: American College of Radiology.</td>
</tr>
<tr>
<td>ANA: antinuclear antibody.</td>
</tr>
<tr>
<td>BILAG: British Isles Lupus Assessment Group Disease Activity Index.</td>
</tr>
<tr>
<td>CLASI: Cutaneous Lupus Disease Area and Severity Index.</td>
</tr>
<tr>
<td>CLE: cutaneous lupus erythematosus.</td>
</tr>
<tr>
<td>CNS: central nervous system.</td>
</tr>
<tr>
<td>DHA: docosahexaenoic acid.</td>
</tr>
<tr>
<td>DHEA: dehydroepiandrosterone.</td>
</tr>
<tr>
<td>DLE: discoid lupus erythematosus.</td>
</tr>
<tr>
<td>DLQI: Dermatology Life Quality Index.</td>
</tr>
<tr>
<td>dsDNA: double-stranded DNA.</td>
</tr>
<tr>
<td>EPA: eicosapentaenoic acid.</td>
</tr>
<tr>
<td>HTLV-1: human T-cell leukaemia virus 1.</td>
</tr>
<tr>
<td>ITT: intention-to-treat.</td>
</tr>
<tr>
<td>JAK/SYK: Janus kinase/spleen tyrosine kinase.</td>
</tr>
<tr>
<td>NM: nanometre.</td>
</tr>
<tr>
<td>NSAIDs: non-steroidal anti-inflammatory drugs.</td>
</tr>
<tr>
<td>RCI: repository corticotropin injection.</td>
</tr>
<tr>
<td>SD: standard deviation.</td>
</tr>
<tr>
<td>SELENA-SLEDAI: Systemic Lupus Erythematosus Disease Activity Index.</td>
</tr>
<tr>
<td>SEM: standard error of the mean.</td>
</tr>
<tr>
<td>SLAM-R: Systemic Lupus Activity Measure, Revised.</td>
</tr>
<tr>
<td>SLE: systemic lupus erythematosus.</td>
</tr>
<tr>
<td>SLEDAI: Systemic Lupus Erythematosus Activity Index.</td>
</tr>
<tr>
<td>SOC: standard of care.</td>
</tr>
<tr>
<td>UV: ultraviolet.</td>
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<tr>
<td>Study</td>
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<tr>
<td>--------------------</td>
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<tr>
<td>Abdou 2008</td>
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<td>Abud-Mendoza 2009</td>
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<tr>
<td>Barikbin 2009</td>
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<td>Bhattoa 2004</td>
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<td>Bjornberg 1963</td>
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<tr>
<td>Furie 2011a</td>
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<tr>
<td>Ginzler 2013</td>
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<tr>
<td>Gordon 2008</td>
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<tr>
<td>Handa 1985</td>
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<tr>
<td>He 2016</td>
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<tr>
<td>Hummers 2013</td>
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<td>Jemec 2009</td>
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<tr>
<td>Kahl 2016</td>
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<td>Study</td>
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<tr>
<td>Kraak 1965</td>
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<tr>
<td>Kuhn 2011a</td>
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<td>Liao 2011</td>
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<td>Liu 2007</td>
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<td>Lu 2015</td>
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<td>Mok 2016</td>
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<tr>
<td>NCT00523588</td>
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<tr>
<td>NCT00775476</td>
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<tr>
<td>NCT01135459</td>
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<tr>
<td>NCT01470313</td>
</tr>
</tbody>
</table>

Information about increased lab values during a clinical trial on this compound is available from the following reference: Sadis, Seth, Mukherjee, Arnab, Olson, Stephen, Dokmanovich, Melba, Maher, Robert, Cai, Chun-Hua, et al. Safety, pharmacokinetics, and pharmacodynamics of PD-0360324, a human monoclonal antibody to monocyte/macrophage colony stimulating factor, in healthy volunteers [abstract]. Arthritis Rheum 2009;60(Suppl 10):408. DOI: 10.1002/art.25491

No published cutaneous data can be found on Internet search |
| NCT01498406      | This trial was registered in December 2011 at http://clinicaltrials.gov and is entitled "Vitamin D status, disease specific and quality of life outcomes in patients with cutaneous lupus". The study was terminated early "secondary to funding issues and low enrolment" |
| NCT01516788      | This trial was registered in January 2012 by Victoria Werth at University of Pennsylvania at http://clinicaltrials.gov and is entitled "Photoprovocation testing subjects with cutaneous lupus". This trial was not an RCT |

**Interventions for cutaneous disease in systemic lupus erythematosus (Review)**

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<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT01689025</td>
<td>This phase 1 trial from Novo Nordisk was published at <a href="http://clinicaltrials.gov">http://clinicaltrials.gov</a> under the title &quot;An investigation of safety and tolerability of NNC0114-0006 in subjects with SLE&quot;. The study was conducted in USA, Hungary, Poland, and Serbia. This study on the anti-interleukin-21 monoclonal antibody was terminated in February 2014</td>
</tr>
<tr>
<td>NCT01709474</td>
<td>This phase 2 randomised trial from the National Institutes of Health/National Institutes of Allergy and Immunological Disease (NIH/NIAMD) from June 2013 is registered at <a href="http://clinicaltrials.org">http://clinicaltrials.org</a> and is entitled &quot;Vitamin D3 in paediatric SLE&quot;. The study was terminated due to slow enrolment, and no results are available on Internet search</td>
</tr>
<tr>
<td>NCT02074020</td>
<td>This study was completed or terminated; no published data are available for evaluation</td>
</tr>
<tr>
<td>NCT02265744</td>
<td>This study of the medication BMS-931699 was terminated, and no published data are available for evaluation</td>
</tr>
<tr>
<td>NCT02514967</td>
<td>This study of blisibimod for patients with SLE was terminated, and no published data are available for evaluation</td>
</tr>
<tr>
<td>NCT02711813</td>
<td>This study of TAB08 for patients with SLE was terminated, and no published data are available for evaluation</td>
</tr>
<tr>
<td>NCT02975336</td>
<td>This was a phase 2, randomised, double-blind, placebo-controlled, dose-finding study evaluating Bruton’s tyrosine kinase inhibitor evobrutinib (also known as M2951) for patients with systemic lupus erythematosus over 12 months. Contact information was posted online for Anand Patel, MD, MS, Senior Medical Director, Neurology and Immunology, Global Development, EMD Serono Research &amp; Development Institute, Inc., Billerica, MA, USA. Study was sponsored by Serono (a business of Merck KGaA, Darmstadt, Germany). The first patient was randomised on 20 January 2017, and CLASI scores were planned outcomes. Study completion was expected at the end of 2019, but the study was terminated, and no data have been posted or published</td>
</tr>
<tr>
<td>Nordmark 2005</td>
<td>This was an RCT of patients with SLE; however study participants did not have a diagnosis of cutaneous disease (exclusion category 1)</td>
</tr>
<tr>
<td>Ohtsuka 2013</td>
<td>This study is described as a &quot;placebo controlled clinical trial&quot;. There is no mention of randomisation. Based on the information published, we cannot include this study because it is not clear whether it was truly randomised (exclusion category 2)</td>
</tr>
<tr>
<td>Okon 2014</td>
<td>This was a case series and a prospective open-label trial of cutaneous lupus erythematosus (CLE) with or without systemic involvement (exclusion category 2)</td>
</tr>
<tr>
<td>Partan 2019</td>
<td>This was a randomised, double-blind, clinical trial of 16 SLE subjects treated with 500 μL Seluang fish oil capsules and 16 SLE subjects treated with placebo capsules; however study participants did not have a diagnosis of cutaneous disease (exclusion category 1)</td>
</tr>
<tr>
<td>Petri 2002</td>
<td>This was an RCT of SLE; however study participants did not have a diagnosis of cutaneous disease (exclusion category 1)</td>
</tr>
<tr>
<td>Pothinamthong 2012</td>
<td>This was an RCT of cutaneous SCLE and DLE (not SLE) (exclusion category 3)</td>
</tr>
<tr>
<td>Presto 2018</td>
<td>This was an RCT including participants with discoid lupus only. Insufficient details on SLE diagnosis were provided (exclusion category 3)</td>
</tr>
<tr>
<td>Roenigk 1980</td>
<td>This was an RCT with participants with chronic cutaneous discoid lupus only and, by definition, no systemic involvement (exclusion category 3)</td>
</tr>
<tr>
<td>Rovin 2019</td>
<td>This was a randomised, controlled double-blind study comparing the efficacy and safety of dose-ranging voclosporin vs placebo in achieving remission among patients with</td>
</tr>
</tbody>
</table>
### Characteristics of studies awaiting classification [ordered by study ID]

**Askenase 2019**

**Methods**

This is a multi-centre, double-blind, randomised, placebo-controlled, 24-week clinical trial evaluating the effect of RCI in reducing disease activity for patients with persistently active SLE despite moderate-dose corticosteroid use.

**Participants**

**Inclusion criteria**

- 270 patients with diagnosis of systemic lupus erythematosus by ACR
Askensenase 2019 (Continued)

Interventions

**Intervention**
A: repository corticotropin injection (RCI)

**Control intervention**
B: placebo

Outcomes

SLE Responder Index-4 (SRI-4)
SLE Disease Activity Index-2000 (SLEDAI-2K)

Notes

This study number is NCT02953821. This study was funded by Mallinckrodt Pharmaceuticals. CLASI results are posted online.

Brunner 2020

Methods

This is a phase 2 randomised safety and efficacy study with parallel assignment and quadruple blinding (of subject, caregiver, investigator, and outcome assessor) in paediatric-onset systemic lupus erythematosus

Participants

**Inclusion criteria**
- Diagnosis of systemic lupus erythematosus
- 100 children

Interventions

**Intervention**
A: belimumab 10 mg/kg

**Control intervention**
B: placebo

Outcomes

SLE Response Index (SRI)
Number and percentage of patients with adverse events
Severe adverse events

Notes

Planned completion date is March 2026; however some results are available in 2020

Hasni 2019

Methods

A cross-over phase 1b, randomised, double-blind, placebo-controlled study with an open-label extension to evaluate safety and tolerability of omalizumab, a humanised IgG1 monoclonal antibody, in patients with lupus (STOP LUPUS)

Participants

**Inclusion criteria**
- 62 subjects with diagnosis of systemic lupus erythematosus by ACR screened; 46 excluded and 16 randomised
### Interventions for cutaneous disease in systemic lupus erythematosus (Review)

**Hasni 2019**

(Continued)

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Intervention</th>
<th>Control intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>omalizumab (n = 10)</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>placebo (n = 6)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>SLEDAI 2K</th>
<th>CLASI</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Notes</th>
<th>This is study number NCT01716312</th>
</tr>
</thead>
</table>

**He 2019**

<table>
<thead>
<tr>
<th>Methods</th>
<th>This was a randomised, double-blind, placebo-controlled trial of efficacy and safety of low-dose IL-2 for treatment of systemic lupus erythematosus</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Participants</th>
<th>Inclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>60 subjects with diagnosis of active systemic lupus erythematosus by ACR</td>
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</table>

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>low-dose IL-2 (n = 30) subcutaneously every other day at a dose of 1 million IU for 2 weeks with standard treatment for 12 weeks and followed up for an additional 12 weeks</td>
</tr>
<tr>
<td>Control intervention</td>
<td>B: placebo (n = 30) subcutaneously every other day for 2 weeks with standard treatment for 12 weeks and followed up for an additional 12 weeks</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Rash</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Oral ulcers</td>
</tr>
<tr>
<td></td>
<td>Adverse events (minor and severe)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Notes</th>
<th>This record refers to both NCT02465580 and NCT02932137</th>
</tr>
</thead>
</table>

**Houssiau 2020**

<table>
<thead>
<tr>
<th>Methods</th>
<th>This was a study of the efficacy and safety of the immunotherapeutic vaccine interferon-α kinoid (IFN-K) in a 36-week phase 2b, randomised, double-blind, placebo (PBO)-controlled trial in adults with active systemic lupus erythematosus (SLE) despite standard of care</th>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Participants</th>
<th>Inclusion criteria</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>180 subjects with diagnosis of systemic lupus erythematosus by ACR</td>
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</table>

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>IFN-K intramuscular injections</td>
</tr>
<tr>
<td>Control intervention</td>
<td>B: placebo (n = 30) intra-articularly for 2 weeks with standard treatment for 12 weeks and followed up for an additional 12 weeks</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Notes</th>
<th>This record refers to both NCT02465580 and NCT02932137</th>
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### Houssiau 2020 (Continued)

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B: placebo intramuscular injections</td>
<td>CLASI</td>
<td>This was NCT02665364. The sponsor (Neovacs) is currently under &quot;reorganisation proceedings&quot;; therefore the trial was terminated early. Published data are available for review</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adverse events (minor and severe)</td>
<td></td>
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</table>

### NCT02437890

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Methods</th>
<th>Participants</th>
<th>Interventions</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>This is a phase 2, multi-centre, randomised, double-blind, placebo-controlled, dose range-finding study</td>
<td><strong>Inclusion criteria</strong>&lt;br&gt;- Diagnosis of systemic lupus erythematosus&lt;br&gt;- 300 participants</td>
<td><strong>Interventions</strong>&lt;br&gt;A: biological medication ALX-0061 dose A every 2 weeks up to and including week 46 (11.5 weeks)&lt;br&gt;B: biological medication ALX-0061 dose B every 2 weeks up to and including week 46 (11.5 weeks)&lt;br&gt;C: biological medication ALX-0061 dose C every 2 weeks up to and including week 46 (11.5 weeks)&lt;br&gt;D: biological medication ALX-0061 dose D every 2 weeks up to and including week 46 (11.5 weeks)&lt;br&gt;E: placebo every 2 weeks up to and including week 46 (11.5 weeks)</td>
<td><strong>Control intervention</strong>&lt;br&gt;</td>
<td>Change from baseline in CLASI</td>
<td>Planned completion was March 2018</td>
</tr>
</tbody>
</table>

### NCT02446899

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Methods</th>
<th>Participants</th>
<th>Interventions</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>This is a multi-centre, multi-national, randomised, double-blind, placebo-controlled, phase 3 study of anifrolumab</td>
<td><strong>Inclusion criteria</strong>&lt;br&gt;- Diagnosis of systemic lupus erythematosus&lt;br&gt;- 360 participants</td>
<td><strong>Intervention</strong>&lt;br&gt;A: anifrolumab intravenously every 4 weeks for a total of 13 doses (12 months)</td>
<td><strong>Control intervention</strong>&lt;br&gt;B: placebo intravenously every 4 weeks for a total of 13 doses (12 months)</td>
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</table>
### NCT02446899 (Continued)

#### Outcomes
50% or greater reduction in CLASI score at week 12 in subgroup of subjects with baseline CLASI score > 10

#### Adverse events

#### Notes
Anifrolumab is also known as Medi-S46. This was NCT02446899

### NCT02446912

#### Methods
This is a phase 3, multi-centre, randomised, parallel, double-blind, placebo-controlled, quadruple (participant, care provider, investigator, outcomes assessor) masked clinical trial

#### Participants
**Inclusion criteria**
- Diagnosis of systemic lupus erythematosus
- Planned participants - 460

#### Interventions
**Intervention**
A: anifrolumab

**Control intervention**
B: placebo

#### Outcomes
Proportion of subjects with > 50% reduction in CLASI activity score at week 12 in the subgroup of subjects with baseline CLASI activity score > 10

#### Notes
Anifrolumab is also known as Medi-S46. This is also known as the TULIP 1 study - NCT02446912

### NCT02554019

#### Methods
This is a phase 2a, multi-centre, randomised, double-blind, placebo-controlled, repeated-dose trial

#### Participants
**Inclusion criteria**
- Diagnosis of systemic lupus erythematosus
- CLASI activity score ≥ 5
- Moderate to severe SLE disease activity demonstrated by SLEDAI-2K total score ≥ 6, including skin and joint involvement
- Planned participants - 36

#### Interventions
**Intervention**
A: 50 mg of BT063 administered by IV infusion 8 times over 12 weeks

**Control intervention**
B: placebo administered by IV infusion 8 times over 12 weeks

#### Outcomes
Improvement in CLASI score

#### Notes
Planned completion was September 2017
Methods

This is a 2-part phase 2 randomised, double-blind, placebo-controlled study

Participants

**Inclusion criteria (part A)**

1. Diagnosis of systemic lupus erythematosus (SLE) fulfilling at least 4 of 11 of the 1997 revised American College of Rheumatology (ACR) classification criteria for SLE along with active skin manifestations and joint involvement
2. At least 4 tender joints and at least 4 swollen joints with at least 4 of the swollen joints in the proximal interphalangeal (PIP) joints, metacarpophalangeal (MCP) joints, and/or wrist
3. Demonstrate at least 1 sign of active lupus skin disease, including acute cutaneous lupus erythematosus (ACLE), subacute cutaneous lupus erythematosus (SCLE), and/or chronic cutaneous lupus erythematosus (CCLE) (e.g. discoid lupus erythematosus (DLE)), with skin activity defined by SLE Disease Activity Index 2000 (SLEDAI-2K) at the time of screening and randomisation

**Inclusion criteria (part B)**

1. Active skin manifestations - Cutaneous Lupus Erythematosus Disease Area and Severity Index Activity (CLASI-A) ≥ 8 and diagnosis of cutaneous lupus erythematosus (CLE) that has been histologically confirmed (in the past or at screening), with or without SLE manifestations

**Exclusion criteria**

1. Active lupus nephritis or moderate to severe or chronic kidney disease
2. Any active skin condition other than CLE that may interfere with the study (e.g. psoriasis, non-LE skin lupus, drug-induced lupus)
3. History of chronic, recurrent (3 or more of the same type of infection in a 12-month period), or recent serious infection (e.g. pneumonia, septicaemia, herpes zoster) as determined by the Investigator and requiring anti-infective treatment within 12 weeks before screening
4. Use of immunosuppressive or disease-modifying treatment for SLE or CLE initiated less than 12 weeks before randomisation

Interventions

**Intervention (Part A)**

A: subcutaneous (SC) BIIB059 at doses of 450 mg every 4 weeks (Q4W) with an additional dose at week 2 for a total of 7 doses (weeks 0, 2, 4, 8, 12, 16, and 20) for 6 months

**Control intervention**

D: subcutaneously (SC) placebo administered every 4 weeks (Q4W) with an additional dose at week 2 for a total of 7 doses (weeks 0, 2, 4, 8, 12, 16, and 20) for 6 months

**Intervention (Part B)**

A: subcutaneous (SC) BIIB059 at dose of 50 mg administered every 4 weeks (Q4W) with an additional loading dose at week 2 for a total of 5 doses (weeks 0, 2, 4, 8, and 12) for 6 months

B: subcutaneous (SC) BIIB059 at dose of 150 mg administered every 4 weeks (Q4W) with an additional loading dose at week 2 for a total of 5 doses (weeks 0, 2, 4, 8, and 12) for 6 months

C: subcutaneous (SC) BIIB059 at dose of 450 mg administered every 4 weeks (Q4W) with an additional loading dose at week 2 for a total of 5 doses (weeks 0, 2, 4, 8, and 12) for 6 months

**Control intervention**

D: subcutaneous (SC) placebo administered every 4 weeks (Q4W) with an additional loading dose at week 2 for a total of 5 doses (weeks 0, 2, 4, 8, and 12) for 6 months

Outcomes

Percent change from baseline in Cutaneous Lupus Erythematosus Disease Area and Severity Index Activity (CLASI-A) score to week 16
### NCT02847598 (Continued)

Percentage of participants with CLASI-50 response at week 24 (Part A) and at weeks 12 and 16 (Part B) [time frame: baseline up to week 24] (CLASI-50 response is defined as a 50% improvement from baseline in CLASI-A score at week 24 (Part A) and at weeks 12 and 16 (Part B)

Percentage of participants with ≥ 4-point reduction in CLASI-A score relative to baseline at weeks 12 and 16 (Part B) and at week 24 (Part A)

**Notes**

This study was sponsored by Biogen

### NCT03958955

**Methods**

This was a trial on the efficacy and safety of twice-daily application of delgocitinib cream 20 mg/g for 6 weeks in subjects with active discoid lupus erythematosus

**Participants**

**Inclusion criteria**

- Planned 27 DLE subjects (also diagnosis of systemic lupus erythematosus by ACR)

**Interventions**

**Intervention**

A: delgocitinib cream

**Control intervention**

B: vehicle

**Outcomes**

CLASI

Adverse events

**Notes**

This study sponsored by Leo Pharma was listed as terminated early in 2020 due to “recruitment challenges”, and no results have been posted to date. We are awaiting published data

### Tanaka 2020

**Methods**

This is a subgroup analysis from a phase 3 randomised placebo-controlled trial of organ system improvements in Japanese patients with systemic lupus erythematosus treated with belimumab

**Participants**

**Inclusion criteria**

- 69 subjects with diagnosis of systemic lupus erythematosus by ACR

**Interventions**

**Intervention**

A: belimumab (n = 39)

**Control intervention**

B: placebo (n = 21)

**Outcomes**

Percentage of patients with improvement in SLEDAI mucocutaneous domain

Adverse events (minor and severe)

**Notes**

Data from NCT01345253
## Methods
Pharmacodynamics, safety, and clinical efficacy of AMG 811, a human anti-interferon-γ antibody, in patients with discoid lupus

### Participants

**Inclusion criteria**

- 20 subjects screened; 16 subjects enrolled and randomised (14 had "comorbid SLE" with diagnosis of DLE [2 with DLE only])

### Interventions

**Intervention**

A: AMG 811 (180 mg) single dose subcutaneously on day 1 and day 85

**Control intervention**

B: placebo

### Outcomes

- CLASI-A scores
- CLASI-D scores
- Physician's assessment of skin disease
- Patient’s self-assessment of skin disease
- SLE Disease Activity Index 2000

### Notes

NCT01164917

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**ACLE**: acute cutaneous lupus erythematosus.
**ACR**: American College of Rheumatology.
**BICLA**: BILAG-based Combined Lupus Assessment.
**BILAG**: British Isles Lupus Assessment Group.
**CCLE**: cutaneous lupus erythematosus.
**CLASI-K**: Cutaneous Lupus Erythematosus Disease Area and Severity Index Activity.
**DLE**: discoid lupus erythematosus.
**dsDNA**: double-stranded DNA.
**IFN-K**: interferon kappa.
**PBO**: placebo.
**RCI**: repository corticotropin injection.
**SCLE**: subacute cutaneous lupus erythematosus.
**SGADA**: Subject Global Assessment of Disease Activity.
**SLE**: systemic lupus erythematosus.
**SLEDAI-2K**: SLE Disease Activity Index-2000.
**SLICC**: Systemic Lupus International Collaborating Clinics.
**SOC**: standard of care.
**SRI-4**: SLE Responder Index-4.
**TYK2**: tyrosine kinase 2.

### Characteristics of ongoing studies [ordered by study ID]

**ISRCTN47873003**

**Study name**
Belimumab after B cell depletion therapy as a new treatment for patients with systemic lupus erythematosus (SLE)

**Methods**
Multi-centre phase 2 randomised double-blind placebo-controlled clinical trial

**Participants**

Inclusion criteria
### Interventions

**Intervention**

A: belimumab according to the standard dosage regime of infusions of 10 mg/kg at 2 week intervals for the first 3 doses, and at 4 week intervals thereafter, up until week 52 (12 months)

**Control intervention**

B: same volume of normal saline infusions (0.9% saline) at the same time points as for the active treatment group

### Outcomes

- Proportion of patients with any disease flare (defined as 1 BILAG A or 2 BILAG B flares) as measured by BILAG 2004 at week -4, week 0, and week 2 and every 4 weeks until week 68
- Time to disease flare (defined as 1 BILAG A or 2 BILAG B flares) as measured by BILAG 2004 at week -4, week 0, and week 2 and every 4 weeks until week 68
- Proportion of patients with 1 BILAG A or 2 BILAG B flares as measured by BILAG 2004 at 24, 52, and 68 weeks
- SLEDAI 2000 as measured by SLEDAI 2000 at 52 weeks
- Systemic lupus erythematosus disease activity as measured by Subject Global Assessment of Disease Activity (SGADA) at 52 weeks

### Starting date

First registration 28/11/2016

### Contact information

Felicia Ikeji  
University College London Comprehensive Clinical Trials Unit  
Gower Street WC1E 6BT  
London, United Kingdom

### Notes

Sponsored by Arthritis Research UK, GlaxoSmithKline Foundation, University College London Biomedical Research Centre; this study is also known as BEAT-Lupus, and the protocol was published in 2020. More information is available at http://isrctn.com/ISRCTN47873003.
### NCT01781611 (Continued)

<table>
<thead>
<tr>
<th>Starting date</th>
<th>February 2013</th>
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<tbody>
<tr>
<td>Contact information</td>
<td>Oklahoma Medical Research Foundation</td>
</tr>
<tr>
<td>Notes</td>
<td>Expected completion is in February 2020. No results posted as of September 2020</td>
</tr>
</tbody>
</table>

### NCT02270957

<table>
<thead>
<tr>
<th>Study name</th>
<th>Clarification of abatacept effects in SLE with integrated biologic and clinical approaches (ABC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>This is a randomised controlled double-blind placebo-controlled trial</td>
</tr>
</tbody>
</table>
| Participants | **Inclusion criteria**  
|             | • Diagnosis of systemic lupus erythematosus  
|             | • Number of participants planned = 60 |
| Interventions | **Intervention**  
|             | A: abatacept (Orencia®) over 6 months |
|             | **Control intervention**  
|             | B: placebo over 6 months |
| Outcomes   | CLASI  
|           | Lupus Foundation of America's REAL™ (Rapid Evaluation of Activity in Lupus) system  
|           | Global SLEDAI  
|           | BICLA  
|           | Adverse events |
| Starting date | January 2014 |
| Contact information | Oklahoma Medical Research Foundation; Bristol Myers Squibb, Joan Merrill MD, Oklahoma Medical Research Foundation |
| Notes | Planned completion of this trial is December 2020 |

### NCT02660944

<table>
<thead>
<tr>
<th>Study name</th>
<th>A phase 2a of RSLV-132 in subjects with systemic lupus erythematosus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>This is a randomised, double-blind, phase 2a, placebo-controlled study</td>
</tr>
</tbody>
</table>
| Participants | **Inclusion criteria**  
|             | • Diagnosis of systemic lupus erythematosus  
|             | • CLASI score ≥ 10 at baseline  
|             | • Planned participants = 50 |
| Interventions | **Intervention** |

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*Interventions for cutaneous disease in systemic lupus erythematosus (Review)*

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### NCT02660944 (Continued)

<table>
<thead>
<tr>
<th>Study name</th>
<th>A randomised single-blinded sham-controlled trial of vague nerve stimulation in systemic lupus erythematosus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>This is a randomised single-blinded (participant only) sham-controlled trial of vague nerve stimulation in systemic lupus erythematosus</td>
</tr>
</tbody>
</table>
| Participants | **Inclusion criteria**  
• Diagnosis of systemic lupus erythematosus  
• Planned participants = 18 |
| Interventions | **Intervention**  
A: device: vagus nerve stimulation  
**Control intervention**  
B: device: sham vagus nerve stimulation |
| Outcomes   | SLE cutaneous activity  
SLE disease activity  
Adverse events: minor and severe |
| Starting date | Study start: 1 September 2018 |
| Contact information | Sponsored by Northwell Health; John and Marcia Goldman Foundation |
| Notes | Planned study end date is 1 November 2020 |

### NCT02822989

<table>
<thead>
<tr>
<th>Study name</th>
<th>A study to evaluate the efficacy and safety of CC-220 in subjects with active systemic lupus erythematosus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>This is a phase 2 multi-centre, randomised, double-blind, placebo-controlled, cross-over study of CC-220 in subjects with active systemic lupus erythematosus</td>
</tr>
</tbody>
</table>
NCT03161483 (Continued)

Participants

**Inclusion criteria**
- Diagnosis of systemic lupus erythematosus
- Planned participants = 280

Interventions

**Interventions**
A: oral CC-220 at dose of 0.45 mg each day for 6 months
B: oral CC-220 at dose of 0.3 mg each day for 6 months
C: oral CC-220 at dose of 0.15 mg each day for 6 months

**Control intervention**
D: identical appearing placebo for 6 months

Outcomes

**Proportion of subjects with ≥ 50% reduction in Cutaneous Lupus Area and Severity Index (CLASI) activity score from baseline in subjects with baseline CLASI activity score ≥ 10 [Time frame: weeks 24 and 52]**
Change from baseline in Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index [Time frame: 52 weeks]
Adverse events: minor and severe

Starting date
July 2017

Contact information
Celgene
Associate Director Clinical Trials
1-888-260-1599
clinicaltrialdisclosure@celgene.com

Notes
Completion date is October 2021. Sponsor was Celgene

NCT03252587

Study name
Oral selective tyrosine kinase 2 (TYK2) inhibition with BMS-986165 in patients with systemic lupus erythematosus: a phase 2, randomized, double-blind, placebo-controlled study

Methods
This is a phase 2, randomised, double-blind, placebo-controlled, global study with quadruple masking (participant, care provider, investigator, outcomes assessor) of an oral selective tyrosine kinase 2 (TYK2) inhibitor with BMS-986165 in patients with systemic lupus erythematosus

Participants

**Inclusion criteria**
- Meets Systemic Lupus International Collaborating Clinics (SLICC) classification criteria for SLE and diagnosed ≥ 24 weeks before screening visit and 1 of the following: (1) antinuclear antibody (ANA) ≥ 1:80 or (2) positive anti-double-stranded DNA (dsDNA) or (3) positive anti-Smith (Sm)
- Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) score ≥ 6 points and clinical SLEDAI-2K score ≥ 4 points

**Exclusion criteria**
- Subjects with drug-induced SLE, certain other autoimmune diseases, and active severe lupus nephritis
- SLE overlap syndromes such as scleroderma and mixed connective tissue disease
- Clinically significant abnormalities on chest X-ray or ECG
- History of any significant drug allergy
- Other protocol-defined inclusion/exclusion criteria could apply
NCT03252587 (Continued)

Interventions

A: oral BMS-986165 dose 1 oral administration with standard of care and steroid tapering
B: oral BMS-986165 dose 2 oral administration with standard of care and steroid tapering
C: oral BMS-986165 dose 3 oral administration with standard of care and steroid tapering

Control intervention

D: oral placebo with standard of care and steroid tapering

Outcomes

Number of participants with Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) activity score ≥ 10 at baseline achieving a CLASI response, defined as a decrease ≥ 50% from baseline CLASI activity score [Time frame: 32 weeks]

Adverse events (minor and severe)

Starting date

Starting date was 1 September 2017

Contact information

Paisley study contact: www.BMSStudyConnect.com; https://www.paisleystudy.com
Sponsor: Bristol Myers Squibb

Notes

Estimated study completion date: December 2020; reference: https://clinicaltrials.gov/ct2/show/NCT03252587

NCT03451422

Study name

A phase 1b/2a study to evaluate the safety and efficacy of AMG 592 in subjects with active systemic lupus erythematosus with inadequate response to standard of care therapy

Methods

The phase 1b part of the study is a double-blind, placebo-controlled, multi-centre, multiple ascending dose (MAD) study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of AMG 592 in subjects with SLE over 3 months. The phase 2a part of the study is a multi-centre, double-blind, placebo-controlled study in subjects with moderate to severe SLE or cutaneous lupus with inadequate response to standard of care therapy over 12 months

Participants

Inclusion criteria

- Diagnosis of systemic lupus erythematosus
- Planned participants = 132
- CLASI score ≥ 10

Interventions

A: subcutaneous injections of AMG592 weekly
B: subcutaneous injections of AMG592 biweekly

Control intervention

C: subcutaneous injections of placebo

Phase 1: 3 months
Phase 2: 12 months

Outcomes

CLASI activity score 50% improvement from baseline at weeks 12, 24, 36, and 52 in subjects with CLASI activity score ≥ 10 at baseline [Time frame: baseline, weeks 12, 24, 36, and 52]
CLASI activity score change from baseline at weeks 12, 36, and 52 in subjects with CLASI activity score ≥ 10 at baseline [Time frame: baseline, weeks 12, 24, 36, and 52]
### NCT03451422 (Continued)

<table>
<thead>
<tr>
<th>Adverse events - minor and severe</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Starting date</strong></td>
</tr>
</tbody>
</table>
| **Contact information** | Amgen Call Center  
medinfo@amgen.com  
866-572-6436 |
| **Notes** | Estimated completion date: 4 January 2022 |

### NCT03517722

| A multi-centre, randomized, double-blind, placebo-controlled, parallel-group study of ustekinum-  
ab in subjects with active systemic lupus erythematosus |
<table>
<thead>
<tr>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study name</strong></td>
</tr>
</tbody>
</table>
| **Methods** | This is a multi-centre, randomised, double-blind, placebo-controlled, parallel-group study of  
ustekinumab in subjects with active systemic lupus erythematosus |
| **Participants** | **Inclusion criteria**  
- Planned 516 subjects with diagnosis of systemic lupus erythematosus by ACR |
| **Interventions** | **Intervention**  
A: ustekinumab  
**Control intervention**  
B: placebo |
| **Outcomes** | CLASI  
Adverse events (minor and severe) |
| **Starting date** | 16 April 2018 |
| **Contact information** | Study sponsor is Janssen Research & Development, LLC |
| **Notes** | Planned completion of the study is 14 December 2023 |

### NCT03616912

<table>
<thead>
<tr>
<th>A study of baricitinib (LY3009104) in participants with systemic lupus erythematosus (BRAVE I)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study name</strong></td>
</tr>
</tbody>
</table>
| **Methods** | This is a randomised, double-blind, placebo-controlled, parallel-group, phase 3 Study of baricitinib  
in patients with systemic lupus erythematosus |
| **Participants** | **Inclusion criteria**  
- Planned 750 subjects with diagnosis of systemic lupus erythematosus by ACR |
| **Interventions** | **Intervention**  
A: baricitinib  
**Control intervention** |

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### NCT03616912 (Continued)

- **Interventions**
  - A: baricitinib
  - Control intervention: B: placebo

- **Outcomes**
  - CLASI
  - Adverse events (minor and severe)

- **Starting date**
  - 2 August 2018

- **Contact information**
  - Contact Eli Lilly at 1-877-CTLILLY (1-877-285-4559)

- **Notes**
  - This is known as the Brave I trial. Planned completion date is 30 November 2021

### NCT03616964

- **Study name**
  - A study of baricitinib in participants with systemic lupus erythematosus (BRAVE II)

- **Methods**
  - A randomised, double-blind, placebo-controlled, parallel-group, phase 3 study of baricitinib in patients with systemic lupus erythematosus

- **Participants**
  - **Inclusion criteria**
    - 750 subjects with diagnosis of systemic lupus erythematosus by ACR

- **Interventions**
  - **Intervention**
    - A: baricitinib
  - **Control intervention**
    - B: placebo

- **Outcomes**
  - CLASI
  - Adverse events (minor and severe)

- **Starting date**
  - 2 August 2018

- **Contact information**
  - Contact Eli Lilly at 1-317-615-4559

- **Notes**
  - This is known as the Brave II trial. Planned completion is 15 November 2021

### NCT03845517

- **Study name**
  - A phase 2b multicenter dose ranging study to evaluate efficacy and safety of PF-06700841 in active systemic lupus erythematosus

- **Methods**
  - This is a phase 2b multi-centre dose-ranging study to evaluate efficacy and safety profile

- **Participants**
  - **Inclusion criteria**
    - Planned 448 subjects with diagnosis of systemic lupus erythematosus by ACR

- **Interventions**
  - **Interventions**
    - A: PF-06700841 at 15 mg
### NCT03845517 (Continued)

**Interventions**

B: PF-06700841 at 30 mg  
C: PF-06700841 at 45 mg  

**Control intervention**

B: placebo

**Outcomes**

Percentage of participants with Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI-A) total activity score ≥ 10 at baseline with ≥ 50% reduction in CLASI-A total activity score  
Adverse events (minor and severe)

**Starting date**

Start date was 18 April 2019

**Contact information**

Pfizer is the sponsor and can be contacted at 1-800-718-1021, or at ClinicalTrials.gov_Inquiries@pfizer.com

**Notes**

Study expected completion is in September 2022

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### NCT03978520

**Study name**

A study to investigate the safety and efficacy of elsubrutinib and upadacitinib given alone or in combination in participants with moderately to severely active systemic lupus erythematosus (SLE)

**Methods**

This is a quadruple-blind, parallel-group placebo-controlled phase 2 study to investigate safety and efficacy

**Participants**

**Inclusion criteria**

- Planned 310 subjects with diagnosis of systemic lupus erythematosus by ACR

**Interventions**

**Interventions**

A: elsubrutinib and upadacitinib  
B: upadacitinib  
C: elsubrutinib

**Control intervention**

B: placebo

**Outcomes**

CLASI  
Adverse events (minor and severe)

**Starting date**

25 July 2019

**Contact information**

ABBVIE CALL CENTER, at 847.283.8955, or abbvieclinicaltrials@abbvie.com

**Notes**

This is study NCT03978520. Planned completion is 2 July 2022
### NCT04058028
**Study name**
A phase 2 dose ranging study to evaluate the efficacy and safety of AMG 570 in subjects with active systemic lupus erythematosus (SLE) with inadequate response to standard of care (SOC) therapy

**Methods**
This is a Bayesian adaptive phase 2, multi-centre, double-blind, randomised, placebo-controlled, 52-week, dose-ranging study in subjects with active systemic lupus erythematosus (SLE) and inadequate response to standard of care (SOC) therapies

**Participants**
**Inclusion criteria**
- Planned 300 subjects with diagnosis of systemic lupus erythematosus by ACR

**Interventions**
**Intervention**
A: AMG 570

**Control intervention**
B: placebo

**Outcomes**
- CLASI
- Adverse events (minor and severe)

**Starting date**
19 February 2020

**Contact information**
Sponsor is Amgen, who can be contacted at http://www.amgentrials.com

**Notes**
Planned completion date is 24 September 2023

### NCT04060888
**Study name**
A multicenter, randomized, double-blind, placebo-controlled, parallel-group study of ustekinumab in Chinese subjects with active systemic lupus erythematosus

**Methods**
This is a multi-centre, randomised, double-blind, placebo-controlled, parallel-group study of ustekinumab in Chinese subjects with active systemic lupus erythematosus

**Participants**
**Inclusion criteria**
- Planned 190 subjects with diagnosis of systemic lupus erythematosus by ACR

**Interventions**
**Intervention**
A: ustekinumab

**Control intervention**
B: placebo

**Outcomes**
- CLASI
- Adverse outcomes (minor and severe)

**Starting date**
5 June 2020

**Contact information**
Study sponsor is Janssen Research and Development
### Study name
An intervention to evaluate the efficacy and safety of belimumab administered in combination with rituximab to adult subjects with systemic lupus erythematosus (SLE) - BISS-BELIEVE

### Methods
A Phase 3, multi-centre, randomised, double-blind, placebo-controlled, 104-week study to evaluate the efficacy and safety of belimumab administered in combination with rituximab to adult subjects with systemic lupus erythematosus (SLE)

### Participants
**Inclusion criteria**
- Planned 292 subjects with diagnosis of systemic lupus erythematosus by ACR

### Interventions
**Intervention**
- A: belimumab and rituximab

**Control intervention**
- B: placebo

### Outcomes
SLEDAI

Adverse events (minor and severe)

### Starting date
1 March 2018

### Contact information
Sponsor of the study is Glaxo-Smith-Kline

### Notes
This is NCT03312907, called BISS-BELIEVE. Protocol was published. Planned completion date is 9 July 2021

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**ACR:** American College of Rheumatology.

**ANA:** antinuclear antibody.

**BICLA:** BILAG-based Combined Lupus Assessment.

**BILAG:** British Isles Lupus Assessment Group.

**CLASI:** Subject Global Assessment of Disease Activity.

**dsDNA:** double-stranded DNA.

**SGADA:** Subject Global Assessment of Disease Activity.

**SLE:** systemic lupus erythematosus.

**SLEDAI-2K:** SLE Disease Activity Index 2000.

**SLICC:** Systemic Lupus International Collaborating Clinics.

**SLICC:** Systemic Lupus International Collaborating Clinics.

**TYK2:** tyrosine kinase 2.

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**DATA AND ANALYSES**
Comparison 1. Oral methotrexate versus placebo

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1 Primary outcome (lupus-specific): absence of malar or discoid rash</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>1.1.1 Short term (6 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>1.2 Secondary outcome (lupus-specific): severe clinical flare (requiring discontinuation of study)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>1.2.1 Long term (12 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>1.3 Adverse events</td>
<td>2</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>1.3.1 Severe short term (6 months)</td>
<td>1</td>
<td>41</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>1.05 [0.16, 6.76]</td>
</tr>
<tr>
<td>1.3.2 Severe long term (12 months)</td>
<td>1</td>
<td>86</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>12.05 [0.69, 211.36]</td>
</tr>
<tr>
<td>1.3.3 Minor short term (6 months)</td>
<td>1</td>
<td>41</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>3.85 [1.26, 11.80]</td>
</tr>
<tr>
<td>1.3.4 Minor long term: adverse mucocutaneous events (12 months)</td>
<td>1</td>
<td>86</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>0.68 [0.39, 1.17]</td>
</tr>
</tbody>
</table>

Analysis 1.1. Comparison 1: Oral methotrexate versus placebo, Outcome 1: Primary outcome (lupus-specific): absence of malar or discoid rash

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Methotrexate</th>
<th>Placebo</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short term (6 months)</td>
<td>17</td>
<td>20</td>
<td>3.57 [1.63, 7.84]</td>
</tr>
</tbody>
</table>

Favors placebo
Favors methotrexate
### Analysis 1.2. Comparison 1: Oral methotrexate versus placebo, Outcome 2: Secondary outcome (lupus-specific): severe clinical flare (requiring discontinuation of study)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Methotrexate Events</th>
<th>Total</th>
<th>Placebo Events</th>
<th>Total</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.2.1 Long term (12 months)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fortin 2008</td>
<td>7 41</td>
<td>10 45</td>
<td>0.77 [0.32 , 1.83]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Risk Ratio: Favors methotrexate

### Analysis 1.3. Comparison 1: Oral methotrexate versus placebo, Outcome 3: Adverse events

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Methotrexate Events</th>
<th>Total</th>
<th>Placebo Events</th>
<th>Total</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.3.1 Severe short term (6 months)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Carneiro 1999     | 2 20               | 2 21  | 1.05 [0.16 , 6.76] | | Total events: 2 2
| Subtotal (95% CI) | 20                 | 21    | 1.05 [0.16 , 6.76] | |
| Heterogeneity: Not applicable | | | |
| Test for overall effect: Z = 0.05 (P = 0.96) | |

| 1.3.2 Severe long term (12 months) |          |       |                |       |                              |
| Fortin 2008     | 5 41               | 0 45  | 12.05 [0.69 , 211.36] | |
| Subtotal (95% CI) | 41                 | 45    | 12.05 [0.69 , 211.36] | |
| Total events: 5 0 | | | |
| Heterogeneity: Not applicable | | | |
| Test for overall effect: Z = 1.70 (P = 0.09) | |

| 1.3.3 Minor short term (6 months) |          |       |                |       |                              |
| Carneiro 1999   | 11 20              | 3 21  | 3.85 [1.26 , 11.80] | |
| Subtotal (95% CI) | 20                 | 21    | 3.85 [1.26 , 11.80] | |
| Total events: 11 3 | | | |
| Heterogeneity: Not applicable | | | |
| Test for overall effect: Z = 2.36 (P = 0.02) | |

| 1.3.4 Minor long term: adverse mucocutaneous events (12 months) |          |       |                |       |                              |
| Fortin 2008     | 13 41              | 21 45 | 0.68 [0.39 , 1.17] | |
| Subtotal (95% CI) | 41                 | 45    | 0.68 [0.39 , 1.17] | |
| Total events: 13 21 | | | |
| Heterogeneity: Not applicable | | | |
| Test for overall effect: Z = 1.38 (P = 0.17) | |
Comparison 2. Oral hydroxychloroquine versus placebo

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1 Primary outcome (lupus-specific): partial improvement in skin lesions during pregnancy</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>2.1.1 Long term (12 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>2.2 Secondary outcome (lupus-specific): clinical flare in skin disease</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>2.2.1 Short term (6 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>2.3 Secondary outcome (lupus-non-specific): vasculitis</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>2.3.1 Long term (48 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>2.4 Secondary outcome (lupus-non-specific): major flare in lupus (vasculitis, skin or other system)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>2.4.1 Long term (48 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>2.5 Secondary outcome (lupus-specific): systemic lupus flare during pregnancy study</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>2.5.1 Long term (12 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>2.6 Adverse events: severe - toxaemia during pregnancy study</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>2.6.1 Long term (12 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>2.7 Adverse events: severe - adverse event related to medication</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>2.7.1 Long term (12 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>2.8 Adverse events: severe - any severe event</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>2.8.1 Short term (6 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>2.9 Adverse events: severe - rash</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
</tbody>
</table>
### Analysis 2.1. Comparison 2: Oral hydroxychloroquine versus placebo, Outcome 1: Primary outcome (lupus-specific): partial improvement in skin lesions during pregnancy

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Hydroxychloroquine</th>
<th>Placebo</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1.1 Long term (12 months) Levy 2001</td>
<td>3</td>
<td>10</td>
<td>7.00 [0.41, 120.16]</td>
</tr>
</tbody>
</table>

### Analysis 2.2. Comparison 2: Oral hydroxychloroquine versus placebo, Outcome 2: Secondary outcome (lupus-specific): clinical flare in skin disease

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Hydroxychloroquine</th>
<th>Placebo</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.2.1 Short term (6 months) Tsakonas 1991</td>
<td>9</td>
<td>25</td>
<td>0.49 [0.28, 0.89]</td>
</tr>
</tbody>
</table>
Analysis 2.3. Comparison 2: Oral hydroxychloroquine versus placebo, Outcome 3: Secondary outcome (lupus-non-specific): vasculitis

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Hydroxychloroquine</th>
<th>Placebo</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events  Total</td>
<td>Events  Total</td>
<td>M-H, Random, 95% CI</td>
<td>M-H, Random, 95% CI</td>
</tr>
<tr>
<td>2.3.1 Long term (48 months)</td>
<td>2  25</td>
<td>3  22</td>
<td>0.59 [0.11, 3.20]</td>
<td>0.01 0.1 1 10 100</td>
</tr>
</tbody>
</table>

Favors hydroxychloroquine Favors placebo

Analysis 2.4. Comparison 2: Oral hydroxychloroquine versus placebo, Outcome 4: Secondary outcome (lupus-non-specific): major flare in lupus (vasculitis, skin or other system)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Hydroxychloroquine</th>
<th>Placebo</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events  Total</td>
<td>Events  Total</td>
<td>M-H, Random, 95% CI</td>
<td>M-H, Random, 95% CI</td>
</tr>
<tr>
<td>2.4.1 Long term (48 months)</td>
<td>7  25</td>
<td>11  22</td>
<td>0.56 [0.26, 1.19]</td>
<td>0.01 0.1 1 10 100</td>
</tr>
</tbody>
</table>

Favors hydroxychloroquine Favors placebo

Analysis 2.5. Comparison 2: Oral hydroxychloroquine versus placebo, Outcome 5: Secondary outcome (lupus-specific): systemic lupus flare during pregnancy study

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Hydroxychloroquine</th>
<th>Placebo</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events  Total</td>
<td>Events  Total</td>
<td>M-H, Random, 95% CI</td>
<td>M-H, Random, 95% CI</td>
</tr>
<tr>
<td>2.5.1 Long term (12 months)</td>
<td>0  10</td>
<td>3  10</td>
<td>0.14 [0.01, 2.45]</td>
<td>0.005 0.1 1 10 200</td>
</tr>
</tbody>
</table>

Favors hydroxychloroquine Favors placebo

Analysis 2.6. Comparison 2: Oral hydroxychloroquine versus placebo, Outcome 6: Adverse events: severe - toxaemia during pregnancy study

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Hydroxychloroquine</th>
<th>Placebo</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events  Total</td>
<td>Events  Total</td>
<td>M-H, Random, 95% CI</td>
<td>M-H, Random, 95% CI</td>
</tr>
<tr>
<td>2.6.1 Long term (12 months)</td>
<td>0  10</td>
<td>3  10</td>
<td>0.14 [0.01, 2.45]</td>
<td>0.002 0.1 1 10 500</td>
</tr>
</tbody>
</table>

Favors hydroxychloroquine Favors placebo
### Analysis 2.7. Comparison 2: Oral hydroxychloroquine versus placebo, Outcome 7: Adverse events: severe - adverse event related to medication

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Hydroxychloroquine</th>
<th>Placebo</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events Total</td>
<td>Events Total</td>
<td>M-H, Random, 95% CI</td>
</tr>
<tr>
<td>2.7.1 Long term (12 months)</td>
<td>2 40</td>
<td>0 31</td>
<td>3.90 [0.19, 78.46]</td>
</tr>
</tbody>
</table>

![Risk Ratio Chart](image)

#### Analysis 2.8. Comparison 2: Oral hydroxychloroquine versus placebo, Outcome 8: Adverse events: severe - any severe event

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Hydroxychloroquine</th>
<th>Placebo</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events Total</td>
<td>Events Total</td>
<td>M-H, Random, 95% CI</td>
</tr>
<tr>
<td>2.8.1 Short term (6 months)</td>
<td>1 25</td>
<td>5 22</td>
<td>0.18 [0.02, 1.39]</td>
</tr>
</tbody>
</table>

![Risk Ratio Chart](image)

### Analysis 2.9. Comparison 2: Oral hydroxychloroquine versus placebo, Outcome 9: Adverse events: severe - rash

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Hydroxychloroquine</th>
<th>Placebo</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events Total</td>
<td>Events Total</td>
<td>M-H, Random, 95% CI</td>
</tr>
<tr>
<td>2.9.1 Long term (12 months)</td>
<td>1 40</td>
<td>0 31</td>
<td>2.34 [0.10, 55.58]</td>
</tr>
</tbody>
</table>

![Risk Ratio Chart](image)

### Analysis 2.10. Comparison 2: Oral hydroxychloroquine versus placebo, Outcome 10: Adverse events: severe - worsening symptoms leading to study withdrawal (lack of treatment efficacy)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Hydroxychloroquine</th>
<th>Placebo</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events Total</td>
<td>Events Total</td>
<td>M-H, Random, 95% CI</td>
</tr>
<tr>
<td>2.10.1 Long term (12 months)</td>
<td>5 40</td>
<td>7 31</td>
<td>0.55 [0.19, 1.58]</td>
</tr>
</tbody>
</table>

![Risk Ratio Chart](image)
### Analysis 2.11. Comparison 2: Oral hydroxychloroquine versus placebo, Outcome 11: Adverse events: severe - sudden death - not thought to be related to medication

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Hydroxychloroquine</th>
<th>Placebo</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.11.1 Long term (12 months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Williams 1994</td>
<td>1</td>
<td>40</td>
<td>0</td>
</tr>
</tbody>
</table>

Risk Ratio: Favor hydroxychloroquine

### Analysis 2.12. Comparison 2: Oral hydroxychloroquine versus placebo, Outcome 12: Adverse events: minor

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Hydroxychloroquine</th>
<th>Placebo</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.12.1 Short term (6 months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tsakonas 1991</td>
<td>3</td>
<td>25</td>
<td>2</td>
</tr>
</tbody>
</table>

Risk Ratio: Favor hydroxychloroquine

### Comparison 3. Oral dehydroepiandrosterone versus placebo

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.1 Primary outcome (lupus-specific): absence of oral stomatitis</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>3.1.1 Long term (12 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>3.2 Primary outcome (lupus-specific): absence of cutaneous rash</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>3.2.1 Long term (12 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>3.3 Primary outcome (lupus-non-specific): absence of alopecia</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>3.3.1 Long term (12 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>3.4 Adverse events: severe - any</td>
<td>2</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>3.4.1 Short term (3 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>3.4.2 Long term (12 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>Outcome or subgroup title</td>
<td>No. of studies</td>
<td>No. of participants</td>
<td>Statistical method</td>
<td>Effect size</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>----------------</td>
<td>---------------------</td>
<td>------------------------------------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>3.5 Adverse events: severe - death</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>3.5.1 Long term (12 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>3.6 Adverse events: severe - cancer diagnosis</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>3.6.1 Long term (12 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>3.7 Adverse events: minor - presence of acne</td>
<td>2</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>3.7.1 Short term (3 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>3.7.2 Long term (12 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>3.8 Adverse events: minor - presence of hirsutism</td>
<td>2</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>3.8.1 Short term (3 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>3.8.2 Long term (12 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>3.9 Adverse events: minor - presence of rash</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>3.9.1 Short term (3 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
</tbody>
</table>

### Analysis 3.1. Comparison 3: Oral dehydroepiandrosterone versus placebo, Outcome 1: Primary outcome (lupus-specific): absence of oral stomatitis

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>DHEA Events</th>
<th>DHEA Total</th>
<th>Placebo Events</th>
<th>Placebo Total</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.1.1 Long term (12 months)</td>
<td>161</td>
<td>189</td>
<td>148</td>
<td>192</td>
<td>1.11 [1.00, 1.22]</td>
<td></td>
</tr>
</tbody>
</table>

Favors placebo

Favors DHEA

---

**Interventions for cutaneous disease in systemic lupus erythematosus (Review)**

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Analysis 3.2. Comparison 3: Oral dehydroepiandrosterone versus placebo, Outcome 2: Primary outcome (lupus-specific): absence of cutaneous rash

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>DHEA Events</th>
<th>Total</th>
<th>placebo Events</th>
<th>Total</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.2.1 Long term (12 months)</td>
<td>Petri 2004</td>
<td>114</td>
<td>189</td>
<td>130</td>
<td>192</td>
</tr>
</tbody>
</table>

Analysis 3.3. Comparison 3: Oral dehydroepiandrosterone versus placebo, Outcome 3: Primary outcome (lupus-non-specific): absence of alopecia

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>DHEA Events</th>
<th>Total</th>
<th>placebo Events</th>
<th>Total</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.3.1 Long term (12 months)</td>
<td>Petri 2004</td>
<td>161</td>
<td>189</td>
<td>153</td>
<td>192</td>
</tr>
</tbody>
</table>

Analysis 3.4. Comparison 3: Oral dehydroepiandrosterone versus placebo, Outcome 4: Adverse events: severe - any

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>DHEA Events</th>
<th>Total</th>
<th>placebo Events</th>
<th>Total</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.4.1 Short term (3 months)</td>
<td>Van Vollenhoven 1995</td>
<td>0</td>
<td>14</td>
<td>0</td>
<td>14</td>
</tr>
<tr>
<td>3.4.2 Long term (12 months)</td>
<td>Petri 2004</td>
<td>14</td>
<td>189</td>
<td>16</td>
<td>192</td>
</tr>
</tbody>
</table>

Analysis 3.5. Comparison 3: Oral dehydroepiandrosterone versus placebo, Outcome 5: Adverse events: severe - death

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>DHEA Events</th>
<th>Total</th>
<th>placebo Events</th>
<th>Total</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.5.1 Long term (12 months)</td>
<td>Petri 2004</td>
<td>0</td>
<td>189</td>
<td>5</td>
<td>192</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>DHEA Events</th>
<th>DHEA Total</th>
<th>placebo Events</th>
<th>placebo Total</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.6.1 Long term (12 months)</td>
<td>0</td>
<td>189</td>
<td>3</td>
<td>192</td>
<td>0.15 [0.01, 2.79]</td>
</tr>
</tbody>
</table>

Analysis 3.7. Comparison 3: Oral dehydroepiandrosterone versus placebo, Outcome 7: Adverse events: minor - presence of acne

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>DHEA Events</th>
<th>DHEA Total</th>
<th>placebo Events</th>
<th>placebo Total</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.7.1 Short term (3 months)</td>
<td>8</td>
<td>14</td>
<td>1</td>
<td>14</td>
<td>8.00 [1.15, 55.80]</td>
</tr>
<tr>
<td>3.7.2 Long term (12 months)</td>
<td>63</td>
<td>189</td>
<td>27</td>
<td>192</td>
<td>2.37 [1.58, 3.55]</td>
</tr>
</tbody>
</table>

Analysis 3.8. Comparison 3: Oral dehydroepiandrosterone versus placebo, Outcome 8: Adverse events: minor - presence of hirsutism

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>DHEA Events</th>
<th>DHEA Total</th>
<th>placebo Events</th>
<th>placebo Total</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.8.1 Short term (3 months)</td>
<td>2</td>
<td>14</td>
<td>4</td>
<td>14</td>
<td>0.50 [0.11, 2.30]</td>
</tr>
<tr>
<td>3.8.2 Long term (12 months)</td>
<td>31</td>
<td>189</td>
<td>3</td>
<td>192</td>
<td>10.50 [3.26, 33.75]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>DHEA Events</th>
<th>placebo Events</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.9.1 Short term (3 months)</td>
<td></td>
<td></td>
<td>0.20 [0.01 , 3.82]</td>
</tr>
<tr>
<td>Van Vollenhoven 1995</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

Comparison 4. Intravenous belimumab (1.0, 4.0, 10.0 mg/kg) versus placebo

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.1 Adverse events: severe at belimumab 1 mg/kg dose</td>
<td>3</td>
<td>1348</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>0.86 [0.62, 1.21]</td>
</tr>
<tr>
<td>4.1.1 Long term (12 months)</td>
<td>2</td>
<td>802</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>0.90 [0.60, 1.36]</td>
</tr>
<tr>
<td>4.1.2 Long term (18 months)</td>
<td>1</td>
<td>546</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>0.79 [0.44, 1.44]</td>
</tr>
<tr>
<td>4.2 Adverse events: severe, at belimumab 10 mg/kg dose</td>
<td>3</td>
<td>1349</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>0.88 [0.63, 1.23]</td>
</tr>
<tr>
<td>4.2.1 Long term (12 months)</td>
<td>2</td>
<td>801</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>0.81 [0.53, 1.24]</td>
</tr>
<tr>
<td>4.2.2 Long term (18 months)</td>
<td>1</td>
<td>548</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>1.01 [0.58, 1.75]</td>
</tr>
<tr>
<td>4.3 Adverse events: minor - skin and subcutaneous skin combined data for doses of 1.0 mg/kg, 4 mg/kg, and 10 mg/kg</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>4.3.1 Long term (12 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
</tbody>
</table>
### Analysis 4.1. Comparison 4: Intravenous belimumab (1.0, 4.0, 10.0 mg/kg) versus placebo, Outcome 1: Adverse events: severe at belimumab 1 mg/kg dose

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Belimumab</th>
<th>Placebo</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Weight</td>
</tr>
<tr>
<td>Navarra 2011</td>
<td>16</td>
<td>288</td>
<td>19</td>
</tr>
<tr>
<td>Wallace 2009</td>
<td>21</td>
<td>114</td>
<td>22</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>402</strong></td>
<td><strong>400</strong></td>
<td><strong>67.4%</strong></td>
</tr>
<tr>
<td>Total events:</td>
<td>37</td>
<td>41</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.00; Chi² = 0.08, df = 1 (P = 0.78); I² = 0%
Test for overall effect: Z = 0.50 (P = 0.62)

**4.1.2 Long term (18 months)**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Belimumab</th>
<th>Placebo</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Weight</td>
</tr>
<tr>
<td>Furie 2011</td>
<td>18</td>
<td>271</td>
<td>23</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>271</strong></td>
<td><strong>275</strong></td>
<td><strong>32.6%</strong></td>
</tr>
<tr>
<td>Total events:</td>
<td>18</td>
<td>23</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Not applicable
Test for overall effect: Z = 0.76 (P = 0.45)

<table>
<thead>
<tr>
<th>Total (95% CI)</th>
<th>673</th>
<th>675</th>
<th>100.0%</th>
<th>0.86 [0.62 , 1.21]</th>
</tr>
</thead>
</table>

Total events: 55
Heterogeneity: Tau² = 0.00; Chi² = 0.20, df = 2 (P = 0.91); I² = 0%
Test for overall effect: Z = 0.84 (P = 0.40)
Test for subgroup differences: Chi² = 0.12, df = 1 (P = 0.73), I² = 0%

### Analysis 4.2. Comparison 4: Intravenous belimumab (1.0, 4.0, 10.0 mg/kg) versus placebo, Outcome 2: Adverse events: severe, at belimumab 10 mg/kg dose

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Belimumab</th>
<th>Placebo</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Weight</td>
</tr>
<tr>
<td>Navarra 2011</td>
<td>15</td>
<td>290</td>
<td>19</td>
</tr>
<tr>
<td>Wallace 2009</td>
<td>18</td>
<td>111</td>
<td>22</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>401</strong></td>
<td><strong>400</strong></td>
<td><strong>62.5%</strong></td>
</tr>
<tr>
<td>Total events:</td>
<td>33</td>
<td>41</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.88); I² = 0%
Test for overall effect: Z = 0.96 (P = 0.34)

**4.2.2 Long term (18 months)**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Belimumab</th>
<th>Placebo</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Weight</td>
</tr>
<tr>
<td>Furie 2011</td>
<td>23</td>
<td>273</td>
<td>23</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>273</strong></td>
<td><strong>275</strong></td>
<td><strong>37.5%</strong></td>
</tr>
<tr>
<td>Total events:</td>
<td>23</td>
<td>23</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Not applicable
Test for overall effect: Z = 0.03 (P = 0.98)

<table>
<thead>
<tr>
<th>Total (95% CI)</th>
<th>674</th>
<th>675</th>
<th>100.0%</th>
<th>0.88 [0.63 , 1.23]</th>
</tr>
</thead>
</table>

Total events: 56
Heterogeneity: Tau² = 0.00; Chi² = 0.39, df = 2 (P = 0.82); I² = 0%
Test for overall effect: Z = 0.74 (P = 0.46)
Test for subgroup differences: Chi² = 0.37, df = 1 (P = 0.54), I² = 0%
Analysis 4.3. Comparison 4: Intravenous belimumab (1.0, 4.0, 10.0 mg/kg) versus placebo, Outcome 3: Adverse events: minor - skin and subcutaneous skin combined data for doses of 1.0 mg/kg, 4 mg/kg, and 10 mg/kg

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Belimumab Events</th>
<th>Belimumab Total</th>
<th>Placebo Events</th>
<th>Placebo Total</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
</table>
| 4.3.1 Long term (12 months) Wallace 2009 | 192              | 336             | 57             | 113           | 1.13 [0.92, 1.39]               | Favors belimumab

Comparison 5. Oral prednisone versus placebo

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.1 Secondary outcome (lupus-specific): flare in skin disease</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>5.1.1 Long term (18 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>5.2 Adverse events: minor</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>5.2.1 Long term (18 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>5.3 Adverse events: severe</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>5.3.1 Long term (18 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Prednisone Events</th>
<th>Prednisone Total</th>
<th>Placebo Events</th>
<th>Placebo Total</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
</table>
| 5.1.1 Long term (18 months) Tseng 2006 | 2                 | 21               | 2              | 20            | 0.95 [0.15, 6.13]               | Favors prednisone

Favors prednisone 0.01 0.1 1 10 100
Favors prednisone 0.01 0.1 1 10 100
### Analysis 5.2. Comparison 5: Oral prednisone versus placebo, Outcome 2: Adverse events: minor

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Prednisone Events</th>
<th>Placebo Events</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.2.1 Long term (18 months)</td>
<td>12</td>
<td>11</td>
<td>1.04 [0.60, 1.79]</td>
</tr>
</tbody>
</table>

#### Risk Ratio

0.01 0.1 1 10 100

Favors prednisone

Favors placebo

### Analysis 5.3. Comparison 5: Oral prednisone versus placebo, Outcome 3: Adverse events: severe

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Prednisone Events</th>
<th>Placebo Events</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.3.1 Long term (18 months)</td>
<td>1</td>
<td>0</td>
<td>2.86 [0.12, 66.44]</td>
</tr>
</tbody>
</table>

#### Risk Ratio

0.01 0.1 1 10 100

Favors prednisone

Favors placebo

### Comparison 6. Oral chloroquine versus placebo

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.1 Primary outcome (lupus-specific): absence of skin lesions</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>6.1.1 Long term (12 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>6.2 Primary outcome (lupus-non-specific): absence of alopecia</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>6.2.1 Long term (12 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>6.3 Adverse events: severe</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>6.3.1 Long term (12 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Chloroquine diphosphate</th>
<th>Placebo</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>6.1.1 Long term (12 months)</td>
<td>Meinao 1996</td>
<td>11</td>
<td>12</td>
</tr>
</tbody>
</table>

Analysis 6.2. Comparison 6: Oral chloroquine versus placebo, Outcome 2: Primary outcome (lupus-non-specific): absence of alopecia

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Chloroquine diphosphate</th>
<th>Placebo</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>6.2.1 Long term (12 months)</td>
<td>Meinao 1996</td>
<td>11</td>
<td>12</td>
</tr>
</tbody>
</table>

Analysis 6.3. Comparison 6: Oral chloroquine versus placebo, Outcome 3: Adverse events: severe

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Chloroquine diphosphate</th>
<th>Placebo</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>6.3.1 Long term (12 months)</td>
<td>Meinao 1996</td>
<td>0</td>
<td>12</td>
</tr>
</tbody>
</table>

Comparison 7. Oral fish oil versus placebo

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.1 Adverse event (severe) requiring withdrawal from study - GI side effect</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>7.1.1 Short term (6 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
</tbody>
</table>
Analysis 7.1. Comparison 7: Oral fish oil versus placebo, Outcome 1: Adverse event (severe) requiring withdrawal from study - GI side effect

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Fish oil</th>
<th>Placebo</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>M-H, Random, 95% CI</td>
</tr>
<tr>
<td>7.1.1 Short term (6 months)</td>
<td>3</td>
<td>30</td>
<td>0</td>
</tr>
<tr>
<td>Wright 2008</td>
<td>7.00 [0.38, 129.93]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Comparison 8. Oral nicardipine versus placebo

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.1 Secondary outcome (lupus-non-specific): severity of Raynaud’s attacks - 150 mm visual analogue scale</td>
<td>1</td>
<td></td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>8.1.1 Short term (1 month)</td>
<td>1</td>
<td></td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>8.2 Secondary outcome (lupus-non-specific): number of Raynaud’s attacks per day</td>
<td>1</td>
<td></td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>8.2.1 Short term (1 month)</td>
<td>1</td>
<td></td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>8.3 Adverse events: severe</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>8.3.1 Short term (1 month)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>8.4 Adverse events: minor - cardiovascular or GI side effect</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>8.4.1 Short term (1 month)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
</tbody>
</table>

Analysis 8.1. Comparison 8: Oral nicardipine versus placebo, Outcome 1: Secondary outcome (lupus-non-specific): severity of Raynaud’s attacks - 150 mm visual analogue scale

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Nicardipine</th>
<th>Placebo</th>
<th>Mean Difference IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
</tr>
<tr>
<td>8.1.1 Short term (1 month)</td>
<td>0.84</td>
<td>0.77</td>
<td>15</td>
</tr>
</tbody>
</table>

Interventions for cutaneous disease in systemic lupus erythematosus (Review)

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Analysis 8.2. Comparison 8: Oral nicardipine versus placebo, Outcome 2: Secondary outcome (lupus-non-specific): number of Raynaud's attacks per day

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Nicardipine</th>
<th>Placebo</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
</tr>
<tr>
<td>8.2.1 Short term (1 month)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rupp 1987</td>
<td>0.62</td>
<td>0.89</td>
<td>15</td>
</tr>
</tbody>
</table>

Analysis 8.3. Comparison 8: Oral nicardipine versus placebo, Outcome 3: Adverse events: severe

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Nicardipine</th>
<th>Placebo</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>8.3.1 Short term (1 month)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rupp 1987</td>
<td>0</td>
<td>15</td>
<td>1</td>
</tr>
</tbody>
</table>

Analysis 8.4. Comparison 8: Oral nicardipine versus placebo, Outcome 4: Adverse events: minor - cardiovascular or GI side effect

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Nicardipine</th>
<th>Placebo</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>8.4.1 Short term (1 month)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rupp 1987</td>
<td>7</td>
<td>15</td>
<td>4</td>
</tr>
</tbody>
</table>

Comparison 9. Oral ginsenosides versus placebo

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>9.1 Primary outcome (lupus-specific): complete clearance of facial erythema</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>9.1.1 Short term (3 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>9.2 Primary outcome (lupus-specific): complete clearance of aphthae</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>Study or subgroup</td>
<td>Ginsenosides</td>
<td>Placebo</td>
<td>Risk Ratio M-H, Random, 95% CI</td>
<td>Risk Ratio M-H, Random, 95% CI</td>
</tr>
<tr>
<td>------------------</td>
<td>--------------</td>
<td>---------</td>
<td>-------------------------------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td><strong>Outcome or subgroup title</strong></td>
<td><strong>No. of studies</strong></td>
<td><strong>No. of participants</strong></td>
<td><strong>Statistical method</strong></td>
<td><strong>Effect size</strong></td>
</tr>
<tr>
<td>9.2.1 Short term (3 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>9.3 Primary outcome (lupus-specific): complete clearance of erythema of hands</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>9.3.1 Short term (3 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>9.4 Primary outcome (lupus-non-specific): complete clearance of alopecia</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>9.4.1 Short term (3 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>9.5 Primary outcome (lupus-non-specific): complete clearance of oedema</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>9.5.1 Short term (3 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>9.6 Adverse events: minor - side effect from medication</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>9.6.1 Short term (3 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
</tbody>
</table>

**Analysis 9.1. Comparison 9: Oral ginsenosides versus placebo, Outcome 1: Primary outcome (lupus-specific): complete clearance of facial erythema**
### Analysis 9.2. Comparison 9: Oral ginsenosides versus placebo, Outcome 2: Primary outcome (lupus-specific): complete clearance of aphthae

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Ginsenosides</th>
<th>Placebo</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>M-H, Random, 95% CI</td>
</tr>
<tr>
<td>9.2.1 Short term (3 months)</td>
<td>5</td>
<td>30</td>
<td>11.00 [0.64, 190.53]</td>
</tr>
</tbody>
</table>

### Analysis 9.3. Comparison 9: Oral ginsenosides versus placebo, Outcome 3: Primary outcome (lupus-specific): complete clearance of erythema of hands

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Ginsenosides</th>
<th>Placebo</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>M-H, Random, 95% CI</td>
</tr>
<tr>
<td>9.3.1 Short term (3 months)</td>
<td>4</td>
<td>30</td>
<td>1.33 [0.33, 5.45]</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Ginsenosides</th>
<th>Placebo</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>M-H, Random, 95% CI</td>
</tr>
<tr>
<td>9.4.1 Short term (3 months)</td>
<td>5</td>
<td>30</td>
<td>11.00 [0.64, 190.53]</td>
</tr>
</tbody>
</table>

### Analysis 9.5. Comparison 9: Oral ginsenosides versus placebo, Outcome 5: Primary outcome (lupus-non-specific): complete clearance of oedema

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Ginsenosides</th>
<th>Placebo</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>M-H, Random, 95% CI</td>
</tr>
<tr>
<td>9.5.1 Short term (3 months)</td>
<td>3</td>
<td>30</td>
<td>0.75 [0.18, 3.07]</td>
</tr>
</tbody>
</table>
### Analysis 9.6. Comparison 9: Oral ginsenosides versus placebo, Outcome 6: Adverse events: minor - side effect from medication

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Ginsenosides</th>
<th>Placebo</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events Total</td>
<td>Events Total</td>
<td>M-H, Random, 95% CI</td>
<td></td>
</tr>
<tr>
<td>9.6.1 Short term (3 months)</td>
<td>You 2010</td>
<td>0 30</td>
<td>1 30</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Risk Ratio: M-H, Random, 95% CI

Favors ginsenosides

Favors placebo

### Comparison 10. Intravenous rituximab versus placebo

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>10.1 Adverse events: severe - severe event not including death</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>10.1.1 Long term (12 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>10.2 Adverse events: severe - death</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>10.2.1 Long term (12 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
</tbody>
</table>

### Analysis 10.1. Comparison 10: Intravenous rituximab versus placebo, Outcome 1: Adverse events: severe - severe event not including death

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Rituximab</th>
<th>Placebo</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events Total</td>
<td>Events Total</td>
<td>M-H, Random, 95% CI</td>
<td></td>
</tr>
<tr>
<td>10.1.1 Long term (12 months)</td>
<td>Merrill 2010a</td>
<td>19 169</td>
<td>13 88</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Risk Ratio: M-H, Random, 95% CI

Favors rituximab

Favors placebo
## Analysis 10.2. Comparison 10: Intravenous rituximab versus placebo, Outcome 2: Adverse events: severe - death

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Rituximab Events</th>
<th>Placebo Events</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>10.2.1 Long term (12 months)</td>
<td>4</td>
<td>1</td>
<td>2.08 [0.24, 18.35]</td>
</tr>
</tbody>
</table>

### Comparison 11. Intravenous abatacept versus placebo

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>11.1 Secondary outcome (lupus-specific): BILAG A or B flare in discoid lesions</td>
<td>1</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
<td></td>
</tr>
<tr>
<td>11.1.1 Long term (12 months)</td>
<td>1</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
<td></td>
</tr>
<tr>
<td>11.2 Secondary outcome (lupus-specific): new BILAG A score for discoid lesions</td>
<td>1</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
<td></td>
</tr>
<tr>
<td>11.2.1 Long term (12 months)</td>
<td>1</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
<td></td>
</tr>
<tr>
<td>11.3 Secondary outcome (lupus-specific): new flare in discoid lesions (based on physician-based assessment)</td>
<td>1</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
<td></td>
</tr>
<tr>
<td>11.3.1 Long term (12 months)</td>
<td>1</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
<td></td>
</tr>
<tr>
<td>11.4 Adverse events: severe</td>
<td>1</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
<td></td>
</tr>
<tr>
<td>11.4.1 Long term (12 months)</td>
<td>1</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
<td></td>
</tr>
</tbody>
</table>

## Analysis 11.1. Comparison 11: Intravenous abatacept versus placebo, Outcome 1: Secondary outcome (lupus-specific): BILAG A or B flare in discoid lesions

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Abatacept Events</th>
<th>Placebo Events</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>11.1.1 Long term (12 months)</td>
<td>35</td>
<td>15</td>
<td>1.08 [0.83, 1.41]</td>
</tr>
</tbody>
</table>
### Analysis 11.2. Comparison 11: Intravenous abatacept versus placebo, Outcome 2: Secondary outcome (lupus-specific): new BILAG score for discoid lesions

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Abatacept</th>
<th>Placebo</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>11.2.1 Long term (12 months)</td>
<td>Merrill 2010b</td>
<td>20 41</td>
<td>8 19</td>
</tr>
</tbody>
</table>

Risk Ratio: M-H, Random, 95% CI

### Analysis 11.3. Comparison 11: Intravenous abatacept versus placebo, Outcome 3: Secondary outcome (lupus-specific): new flare in discoid lesions (based on physician-based assessment)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Abatacept</th>
<th>Placebo</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>11.3.1 Long term (12 months)</td>
<td>Merrill 2010b</td>
<td>28 41</td>
<td>15 19</td>
</tr>
</tbody>
</table>

Risk Ratio: M-H, Random, 95% CI

### Analysis 11.4. Comparison 11: Intravenous abatacept versus placebo, Outcome 4: Adverse events: severe

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Abatacept</th>
<th>Placebo</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>11.4.1 Long term (12 months)</td>
<td>Merrill 2010b</td>
<td>10 121</td>
<td>3 59</td>
</tr>
</tbody>
</table>

Risk Ratio: M-H, Random, 95% CI

### Comparison 12. Oral zileuton versus placebo

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>12.1 Lupus-non-specific secondary outcome: SLAM score integument domain (mean change from baseline)</td>
<td>1</td>
<td></td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>12.1.1 Short term (2 months - ‘57 days’)</td>
<td>1</td>
<td></td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>12.2 Adverse events: severe</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
</tbody>
</table>
### Analysis 12.1. Comparison 12: Oral zileuton versus placebo, Outcome 1: Lupus-non-specific secondary outcome: SLAM score integument domain (mean change from baseline)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Zileuton</th>
<th>Placebo</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
<td>Mean</td>
</tr>
<tr>
<td>Hackshaw 1995</td>
<td>-0.2</td>
<td>1.2394</td>
<td>0.33</td>
</tr>
</tbody>
</table>

### Analysis 12.2. Comparison 12: Oral zileuton versus placebo, Outcome 2: Adverse events: severe

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Zileuton</th>
<th>Placebo</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>Hackshaw 1995</td>
<td>2</td>
<td>20</td>
<td>0</td>
</tr>
</tbody>
</table>

### Comparison 13. Intravenous sifalimumab versus placebo

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>13.1 Secondary outcome (lupus-specific): proportion with &quot;SLE flare&quot; for combined doses vs placebo</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>13.1.1 Short term (3 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>13.2 Secondary outcome: proportion with improvement in &quot;CLASI&quot; at 200 mg dose</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>13.3 Secondary outcome: proportion with improvement in &quot;CLASI&quot; at 600 mg dose</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>13.4 Secondary outcome: proportion with improvement in &quot;CLASI&quot; at 1200 mg dose</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>Outcome or subgroup title</td>
<td>No. of studies</td>
<td>No. of participants</td>
<td>Statistical method</td>
<td>Effect size</td>
</tr>
<tr>
<td>---------------------------</td>
<td>---------------</td>
<td>---------------------</td>
<td>--------------------</td>
<td>-------------</td>
</tr>
<tr>
<td>13.5 Secondary outcome: proportion with improvement in &quot;CLASI&quot; at combined doses</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>13.6 Adverse events: severe (death)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>13.6.1 3 mg/kg long term (12.5 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>13.6.2 10 mg/kg long term (12.5 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>13.7 Adverse events: all severe adverse events including death</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>13.7.1 0.3 mg/kg long term (12.5 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>13.7.2 1 mg/kg long term (12.5 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>13.7.3 3 mg/kg long term (12.5 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>13.7.4 10 mg/kg long term (12.5 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>13.8 Adverse events: all severe adverse events</td>
<td>2</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>13.8.1 Long term (12.5 months) 0.3 mg/kg dose</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>13.8.2 Long term (12.5 months) 1 mg/kg dose</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>13.8.3 Long term (12 months) 200 mg dose</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>13.8.4 Long term (12 months) 600 mg dose</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>13.8.5 Long term (12 months) 1200 mg dose</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>13.8.6 Long term (12 months) combined doses (200 mg, 600 mg, and 1200 mg)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>13.9 Adverse events: minor - pruritus, papular rash, or pruritic rash for combined doses</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>13.9.1 Short term (3 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
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</tbody>
</table>
### Outcome or subgroup title

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>13.10 Adverse events: minor - viral infection rash such as herpes zoster or herpes simplex for combined doses</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>13.10.1 Short term (3 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>13.11 Adverse events: minor for all doses combined</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>13.11.1 Short term (12.5 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>13.12 Adverse events: minor</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>13.12.1 3 mg/kg long term (12 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>13.12.2 10 mg/kg long term (12.5 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Sifalimumab</th>
<th>Placebo</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Merrill 2011</td>
<td>9</td>
<td>8</td>
<td>0.58 [0.27, 1.23]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Sifalimumab</th>
<th>Placebo</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Khamashta 2016</td>
<td>24</td>
<td>17</td>
<td>1.50 [1.00, 2.23]</td>
</tr>
</tbody>
</table>

### Analysis 13.2. Comparison 13: Intravenous sifalimumab versus placebo, Outcome 2: Secondary outcome: proportion with improvement in "CLASI" at 200 mg dose
### Analysis 13.3. Comparison 13: Intravenous sifalimumab versus placebo, Outcome 3: Secondary outcome: proportion with improvement in "CLASI" at 600 mg dose

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Sifalimumab</th>
<th>Placebo</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Khamashata 2016</td>
<td>19</td>
<td>17</td>
<td>1.19 [0.76, 1.86]</td>
</tr>
</tbody>
</table>

### Analysis 13.4. Comparison 13: Intravenous sifalimumab versus placebo, Outcome 4: Secondary outcome: proportion with improvement in "CLASI" at 1200 mg dose

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Sifalimumab</th>
<th>Placebo</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Khamashata 2016</td>
<td>19</td>
<td>17</td>
<td>1.50 [1.00, 2.27]</td>
</tr>
</tbody>
</table>

### Analysis 13.5. Comparison 13: Intravenous sifalimumab versus placebo, Outcome 5: Secondary outcome: proportion with improvement in "CLASI" at combined doses

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Sifalimumab</th>
<th>Placebo</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Khamashata 2016</td>
<td>62</td>
<td>17</td>
<td>1.39 [0.96, 2.01]</td>
</tr>
</tbody>
</table>

### Analysis 13.6. Comparison 13: Intravenous sifalimumab versus placebo, Outcome 6: Adverse events: severe (death)

#### 13.6.1 3 mg/kg long term (12.5 months)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Sifalimumab</th>
<th>Placebo</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Petri 2013</td>
<td>0</td>
<td>0</td>
<td>Not estimable</td>
</tr>
</tbody>
</table>

#### 13.6.2 10 mg/kg long term (12.5 months)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Sifalimumab</th>
<th>Placebo</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Petri 2013</td>
<td>2</td>
<td>0</td>
<td>4.66 [0.23, 94.18]</td>
</tr>
</tbody>
</table>
Analysis 13.7. Comparison 13: Intravenous sifalimumab versus placebo, Outcome 7: Adverse events: all severe adverse events including death

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Sifalimumab</th>
<th>Placebo</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>13.7.1 0.3 mg/kg long term (12.5 months) Petri 2013</td>
<td>7</td>
<td>26</td>
<td>12</td>
</tr>
<tr>
<td>13.7.2 1 mg/kg long term (12.5 months) Petri 2013</td>
<td>3</td>
<td>25</td>
<td>12</td>
</tr>
<tr>
<td>13.7.3 3 mg/kg long term (12.5 months) Petri 2013</td>
<td>7</td>
<td>27</td>
<td>12</td>
</tr>
<tr>
<td>13.7.4 10 mg/kg long term (12.5 months) Petri 2013</td>
<td>10</td>
<td>43</td>
<td>12</td>
</tr>
</tbody>
</table>

Analysis 13.8. Comparison 13: Intravenous sifalimumab versus placebo, Outcome 8: Adverse events: all severe adverse events

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Sifalimumab</th>
<th>Placebo</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>13.8.1 Long term (12.5 months) 0.3 mg/kg dose Petri 2013</td>
<td>0</td>
<td>26</td>
<td>0</td>
</tr>
<tr>
<td>13.8.2 Long term (12.5 months) 1 mg/kg dose Petri 2013</td>
<td>1</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td>13.8.3 Long term (12 months) 200 mg dose Khamashhta 2016</td>
<td>16</td>
<td>108</td>
<td>19</td>
</tr>
<tr>
<td>13.8.4 Long term (12 months) 600 mg dose Khamashhta 2016</td>
<td>22</td>
<td>108</td>
<td>19</td>
</tr>
<tr>
<td>13.8.5 Long term (12 months) 1200 mg Khamashhta 2016</td>
<td>21</td>
<td>107</td>
<td>19</td>
</tr>
<tr>
<td>13.8.6 Long term (12 months) combined doses (200 mg, 600 mg, and 1200 mg) Khamashhta 2016</td>
<td>59</td>
<td>323</td>
<td>19</td>
</tr>
</tbody>
</table>
Analysis 13.9. Comparison 13: Intravenous sifalimumab versus placebo, Outcome 9: Adverse events: minor - pruritus, papular rash, or pruritic rash for combined doses

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Sifalimumab</th>
<th>Placebo</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>13.9.1 Short term (3 months) Merrill 2011</td>
<td>Events: 4, Total: 33</td>
<td>Events: 3, Total: 17</td>
<td>0.69 [0.17, 2.72]</td>
</tr>
</tbody>
</table>

Analysis 13.10. Comparison 13: Intravenous sifalimumab versus placebo, Outcome 10: Adverse events: minor - viral infection rash such as herpes zoster or herpes simplex for combined doses

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Sifalimumab</th>
<th>Placebo</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>13.10.1 Short term (3 months) Merrill 2011</td>
<td>Events: 2, Total: 33</td>
<td>Events: 1, Total: 17</td>
<td>1.03 [0.10, 10.57]</td>
</tr>
</tbody>
</table>

Analysis 13.11. Comparison 13: Intravenous sifalimumab versus placebo, Outcome 11: Adverse events: minor for all doses combined

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Sifalimumab</th>
<th>Placebo</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>13.11.1 Short term (12.5 months) Petri 2013</td>
<td>Events: 85, Total: 121</td>
<td>Events: 26, Total: 40</td>
<td>1.08 [0.84, 1.40]</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Sifalimumab</th>
<th>Placebo</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>13.12.1 3 mg/kg long term (12 months) Petri 2013</td>
<td>Events: 2, Total: 27</td>
<td>Events: 0, Total: 40</td>
<td>7.32 [0.37, 146.78]</td>
</tr>
<tr>
<td>13.12.2 10 mg/kg long term (12.5 months) Petri 2013</td>
<td>Events: 2, Total: 43</td>
<td>Events: 0, Total: 40</td>
<td>4.66 [0.23, 94.18]</td>
</tr>
</tbody>
</table>
Comparison 14. Intravenous sirukumab versus placebo

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>14.1 Adverse events: severe for combined doses vs placebo</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>14.1.1 Short term (4.5 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>14.2 Adverse event: minor for combined doses vs placebo</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>14.2.1 Short term (4.5 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
</tbody>
</table>

Analysis 14.1. Comparison 14: Intravenous sirukumab versus placebo, Outcome 1: Adverse events: severe for combined doses vs placebo

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Sirukumab Events</th>
<th>Sirukumab Total</th>
<th>Placebo Events</th>
<th>Placebo Total</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>14.1.1 Short term (4.5 months) Szepietowski 2013</td>
<td>2</td>
<td>10</td>
<td>0</td>
<td>5</td>
<td>2.73 [0.15, 48.04]</td>
</tr>
</tbody>
</table>

Favors sirukumab Favours placebo

Analysis 14.2. Comparison 14: Intravenous sirukumab versus placebo, Outcome 2: Adverse event: minor for combined doses vs placebo

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Sirukumab Events</th>
<th>Sirukumab Total</th>
<th>Placebo Events</th>
<th>Placebo Total</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>14.2.1 Short term (4.5 months) Szepietowski 2013</td>
<td>4</td>
<td>5</td>
<td>9</td>
<td>10</td>
<td>0.89 [0.55, 1.44]</td>
</tr>
</tbody>
</table>

Favors sirukumab Favours placebo

Comparison 15. Intravenous blisibimod versus placebo

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>15.1 Adverse events: severe - all severe events including death</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
</tbody>
</table>
### Analysis 15.1. Comparison 15: Intravenous blisibimod versus placebo, Outcome 1: Adverse events: severe - all severe events including death

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>blisibimod</th>
<th>placebo</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>15.1.1 Severe long term (12 months)</td>
<td>16 280</td>
<td>21 266</td>
<td>0.72 [0.39, 1.36]</td>
</tr>
</tbody>
</table>

Favors blisibimod

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>blisibimod</th>
<th>placebo</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>15.1.1 Severe long term (12 months)</td>
<td>16 280</td>
<td>21 266</td>
<td>0.72 [0.39, 1.36]</td>
</tr>
</tbody>
</table>

Favors placebo

### Comparison 16. Intravenous epratuzumab versus placebo

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>16.1 Adverse events</td>
<td>2</td>
<td></td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>16.1.1 Severe short term (3 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>16.1.2 Severe long term (12 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>16.1.3 Minor short term (3 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>16.1.4 Minor long term (12 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>Totals not selected</td>
</tr>
</tbody>
</table>
Analysis 16.1. Comparison 16: intravenous epratuzumab versus placebo, Outcome 1: Adverse events

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>epratuzumab</th>
<th>placebo</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>16.1.1 Severe short term (3 months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wallace 2013</td>
<td>3</td>
<td>2</td>
<td>0.30 [0.05, 1.76]</td>
</tr>
<tr>
<td>16.1.2 Severe long term (12 months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wallace 2014</td>
<td>3</td>
<td>3</td>
<td>0.73 [0.16, 3.40]</td>
</tr>
<tr>
<td>16.1.3 Minor short term (3 months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wallace 2013</td>
<td>127</td>
<td>25</td>
<td>1.03 [0.80, 1.32]</td>
</tr>
<tr>
<td>16.1.4 Minor long term (12 months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wallace 2014</td>
<td>44</td>
<td>34</td>
<td>0.94 [0.81, 1.09]</td>
</tr>
</tbody>
</table>

Comparison 17. Intravenous atacicept versus placebo

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>17.1 Adverse events: minor - eczema, at-</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>acicept 3 mg/kg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17.1.1 Short term (6 weeks)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>17.2 Adverse events: minor - local site</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>reaction (redness, bruising, tenderness)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>for all doses combined</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17.2.1 Short term (6 weeks)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>17.3 Adverse events: minor - other minor</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>reaction (not eczema or local site reaction)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17.3.1 Short term (2 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
</tbody>
</table>
### Analysis 17.1. Comparison 17: Intravenous atacicept versus placebo, Outcome 1: Adverse events: minor - eczema, atacicept 3 mg/kg

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Atacicept</th>
<th>Placebo</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>M-H, Random, 95% CI</td>
</tr>
<tr>
<td>17.1.1 Short term (6 weeks)</td>
<td>1</td>
<td>5</td>
<td>$2.50 \ [0.13 , 48.85]$</td>
</tr>
</tbody>
</table>

### Analysis 17.2. Comparison 17: Intravenous atacicept versus placebo, Outcome 2: Adverse events: minor - local site reaction (redness, bruising, tenderness) for all doses combined

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Atacicept</th>
<th>Placebo</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>M-H, Random, 95% CI</td>
</tr>
<tr>
<td>17.2.1 Short term (6 weeks)</td>
<td>7</td>
<td>20</td>
<td>$0.70 \ [0.22 , 2.21]$</td>
</tr>
</tbody>
</table>

### Analysis 17.3. Comparison 17: Intravenous atacicept versus placebo, Outcome 3: Adverse events: minor - other minor reaction (not eczema or local site reaction)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Atacicept</th>
<th>Placebo</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>M-H, Random, 95% CI</td>
</tr>
<tr>
<td>17.3.1 Short term (2 months)</td>
<td>0</td>
<td>5</td>
<td>$0.28 \ [0.01 , 5.43]$</td>
</tr>
</tbody>
</table>

### Comparison 18. Subcutaneous tabalumab versus placebo

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>18.1 Adverse events</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>18.1.1 Severe long term (12 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>18.1.2 Minor long term (12 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
</tbody>
</table>
Analysis 18.1. Comparison 18: Subcutaneous tabalumab versus placebo, Outcome 1: Adverse events

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>tabalumab</th>
<th>placebo</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>tabalumab</td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>18.1.1 Severe long term (12 months)</td>
<td>Merrill 2016</td>
<td>38</td>
<td>745</td>
<td>27</td>
</tr>
<tr>
<td>18.1.2 Minor long term (12 months)</td>
<td>Merrill 2016</td>
<td>575</td>
<td>745</td>
<td>276</td>
</tr>
</tbody>
</table>

Comparison 19. Oral baricitinib versus placebo

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>19.1 Adverse events</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>19.1.1 Severe short term (6 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>19.1.2 Minor short term (6 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
</tbody>
</table>

Analysis 19.1. Comparison 19: Oral baricitinib versus placebo, Outcome 1: Adverse events

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Baricitinib</th>
<th>Placebo</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>19.1.1 Severe short term (6 months)</td>
<td>Wallace 2018</td>
<td>5</td>
<td>105</td>
<td>21</td>
</tr>
<tr>
<td>19.1.2 Minor short term (6 months)</td>
<td>Wallace 2018</td>
<td>63</td>
<td>105</td>
<td>130</td>
</tr>
</tbody>
</table>

Comparison 20. Intravenous and subcutaneous ustekinumab versus placebo

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>20.1 Secondary outcome: CLASI activity score: greater than 50% improvement from baseline</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
</tbody>
</table>
### Outcome or subgroup title

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>20.2 Adverse events</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>20.2.1 Severe short term (6 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>20.2.2 Minor short term (6 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
</tbody>
</table>

### Analysis 20.1. Comparison 20: Intravenous and subcutaneous ustekinumab versus placebo,
Outcome 1: Secondary outcome: CLASI activity score: greater than 50% improvement from baseline

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Ustekinumab</th>
<th>Placebo</th>
<th>Risk Ratio (M-H, Random, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van Vollenhoven 2018</td>
<td>17</td>
<td>6</td>
<td>1.51 [0.73, 3.10]</td>
</tr>
</tbody>
</table>

### Analysis 20.2. Comparison 20: Intravenous and subcutaneous ustekinumab versus placebo, Outcome 2: Adverse events

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Ustekinumab</th>
<th>Placebo</th>
<th>Risk Ratio (M-H, Random, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20.2.1 Severe short term (6 months)</td>
<td>4</td>
<td>4</td>
<td>0.70 [0.19, 2.64]</td>
</tr>
<tr>
<td>Van Vollenhoven 2018</td>
<td>60</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>20.2.2 Minor short term (6 months)</td>
<td>43</td>
<td>24</td>
<td>1.25 [0.92, 1.70]</td>
</tr>
</tbody>
</table>

### Comparison 21. Topical R932333 versus placebo vehicle

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>21.1 Adverse events</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>21.1.1 Minor short term (3 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
</tbody>
</table>
### Analysis 21.1. Comparison 21: Topical R932333 versus placebo vehicle, Outcome 1: Adverse events

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>R932333</th>
<th>placebo</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>21.1.1 Minor short term (3 months)</td>
<td>16/36</td>
<td>10/18</td>
<td>0.80 [0.46, 1.39]</td>
</tr>
</tbody>
</table>

### Comparison 22. Subcutaneous lulizumab versus placebo

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>22.1 Adverse events</td>
<td>1</td>
<td></td>
<td>Risk Ratio M-H, Random, 95% CI</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>22.1.1 Severe short term (6 months)</td>
<td>1</td>
<td>14/275</td>
<td>3.61 [0.48, 27.03]</td>
<td></td>
</tr>
</tbody>
</table>

### Analysis 22.1. Comparison 22: Subcutaneous lulizumab versus placebo, Outcome 1: Adverse events

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>lulizumab</th>
<th>placebo</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>22.1.1 Severe short term (6 months)</td>
<td>14/275</td>
<td>1/71</td>
<td>3.61 [0.48, 27.03]</td>
</tr>
</tbody>
</table>

### Comparison 23. Intravenous belimumab versus intravenous belimumab dose comparison

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>23.1 Adverse events: severe, 1 mg/kg vs 10 mg/kg</td>
<td>3</td>
<td>1347</td>
<td>Risk Ratio M-H, Random, 95% CI</td>
<td>0.98 [0.69, 1.40]</td>
</tr>
<tr>
<td>23.1.1 Severe long term (12 months)</td>
<td>2</td>
<td>803</td>
<td>Risk Ratio M-H, Random, 95% CI</td>
<td>1.11 [0.72, 1.72]</td>
</tr>
<tr>
<td>23.1.2 Severe long term (18 months)</td>
<td>1</td>
<td>544</td>
<td>Risk Ratio M-H, Random, 95% CI</td>
<td>0.79 [0.44, 1.43]</td>
</tr>
<tr>
<td>23.2 Adverse events: skin and subcutaneous tissue, 1 mg/kg vs 4 mg/kg</td>
<td>1</td>
<td></td>
<td>Risk Ratio M-H, Random, 95% CI</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>23.2.1 Minor long term (12 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio M-H, Random, 95% CI</td>
<td>Totals not selected</td>
</tr>
</tbody>
</table>
### Analysis 23.1. Comparison 23: Intravenous belimumab versus intravenous belimumab dose comparison, Outcome 1: Adverse events: severe, 1 mg/kg vs 10 mg/kg

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>belimumab 1mg/kg</th>
<th>belimumab 10mg/kg</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>23.1.1 Severe long term (12 months)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Navarra 2011</td>
<td>16</td>
<td>289</td>
<td>15</td>
<td>290</td>
<td>26.6%</td>
</tr>
<tr>
<td>Wallace 2009</td>
<td>21</td>
<td>114</td>
<td>18</td>
<td>111</td>
<td>38.0%</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>402</td>
<td>401</td>
<td>111</td>
<td>38.0%</td>
<td></td>
</tr>
<tr>
<td>Total events:</td>
<td>37</td>
<td>33</td>
<td>402</td>
<td>64.6%</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tau^2</td>
<td>0.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chi²</td>
<td>0.02</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>df</td>
<td>1 (P = 0.90); P = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect:</td>
<td>Z = 0.47 (P = 0.64)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>23.1.2 Severe long term (18 months)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Furie 2011</td>
<td>18</td>
<td>271</td>
<td>23</td>
<td>273</td>
<td>35.4%</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>271</td>
<td>273</td>
<td>273</td>
<td>35.4%</td>
<td></td>
</tr>
<tr>
<td>Total events:</td>
<td>18</td>
<td>23</td>
<td>273</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect:</td>
<td>Z = 0.79 (P = 0.43)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>673</td>
<td>674</td>
<td>674</td>
<td>100.0%</td>
<td></td>
</tr>
<tr>
<td>Total events:</td>
<td>55</td>
<td>56</td>
<td>674</td>
<td>90.0%</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tau^2</td>
<td>0.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chi²</td>
<td>0.84</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>df</td>
<td>2 (P = 0.66); P = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect:</td>
<td>Z = 0.09 (P = 0.93)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for subgroup differences:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chi²</td>
<td>0.82</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>df</td>
<td>1 (P = 0.36); P = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Favors 1mg/kg dose</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Analysis 23.2. Comparison 23: Intravenous belimumab versus intravenous belimumab dose comparison, Outcome 2: Adverse events: skin and subcutaneous tissue, 1 mg/kg vs 4 mg/kg

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>belimumab 1mg/kg</th>
<th>belimumab 4mg/kg</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>23.2.1 Minor long term (12 months)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wallace 2009</td>
<td>72</td>
<td>114</td>
<td>111</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.08 [0.87 , 1.33]</td>
</tr>
</tbody>
</table>

### Interventions for cutaneous disease in systemic lupus erythematosus (Review)

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### Analysis 23.3. Comparison 23: Intravenous belimumab versus intravenous belimumab dose comparison, Outcome 3: Adverse events: skin and subcutaneous tissue, 1 mg/kg vs 10 mg/kg

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>belimumab 1 mg/kg</th>
<th>belimumab 10 mg/kg</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>23.3.1 Minor long term (12 months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wallace 2009</td>
<td>72 Events</td>
<td>114 Total</td>
<td>55 Events</td>
</tr>
</tbody>
</table>

**Risk Ratio**
- **M-H, Random, 95% CI**
  - **0.05**
  - **0.2**
  - **1**
  - **5**
  - **20**

Favors 1 mg/kg
Favors 10 mg/kg

### Analysis 23.4. Comparison 23: Intravenous belimumab versus intravenous belimumab dose comparison, Outcome 4: Adverse events: skin and subcutaneous tissue, 4 mg/kg vs 10 mg/kg

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>belimumab 4 mg/kg</th>
<th>belimumab 10 mg/kg</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>23.4.1 Minor long term (12 months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wallace 2009</td>
<td>65 Events</td>
<td>111 Total</td>
<td>55 Events</td>
</tr>
</tbody>
</table>

**Risk Ratio**
- **M-H, Random, 95% CI**
  - **0.2**
  - **0.5**
  - **1**
  - **2**
  - **5**

Favors 4 mg/kg
Favors 10 mg/kg

### Comparison 24. Intravenous atacicept versus intravenous atacicept dose comparison

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>24.1 Adverse events: minor - eczema</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>24.1.1 Short term (2 months), 3 mg/kg vs 9 mg/kg</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>24.1.2 Short term (2 months), 3 mg/kg vs 18 mg/kg</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>24.2 Adverse events: other minor adverse event (not eczema or local site reaction)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>24.2.1 Short term (2 months), 9 mg/kg vs 18 mg/kg</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>24.2.2 Short term (2 months), 3 mg/kg vs 18 mg/kg</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>24.2.3 Short term (2 months), 3 mg/kg vs 9 mg/kg</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>24.2.4 Minor short term (2 months), single 9 mg/kg dose vs two 9 mg/kg doses</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
</tbody>
</table>
Analysis 24.1. Comparison 24: Intravenous atacicept versus intravenous atacicept dose comparison, Outcome 1: Adverse events: minor - eczema

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>atacicept 3mg/kg</th>
<th>atacicept 9mg/kg</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>24.1.1 Short term (2 months), 3 mg/kg vs 9 mg/kg</td>
<td>1</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Pena-Rossi 2009</td>
<td>24.1.2 Short term (2 months), 3 mg/kg vs 18 mg/kg</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Pena-Rossi 2009</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Analysis 24.2. Comparison 24: Intravenous atacicept versus intravenous atacicept dose comparison, Outcome 2: Adverse events: other minor adverse event (not eczema or local site reaction)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>atacicept 9mg/kg</th>
<th>atacicept 18mg/kg</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>24.2.1 Short term (2 months), 9 mg/kg vs 18 mg/kg</td>
<td>1</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Pena-Rossi 2009</td>
<td>24.2.2 Short term (2 months), 3 mg/kg vs 18 mg/kg</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Pena-Rossi 2009</td>
<td>24.2.3 Short term (2 months), 3 mg/kg vs 9 mg/kg</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Pena-Rossi 2009</td>
<td>24.2.4 Minor short term (2 months), single 9 mg/kg dose vs two 9 mg/kg doses</td>
<td>1</td>
<td>5</td>
</tr>
</tbody>
</table>

Comparison 25. Intravenous sifalimumab versus intravenous sifalimumab dose comparison

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>25.1 Secondary outcome: proportion with improvement in &quot;CLASI&quot; at 200 mg dose vs 600 mg dose</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>25.2 Secondary outcome: proportion with improvement in &quot;CLASI&quot; at 600 mg dose vs 1200 mg dose</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>25.3 Secondary outcome: proportion with improvement in &quot;CLASI&quot; at 200 mg dose vs 1200 mg dose</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>25.4 Adverse events: severe - all, including death at 200 mg dose vs 600 mg dose</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>Outcome or subgroup title</td>
<td>No. of studies</td>
<td>No. of participants</td>
<td>Statistical method</td>
<td>Effect size</td>
</tr>
<tr>
<td>--------------------------------------------------------------------------------------------</td>
<td>----------------</td>
<td>---------------------</td>
<td>----------------------------</td>
<td>---------------------------</td>
</tr>
<tr>
<td>25.5 Adverse events: severe - all, including death at 600 mg dose vs 1200 mg dose</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>25.6 Adverse events: severe - all, including death at 200 mg dose vs 1200 mg dose</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>25.7 Adverse events: severe - all, including death at 0.3 mg/kg dose vs 1 mg/kg dose</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>25.7.1 Long term (12.5 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>25.8 Adverse events: severe - all, including death at 0.3 mg/kg dose vs 3 mg/kg dose</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>25.8.1 Long term (12.5 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>25.9 Adverse events: severe - all, including death at 0.3 mg/kg dose vs 10 mg/kg dose</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>25.9.1 Long term (12.5 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>25.10 Adverse events: severe - all, including death at 1 mg/kg dose vs 3 mg/kg dose</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>25.10.1 Long term (12.5 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>25.11 Adverse events: severe - all, including death at 1 mg/kg dose vs 10 mg/kg dose</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>25.11.1 Long term (12.5 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>25.12 Adverse events: severe - all, including death at 3 mg/kg dose vs 10 mg/kg dose</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>25.12.1 Long term (12.5 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>25.13 Adverse events: severe - death at 0.3 mg/kg dose vs 1 mg/kg dose</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>25.13.1 Long term (12.5 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>25.14 Adverse events: severe - death at 0.3 mg/kg dose vs 10 mg/kg dose</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>25.14.1 Long term (12.5 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>Outcome or subgroup title</td>
<td>No. of studies</td>
<td>No. of participants</td>
<td>Statistical method</td>
<td>Effect size</td>
</tr>
<tr>
<td>------------------------------------------------------------------------------------------</td>
<td>----------------</td>
<td>---------------------</td>
<td>---------------------------------------------</td>
<td>------------------------------</td>
</tr>
<tr>
<td>25.15 Adverse events: severe - death at 1 mg/kg dose vs 3 mg/kg dose</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>25.15.1 Long term (12.5 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>25.16 Adverse events: severe - death at 1 mg/kg dose vs 10 mg/kg dose</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>25.16.1 Long term (12.5 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>25.17 Adverse events: severe - death at 3 mg/kg dose vs 10 mg/kg dose</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>25.17.1 Long term (12.5 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>25.18 Adverse events: minor - zoster at 0.3 mg/kg dose vs 3 mg/kg dose</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>25.18.1 Long term (12.5 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>25.19 Adverse events: minor - zoster at 0.3 mg/kg dose vs 10 mg/kg dose</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>25.19.1 Long term (12.5 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>25.20 Adverse events: minor - zoster at 1 mg/kg dose vs 3 mg/kg dose</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>25.20.1 Long term (12.5 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>25.21 Adverse events: minor - zoster at 1 mg/kg dose vs 10 mg/kg dose</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>25.21.1 Long term (12.5 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>25.22 Adverse events: minor - zoster at 3 mg/kg dose vs 10 mg/kg dose</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>25.22.1 Long term (12.5 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
</tbody>
</table>
### Analysis 25.1. Comparison 25: Intravenous sifalimumab versus intravenous sifalimumab dose comparison, Outcome 1: Secondary outcome: proportion with improvement in "CLASI" at 200 mg dose vs 600 mg dose

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Sifalimumab 200 mg dose</th>
<th>Sifalimumab 600 mg dose</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td></td>
</tr>
<tr>
<td>Khamashta 2016</td>
<td>24</td>
<td>33</td>
<td>1.26 [0.88 , 1.81]</td>
</tr>
</tbody>
</table>

### Analysis 25.2. Comparison 25: Intravenous sifalimumab versus intravenous sifalimumab dose comparison, Outcome 2: Secondary outcome: proportion with improvement in "CLASI" at 600 mg dose vs 1200 mg dose

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Sifalimumab 600 mg dose</th>
<th>Sifalimumab 1200 mg dose</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td></td>
</tr>
<tr>
<td>Khamashta 2016</td>
<td>19</td>
<td>33</td>
<td>0.79 [0.54 , 1.15]</td>
</tr>
</tbody>
</table>

### Analysis 25.3. Comparison 25: Intravenous sifalimumab versus intravenous sifalimumab dose comparison, Outcome 3: Secondary outcome: proportion with improvement in "CLASI" at 200 mg dose vs 1200 mg dose

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Sifalimumab 200 mg dose</th>
<th>Sifalimumab 1200 mg dose</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td></td>
</tr>
<tr>
<td>Khamashta 2016</td>
<td>24</td>
<td>33</td>
<td>1.00 [0.73 , 1.36]</td>
</tr>
</tbody>
</table>

### Analysis 25.4. Comparison 25: Intravenous sifalimumab versus intravenous sifalimumab dose comparison, Outcome 4: Adverse events: severe - all, including death at 200 mg dose vs 600 mg dose

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Sifalimumab 200 mg dose</th>
<th>Sifalimumab 600 mg dose</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td></td>
</tr>
<tr>
<td>Khamashta 2016</td>
<td>16</td>
<td>108</td>
<td>0.73 [0.40 , 1.31]</td>
</tr>
</tbody>
</table>

### Analysis 25.5. Comparison 25: Intravenous sifalimumab versus intravenous sifalimumab dose comparison, Outcome 5: Adverse events: severe - all, including death at 600 mg dose vs 1200 mg dose

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Sifalimumab 600 mg dose</th>
<th>Sifalimumab 1200 mg dose</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td></td>
</tr>
<tr>
<td>Khamashta 2016</td>
<td>22</td>
<td>108</td>
<td>1.04 [0.61 , 1.77]</td>
</tr>
</tbody>
</table>
**Analysis 25.6.** Comparison 25: Intravenous sifalimumab versus intravenous sifalimumab dose comparison, Outcome 6: Adverse events: severe - all, including death at 200 mg dose vs 1200 mg dose

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>sifalimumab 200 mg Events</th>
<th>sifalimumab 200 mg Total</th>
<th>sifalimumab 1200 mg Events</th>
<th>sifalimumab 1200 mg Total</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Khamashtha 2016</td>
<td>16</td>
<td>100</td>
<td>21</td>
<td>107</td>
<td>0.75 [0.42, 1.37]</td>
</tr>
</tbody>
</table>

**Analysis 25.7.** Comparison 25: Intravenous sifalimumab versus intravenous sifalimumab dose comparison, Outcome 7: Adverse events: severe - all, including death at 0.3 mg/kg dose vs 1 mg/kg dose

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>0.3 mg/kg Events</th>
<th>0.3 mg/kg Total</th>
<th>1 mg/kg Events</th>
<th>1 mg/kg Total</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>25.7.1 Long term (12.5 months) Petri 2013</td>
<td>7</td>
<td>26</td>
<td>3</td>
<td>25</td>
<td>2.24 [0.65, 7.72]</td>
</tr>
</tbody>
</table>

**Analysis 25.8.** Comparison 25: Intravenous sifalimumab versus intravenous sifalimumab dose comparison, Outcome 8: Adverse events: severe - all, including death at 0.3 mg/kg dose vs 3 mg/kg dose

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>sifalimumab 0.3 mg/kg Events</th>
<th>sifalimumab 0.3 mg/kg Total</th>
<th>sifalimumab 3 mg/kg Events</th>
<th>sifalimumab 3 mg/kg Total</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>25.8.1 Long term (12.5 months) Petri 2013</td>
<td>7</td>
<td>26</td>
<td>7</td>
<td>27</td>
<td>1.04 [0.42, 2.55]</td>
</tr>
</tbody>
</table>

**Analysis 25.9.** Comparison 25: Intravenous sifalimumab versus intravenous sifalimumab dose comparison, Outcome 9: Adverse events: severe - all, including death at 0.3 mg/kg dose vs 10 mg/kg dose

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>sifalimumab 0.3 mg/kg Events</th>
<th>sifalimumab 0.3 mg/kg Total</th>
<th>sifalimumab 10 mg/kg Events</th>
<th>sifalimumab 10 mg/kg Total</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>25.9.1 Long term (12.5 months) Petri 2013</td>
<td>7</td>
<td>26</td>
<td>10</td>
<td>43</td>
<td>1.16 [0.50, 2.67]</td>
</tr>
</tbody>
</table>
## Analysis 25.10. Comparison 25: Intravenous sifalimumab versus intravenous sifalimumab dose comparison, Outcome 10: Adverse events: severe - all, including death at 1 mg/kg dose vs 3 mg/kg dose

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>sifalimumab 1 mg/kg</th>
<th>sifalimumab 3 mg/kg</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>25.10.1 Long term (12.5 months)</td>
<td>3</td>
<td>25</td>
<td>0.46 [0.13, 1.60]</td>
</tr>
</tbody>
</table>

## Analysis 25.11. Comparison 25: Intravenous sifalimumab versus intravenous sifalimumab dose comparison, Outcome 11: Adverse events: severe - all, including death at 1 mg/kg dose vs 10 mg/kg dose

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>sifalimumab 1 mg/kg</th>
<th>sifalimumab 10 mg/kg</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>25.11.1 Long term (12.5 months)</td>
<td>3</td>
<td>25</td>
<td>0.52 [0.16, 1.70]</td>
</tr>
</tbody>
</table>

## Analysis 25.12. Comparison 25: Intravenous sifalimumab versus intravenous sifalimumab dose comparison, Outcome 12: Adverse events: severe - all, including death at 3 mg/kg dose vs 10 mg/kg dose

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>sifalimumab 3 mg/kg</th>
<th>sifalimumab 10 mg/kg</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>25.12.1 Long term (12.5 months)</td>
<td>7</td>
<td>27</td>
<td>1.11 [0.48, 2.58]</td>
</tr>
</tbody>
</table>

## Analysis 25.13. Comparison 25: Intravenous sifalimumab versus intravenous sifalimumab dose comparison, Outcome 13: Adverse events: severe - death at 0.3 mg/kg dose vs 1 mg/kg dose

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>sifalimumab 0.3 mg/kg</th>
<th>sifalimumab 1 mg/kg</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>25.13.1 Long term (12.5 months)</td>
<td>0</td>
<td>26</td>
<td>0.32 [0.01, 7.53]</td>
</tr>
</tbody>
</table>
**Analysis 25.14.** Comparison 25: Intravenous sifalimumab versus intravenous sifalimumab dose comparison, Outcome 14: Adverse events: severe - death at 0.3 mg/kg dose vs 10 mg/kg dose

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>sifalimumab 0.3 mg/kg</th>
<th>sifalimumab 10 mg/kg</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>25.14.1 Long term (12.5 months)</td>
<td>Petri 2013</td>
<td>Events: 0</td>
<td>Total: 26</td>
</tr>
</tbody>
</table>

![Graph showing the comparison of intravenous sifalimumab dose with risk ratios.]

**Analysis 25.15.** Comparison 25: Intravenous sifalimumab versus intravenous sifalimumab dose comparison, Outcome 15: Adverse events: severe - death at 1 mg/kg dose vs 3 mg/kg dose

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>sifalimumab 1 mg/kg</th>
<th>sifalimumab 3 mg/kg</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>25.15.1 Long term (12.5 months)</td>
<td>Petri 2013</td>
<td>Events: 1</td>
<td>Total: 25</td>
</tr>
</tbody>
</table>

![Graph showing the comparison of intravenous sifalimumab dose with risk ratios.]

**Analysis 25.16.** Comparison 25: Intravenous sifalimumab versus intravenous sifalimumab dose comparison, Outcome 16: Adverse events: severe - death at 1 mg/kg dose vs 10 mg/kg dose

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>sifalimumab 1 mg/kg</th>
<th>sifalimumab 10 mg/kg</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>25.16.1 Long term (12.5 months)</td>
<td>Petri 2013</td>
<td>Events: 1</td>
<td>Total: 25</td>
</tr>
</tbody>
</table>

![Graph showing the comparison of intravenous sifalimumab dose with risk ratios.]

**Analysis 25.17.** Comparison 25: Intravenous sifalimumab versus intravenous sifalimumab dose comparison, Outcome 17: Adverse events: severe - death at 3 mg/kg dose vs 10 mg/kg dose

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>sifalimumab 3 mg/kg</th>
<th>sifalimumab 10 mg/kg</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>25.17.1 Long term (12.5 months)</td>
<td>Petri 2013</td>
<td>Events: 0</td>
<td>Total: 27</td>
</tr>
</tbody>
</table>

![Graph showing the comparison of intravenous sifalimumab dose with risk ratios.]

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**Interventions for cutaneous disease in systemic lupus erythematosus (Review)**

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### Analysis 25.18. Comparison 25: Intravenous sifalimumab versus intravenous sifalimumab dose comparison, Outcome 18: Adverse events: minor - zoster at 0.3 mg/kg dose vs 3 mg/kg dose

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>sifalimumab 0.3 mg/kg</th>
<th>sifalimumab 3 mg/kg</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Petri 2013 (12.5 months)</td>
<td>0</td>
<td>26</td>
<td>0.21 [0.01, 4.12]</td>
</tr>
</tbody>
</table>

### Analysis 25.19. Comparison 25: Intravenous sifalimumab versus intravenous sifalimumab dose comparison, Outcome 19: Adverse events: minor - zoster at 0.3 mg/kg dose vs 10 mg/kg dose

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>sifalimumab 0.3 mg/kg</th>
<th>sifalimumab 10 mg/kg</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Petri 2013 (12.5 months)</td>
<td>0</td>
<td>26</td>
<td>0.33 [0.02, 6.54]</td>
</tr>
</tbody>
</table>

### Analysis 25.20. Comparison 25: Intravenous sifalimumab versus intravenous sifalimumab dose comparison, Outcome 20: Adverse events: minor - zoster at 1 mg/kg dose vs 3 mg/kg dose

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>sifalimumab 1 mg/kg</th>
<th>sifalimumab 3 mg/kg</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Petri 2013 (12.5 months)</td>
<td>0</td>
<td>25</td>
<td>0.22 [0.01, 4.28]</td>
</tr>
</tbody>
</table>

### Analysis 25.21. Comparison 25: Intravenous sifalimumab versus intravenous sifalimumab dose comparison, Outcome 21: Adverse events: minor - zoster at 1 mg/kg dose vs 10 mg/kg dose

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>sifalimumab 1 mg/kg</th>
<th>sifalimumab 10 mg/kg</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Petri 2013 (12.5 months)</td>
<td>0</td>
<td>25</td>
<td>0.34 [0.02, 6.78]</td>
</tr>
</tbody>
</table>
### Analysis 25.22. Comparison 25: Intravenous sifalimumab versus intravenous sifalimumab dose comparison, Outcome 22: Adverse events: minor - zoster at 3 mg/kg dose vs 10 mg/kg dose

| Study or Subgroup | sifalimumab 3 mg/kg | sifalimumab 10 mg/kg | Risk Ratio  
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>25.22.1 Long term (12.5 months)</td>
<td>Petri 2013</td>
<td>2</td>
<td>27</td>
</tr>
</tbody>
</table>

### Comparison 26. Oral clofazimine versus oral chloroquine

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>26.1 Primary outcome (lupus-specific): complete clearance of malar, SCLE, or discoid rash</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>26.1.1 Short term (6 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>26.2 Primary outcome (lupus-specific): partial clearance of malar, SCLE, or discoid rash</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>26.2.1 Short term (6 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>26.3 Adverse events: severe - severe flare in lupus requiring withdrawal from study</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>26.3.1 Short term (6 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>26.4 Adverse events: minor</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>26.4.1 Short term (6 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
</tbody>
</table>
### Analysis 26.1. Comparison 26: Oral clofazimine versus oral chloroquine, Outcome 1: Primary outcome (lupus-specific): complete clearance of malar, SCLE, or discoid rash

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Clofazimine</th>
<th>Chloroquine</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>26.1.1 Short term (6 months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bezerra 2005</td>
<td>3 Events</td>
<td>16 Events</td>
<td>7 Events Total 17</td>
</tr>
</tbody>
</table>

### Analysis 26.2. Comparison 26: Oral clofazimine versus oral chloroquine, Outcome 2: Primary outcome (lupus-specific): partial clearance of malar, SCLE, or discoid rash

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Clofazimine</th>
<th>Chloroquine</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>26.2.1 Short term (6 months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bezerra 2005</td>
<td>12 Events</td>
<td>16 Events</td>
<td>14 Events Total 17</td>
</tr>
</tbody>
</table>

### Analysis 26.3. Comparison 26: Oral clofazimine versus oral chloroquine, Outcome 3: Adverse events: severe - severe flare in lupus requiring withdrawal from study

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Clofazimine</th>
<th>Chloroquine</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>26.3.1 Short term (6 months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bezerra 2005</td>
<td>5 Events</td>
<td>16 Events</td>
<td>1 Events Total 17</td>
</tr>
</tbody>
</table>

### Analysis 26.4. Comparison 26: Oral clofazimine versus oral chloroquine, Outcome 4: Adverse events: minor

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Clofazimine</th>
<th>Chloroquine</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>26.4.1 Short term (6 months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bezerra 2005</td>
<td>11 Events</td>
<td>16 Events</td>
<td>12 Events Total 17</td>
</tr>
</tbody>
</table>
## Comparison 27. Oral ciclosporin versus oral azathioprine

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>27.1 Primary outcome (lupus-specific): complete clearance of malar rash (intent-to-treat analysis)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>27.1.1 Long term (12 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>27.2 Primary outcome (lupus-specific): complete clearance of oral ulcers (intent-to-treat analysis)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>27.2.1 Long term (12 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>27.3 Adverse events: all severe events combined</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>27.3.1 Long term (12 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>27.4 Adverse events: subset of severe adverse events due to lack of effect of medication only</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>27.4.1 Long term (12 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>27.5 Adverse events: minor</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>27.5.1 Long term (12 months): gum hypertrophy</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>27.5.2 Long term (12 months): alopecia</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>27.5.3 Long term (12 months): herpes zoster</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>27.5.4 Long term (12 months): non-lupus rash</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>27.5.5 Long term (12 months): acne</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
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</tr>
<tr>
<td>27.5.6 Long term (12 months): hirsutism</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>27.5.7 Long term (12 months): herpes simplex</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
</tbody>
</table>
Analysis 27.1. Comparison 27: Oral ciclosporin versus oral azathioprine, Outcome 1: Primary outcome (lupus-specific): complete clearance of malar rash (intent-to-treat analysis)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Ciclosporin</th>
<th>Azathioprine</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>27.1.1 Long term (12 months) Griffiths 2010</td>
<td>14</td>
<td>47</td>
<td>15</td>
</tr>
</tbody>
</table>

Favors azathioprine
Favors ciclosporin

Analysis 27.2. Comparison 27: Oral ciclosporin versus oral azathioprine, Outcome 2: Primary outcome (lupus-specific): complete clearance of oral ulcers (intent-to-treat analysis)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Ciclosporin</th>
<th>Azathioprine</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>27.2.1 Long term (12 months) Griffiths 2010</td>
<td>23</td>
<td>47</td>
<td>14</td>
</tr>
</tbody>
</table>

Favors azathioprine
Favors ciclosporin

Analysis 27.3. Comparison 27: Oral ciclosporin versus oral azathioprine, Outcome 3: Adverse events: all severe events combined

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Ciclosporin</th>
<th>Azathioprine</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>27.3.1 Long term (12 months) Griffiths 2010</td>
<td>14</td>
<td>47</td>
<td>14</td>
</tr>
</tbody>
</table>

Favors ciclosporin
Favors azathioprine

Analysis 27.4. Comparison 27: Oral ciclosporin versus oral azathioprine, Outcome 4: Adverse events: subset of severe adverse events due to lack of effect of medication only

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Ciclosporin</th>
<th>Azathioprine</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>27.4.1 Long term (12 months) Griffiths 2010</td>
<td>5</td>
<td>47</td>
<td>2</td>
</tr>
</tbody>
</table>

Favors ciclosporin
Favors azathioprine
### Analysis 27.5. Comparison 27: Oral ciclosporin versus oral azathioprine, Outcome 5: Adverse events: minor

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Ciclosporin</th>
<th>Azathioprine</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>27.5.1 Long term (12 months): gum hypertrophy</td>
<td>3/47</td>
<td>0/42</td>
<td>6.27 [0.33, 117.96]</td>
</tr>
<tr>
<td>Griffiths 2010</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>27.5.2 Long term (12 months): alopecia</td>
<td>6/47</td>
<td>7/42</td>
<td>0.77 [0.28, 2.10]</td>
</tr>
<tr>
<td>Griffiths 2010</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>27.5.3 Long term (12 months): herpes zoster</td>
<td>0/47</td>
<td>2/42</td>
<td>0.18 [0.01, 3.63]</td>
</tr>
<tr>
<td>Griffiths 2010</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>27.5.4 Long term (12 months): non-lupus rash</td>
<td>9/47</td>
<td>12/42</td>
<td>0.67 [0.31, 1.43]</td>
</tr>
<tr>
<td>Griffiths 2010</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>27.5.5 Long term (12 months): acne</td>
<td>0/47</td>
<td>3/42</td>
<td>0.13 [0.01, 2.41]</td>
</tr>
<tr>
<td>Griffiths 2010</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>27.5.6 Long term (12 months): hirsutism</td>
<td>11/47</td>
<td>1/42</td>
<td>9.83 [1.32, 72.95]</td>
</tr>
<tr>
<td>Griffiths 2010</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>27.5.7 Long term (12 months): herpes simplex</td>
<td>2/47</td>
<td>3/42</td>
<td>0.60 [0.10, 3.39]</td>
</tr>
<tr>
<td>Griffiths 2010</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Comparison 28. Oral methotrexate versus oral chloroquine

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>28.1 Primary outcome (lupus-specific): complete clearance of skin rash (ITT analysis)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>28.1.1 Short term (6 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>28.2 Primary outcome (lupus-specific): complete clearance of skin rash (authors’ per-protocol analysis)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>28.2.1 Short term (6 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>28.3 Primary outcome (lupus-specific): complete clearance of skin rash during 6 month study (subset of patients with skin findings at baseline)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>28.3.1 Short term (6 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
</tbody>
</table>
### Outcome or subgroup title

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>28.4 Adverse events</td>
<td>1</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>28.4.1 Severe short term (6 months)</td>
<td>1</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>28.4.2 Minor short term (6 months)</td>
<td>1</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
</tbody>
</table>

---


#### Study or Subgroup

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>methotrexate</th>
<th>chloroquine</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>28.1.1 Short term (6 months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Islam 2012</td>
<td>6</td>
<td>15</td>
<td>16</td>
</tr>
</tbody>
</table>

#### Risk Ratio

- Favors chloroquine
- Favors methotrexate

---

### Analysis 28.2. Comparison 28: Oral methotrexate versus oral chloroquine, Outcome 2: Primary outcome (lupus-specific): complete clearance of skin rash (authors' per-protocol analysis)

#### Study or Subgroup

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>methotrexate</th>
<th>chloroquine</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>28.2.1 Short term (6 months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Islam 2012</td>
<td>6</td>
<td>13</td>
<td>16</td>
</tr>
</tbody>
</table>

#### Risk Ratio

- Favors chloroquine
- Favors methotrexate

---

### Analysis 28.3. Comparison 28: Oral methotrexate versus oral chloroquine, Outcome 3: Primary outcome (lupus-specific): complete clearance of skin rash during 6 month study (subset of patients with skin findings at baseline)

#### Study or Subgroup

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>methotrexate</th>
<th>chloroquine</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>28.3.1 Short term (6 months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Islam 2012</td>
<td>6</td>
<td>6</td>
<td>16</td>
</tr>
</tbody>
</table>

#### Risk Ratio

- Favors chloroquine
- Favors methotrexate
Analysis 28.4. Comparison 28: Oral methotrexate versus oral chloroquine, Outcome 4: Adverse events

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>methotrexate</th>
<th>chloroquine</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Events</td>
<td>M-H, Random, 95% CI</td>
</tr>
<tr>
<td>28.4.1 Severe short term (6 months)</td>
<td>Islam 2012</td>
<td>2</td>
<td>15</td>
</tr>
<tr>
<td>28.4.2 Minor short term (6 months)</td>
<td>Islam 2012</td>
<td>9</td>
<td>15</td>
</tr>
</tbody>
</table>

Comparison 29. Oral mycophenolate versus azathioprine or dapsone

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>29.1 Primary outcome (lupus-specific): partial improvement</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>29.1.1 Short term (4 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>29.2 Adverse events</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>29.2.1 Severe short term (4 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>29.2.2 Minor short term (4 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
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</table>

Analysis 29.1. Comparison 29: Oral mycophenolate versus azathioprine or dapsone, Outcome 1: Primary outcome (lupus-specific): partial improvement

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mycophenolate</th>
<th>Azathioprine or dapsone</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Events</td>
<td>M-H, Random, 95% CI</td>
</tr>
<tr>
<td>29.1.1 Short term (4 months)</td>
<td>Yahya 2013</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>
Analysis 29.2. Comparison 29: Oral mycophenolate versus azathioprine or dapsone, Outcome 2: Adverse events

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mycophenolate</th>
<th>Azathioprine or dapsone</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>29.2.1 Severe short term (4 months)</td>
<td>0/8</td>
<td>2/6</td>
<td>0.16 [0.01, 2.75]</td>
</tr>
<tr>
<td>Yahya 2013</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>29.2.2 Minor short term (4 months)</td>
<td>1/8</td>
<td>0/6</td>
<td>2.33 [0.11, 48.99]</td>
</tr>
<tr>
<td>Yahya 2013</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Comparison 30. Oral Zi Shen Qing (Chinese herbal medicine) versus hydroxychloroquine

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>30.1 Adverse events: severe</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>30.1.1 Short term (3 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>30.2 Adverse events: minor</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>30.2.1 Short term (3 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
</tbody>
</table>

Analysis 30.1. Comparison 30: Oral Zi Shen Qing (Chinese herbal medicine) versus hydroxychloroquine, Outcome 1: Adverse events: severe

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Zi Shen Qing</th>
<th>hydroxychloroquine</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>30.1.1 Short term (3 months)</td>
<td>4/42</td>
<td>3/42</td>
<td>1.33 [0.32, 5.60]</td>
<td></td>
</tr>
<tr>
<td>Zhong 2013</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
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</table>

Analysis 30.2. Comparison 30: Oral Zi Shen Qing (Chinese herbal medicine) versus hydroxychloroquine, Outcome 2: Adverse events: minor

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Zi Shen Qing</th>
<th>hydroxychloroquine</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>30.2.1 Short term (3 months)</td>
<td>5/42</td>
<td>8/42</td>
<td>0.63 [0.22, 1.75]</td>
<td></td>
</tr>
<tr>
<td>Zhong 2013</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
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</table>
Comparison 31. Intravenous ciclosporin A plus steroids versus intravenous steroids alone

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>31.1 Primary outcome (lupus-specific): complete resolution of erythematos manifestations</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>31.1.1 Short term (3 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>31.1.2 Long term (12 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>31.2 Adverse events</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>31.2.1 Severe long term (12 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>31.2.2 Minor long term (12 months): mucocutaneous alterations only (hypertrichosis, striae rubrae)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>31.2.3 Minor long term (12 months): combined mucocutaneous and other organ systems</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
</tbody>
</table>

Analysis 31.1. Comparison 31: Intravenous ciclosporin A plus steroids versus intravenous steroids alone, Outcome 1: Primary outcome (lupus-specific): complete resolution of erythematos manifestations

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Cyclosporine/Prednisone</th>
<th>Prednisone alone</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Cyclosporine/Prednisone</th>
<th>Prednisone alone</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
</tbody>
</table>

- 31.1.1 Short term (3 months) Dammacco 2000 1 10 0 8 2.45 [0.11, 53.25]
- 31.1.2 Long term (12 months) Dammacco 2000 7 10 0 8 12.27 [0.81, 187.01]

Favors prednisone alone Favors ciclosporine/prednisone
Analysis 31.2. Comparison 31: Intravenous ciclosporin A plus steroids versus intravenous steroids alone, Outcome 2: Adverse events

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Cyclosporine/Prednisone</th>
<th>Prednisone alone</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>31.2.1 Severe long term (12 months)</td>
<td>Dammacco 2000</td>
<td>2 10 4 8</td>
<td>0.40 [0.10, 1.66]</td>
</tr>
<tr>
<td>31.2.2 Minor long term (12 months): mucocutaneous alterations only (hypertrichosis, striae rubrae)</td>
<td>Dammacco 2000</td>
<td>0 10 4 8</td>
<td>0.09 [0.01, 1.47]</td>
</tr>
<tr>
<td>31.2.3 Minor long term (12 months): combined mucocutaneous and other organ systems</td>
<td>Dammacco 2000</td>
<td>6 10 5 8</td>
<td>0.96 [0.46, 2.01]</td>
</tr>
</tbody>
</table>

Comparison 32. Intravenous rituximab versus intravenous cyclophosphamide

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>32.1 Adverse events: minor - cutaneous rash, itching</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>32.1.1 Long term (12 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
</tbody>
</table>

Analysis 32.1. Comparison 32: Intravenous rituximab versus intravenous cyclophosphamide, Outcome 1: Adverse events: minor - cutaneous rash, itching

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Rituximab</th>
<th>Cyclophosphamide</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>32.1.1 Long term (12 months)</td>
<td>Andrade-Ortega 2009</td>
<td>3 10 0 9</td>
<td>6.36 [0.37, 108.56]</td>
<td></td>
</tr>
</tbody>
</table>

Comparison 33. "Early treatment" (serology) with prednisone and/or cytotoxic agents versus "later treatment" (clinical flare)

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>33.1 Adverse events: minor</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>33.1.1 Short term (6 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>33.2 Adverse events: severe</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>33.2.1 Short term (6 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
</tbody>
</table>
Analysis 33.1. Comparison 33: "Early treatment" (serology) with prednisone and/or cytotoxic agents versus "later treatment" (clinical flare), Outcome 1: Adverse events: minor

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Early treatment</th>
<th>Later treatment</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events Total</td>
<td>Events Total</td>
<td>M-H, Random, 95% CI</td>
<td>M-H, Random, 95% CI</td>
</tr>
<tr>
<td>33.1.1 Short term (6 months)</td>
<td>18 22</td>
<td>17 24</td>
<td>1.16 [0.84, 1.60]</td>
<td></td>
</tr>
</tbody>
</table>

Risk Ratio M-H, Random, 95% CI

Favors early treatment | Favors late treatment

Analysis 33.2. Comparison 33: "Early treatment" (serology) with prednisone and/or cytotoxic agents versus "later treatment" (clinical flare), Outcome 2: Adverse events: severe

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Early treatment</th>
<th>Later treatment</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events Total</td>
<td>Events Total</td>
<td>M-H, Random, 95% CI</td>
<td>M-H, Random, 95% CI</td>
</tr>
<tr>
<td>33.2.1 Short term (6 months)</td>
<td>6 22</td>
<td>1 24</td>
<td>6.55 [0.85, 50.16]</td>
<td></td>
</tr>
</tbody>
</table>

Risk Ratio M-H, Random, 95% CI

Favors early treatment | Favors late treatment

Comparison 34. Intravenous pulse high-dose cyclophosphamide versus intravenous monthly lower-dose cyclophosphamide

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>34.1 Adverse events: severe - death</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>34.1.1 Long term (24 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>34.2 Adverse events: severe - infection, cardiac arrest (not including death)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>34.2.1 Long term (24 months)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
</tbody>
</table>
### Analysis 34.1. Comparison 34: Intravenous pulse high-dose cyclophosphamide versus intravenous monthly lower-dose cyclophosphamide, Outcome 1: Adverse events: severe - death

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>High dose</th>
<th>Lower dose</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td></td>
</tr>
<tr>
<td>34.1.1 Long term (24 months) Petri 2010</td>
<td>1</td>
<td>24</td>
<td>0</td>
</tr>
</tbody>
</table>

Risk Ratio: M-H, Random, 95% CI: 0.002 0.1 1 10 500

Favors high dose Favors low dose

### Analysis 34.2. Comparison 34: Intravenous pulse high-dose cyclophosphamide versus intravenous monthly lower-dose cyclophosphamide, Outcome 2: Adverse events: severe - infection, cardiac arrest (not including death)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>high dose</th>
<th>monthly (lower) dose</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>34.2.1 Long term (24 months) Petri 2010</td>
<td>1</td>
<td>24</td>
<td>1</td>
</tr>
</tbody>
</table>

Risk Ratio: M-H, Random, 95% CI: 0.01 0.1 1 10 100

Favors high dose Favors low dose

### Comparison 35. Topical tacrolimus versus topical clobetasol

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>35.1 Primary outcome (lupus-specific): erythema</td>
<td>1</td>
<td></td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>35.1.1 Short term (2 months)</td>
<td>1</td>
<td></td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>35.2 Primary outcome (lupus-specific): desquamation</td>
<td>1</td>
<td></td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>35.2.1 Short term (2 months)</td>
<td>1</td>
<td></td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>35.3 Primary outcome (lupus-specific): skin induration</td>
<td>1</td>
<td></td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>35.3.1 Short term (2 months)</td>
<td>1</td>
<td></td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
</tbody>
</table>
### Analysis 35.1. Comparison 35: Topical tacrolimus versus topical clobetasol, Outcome 1: Primary outcome (lupus-specific): erythema

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>tacrolimus</th>
<th>clobetasol</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
<td>Mean</td>
</tr>
<tr>
<td>35.1.1 Short term (2 months)</td>
<td>1.17</td>
<td>0.69</td>
<td>18</td>
</tr>
</tbody>
</table>

### Analysis 35.2. Comparison 35: Topical tacrolimus versus topical clobetasol, Outcome 2: Primary outcome (lupus-specific): desquamation

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>tacrolimus</th>
<th>clobetasol</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
<td>Mean</td>
</tr>
<tr>
<td>35.2.1 Short term (2 months)</td>
<td>0.5</td>
<td>0.57</td>
<td>18</td>
</tr>
</tbody>
</table>

### Analysis 35.3. Comparison 35: Topical tacrolimus versus topical clobetasol, Outcome 3: Primary outcome (lupus-specific): skin induration

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>tacrolimus</th>
<th>clobetasol</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
<td>Mean</td>
</tr>
<tr>
<td>35.3.1 Short term (2 months)</td>
<td>0.67</td>
<td>0.62</td>
<td>18</td>
</tr>
</tbody>
</table>

### ADDITIONAL TABLES

#### Table 1. Glossary of terms

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>alopecia</td>
<td>hair loss</td>
</tr>
<tr>
<td>American College of Rheumatology (ACR) criteria</td>
<td>criteria needed to make the diagnosis of systemic lupus erythematosus (SLE) formulated by an ACR consensus committee; publication of this information was provided by Tan 1982</td>
</tr>
<tr>
<td>antimalarial medications</td>
<td>Medications that were initially used for their antimalarial effects but are also known to have anti-inflammatory and anti-autoimmune properties. Examples are hydroxychloroquine, chloroquine, and quinacrine</td>
</tr>
<tr>
<td>aphthous ulcers</td>
<td>oral ulcers</td>
</tr>
<tr>
<td>autoimmune</td>
<td>diseases in which the body’s defences are directed in error against itself</td>
</tr>
</tbody>
</table>
calcineurin inhibitors: medications that change the immune system response by inhibiting a protein called calcineurin; examples are pimecrolimus and tacrolimus.

discoid lupus erythematosus (DLE): chronic ‘lupus-specific’ skin lesion characterised by discoid (coin-shaped) plaques.

hirsutism: excessive hair growth in unwanted locations, such as facial or body hair in women.

immunomodulator medications: medications that change or modulate the immune system response.

immune system: the body's defence system.

inflammation: the immune system's response to something that bothers it.

lupus-specific skin symptoms: Skin symptoms that are found exclusively in people with lupus erythematosus and are not seen in other diseases. Lupus-specific skin symptoms are further subcategorised into 3 groups based on length of time that skin symptoms are typically present: acute, subacute, and chronic.

lupus-non-specific skin symptoms: Skin symptoms occurring in people who have been diagnosed with SLE by ACR criteria but that are not exclusive to SLE (i.e. also found in other autoimmune conditions). Some of the most common lupus-non-specific skin symptoms are photosensitivity, oral ulcers, alopecia, Raynaud’s phenomenon, and vasculitis.

malar rash: classic 'butterfly-shaped rash' seen across the bridge of the nose and both cheeks in systemic lupus erythematosus.

panniculitis: fat inflammation.

photosensitivity: excessive sensitivity to sunlight.

Raynaud’s phenomenon or disease: spasm of blood vessels in fingers and toes; can be primary (occurring without another known disease association) or secondary (occurring in association with an autoimmune disease such as SLE).

ribonuclear protein, Ro and La antibodies: characteristic antibodies in the blood found in SCLE.

subacute cutaneous lupus erythematosus (SCLE): a form of lupus-specific skin symptoms characterised by round or polycyclic inflamed skin lesions occurring on areas exposed to the sun.

systemic lupus erythematosus (SLE): an autoimmune disease that results in damage to multiple organ systems; also known as lupus.

vasculitis: inflammation of blood vessels.

ACR: American College of Rheumatology.
SCLE: subacute cutaneous lupus erythematosus.
SLE: systemic lupus erythematosus.

### Table 1. Glossary of terms (Continued)

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotics</td>
<td>clofazimine</td>
</tr>
<tr>
<td>Mechanism of Action</td>
<td>Immunosuppressant; anti-inflammatory</td>
</tr>
<tr>
<td>RCT specifically for cutaneous disease in SLE?</td>
<td>Bezerra 2005</td>
</tr>
<tr>
<td>Interventions for cutaneous disease in systemic lupus erythematosus (Review)</td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td><strong>Antimalarials (oral)</strong></td>
<td>chloroquine</td>
</tr>
<tr>
<td></td>
<td>hydroxychloroquine</td>
</tr>
<tr>
<td><strong>Behavioural interventions</strong></td>
<td>smoking cessation</td>
</tr>
<tr>
<td></td>
<td>sunscreen</td>
</tr>
<tr>
<td></td>
<td>protective clothing</td>
</tr>
<tr>
<td></td>
<td>avoid/stop trigger medications</td>
</tr>
<tr>
<td><strong>Beta-2-adrenergic receptor agonists</strong></td>
<td>levosalbutamol cream (R-salbutamol sulfate 0.05% cream)</td>
</tr>
<tr>
<td><strong>Biologic therapies (intravenous)</strong></td>
<td>abatacept</td>
</tr>
<tr>
<td></td>
<td>atacicept</td>
</tr>
<tr>
<td></td>
<td>blisibimod (aka A-623 or AMG-623)</td>
</tr>
<tr>
<td></td>
<td>SM101</td>
</tr>
<tr>
<td><strong>Calcineurin inhibitors (oral)</strong></td>
<td>ciclosporin</td>
</tr>
<tr>
<td></td>
<td>tacrolimus ointment</td>
</tr>
<tr>
<td><strong>Calcineurin inhibitors (topical)</strong></td>
<td></td>
</tr>
</tbody>
</table>
### Table 2. Summary of treatments for cutaneous disease in SLE (Continued)

<table>
<thead>
<tr>
<th>Interventions for cutaneous disease in systemic lupus erythematosus (Review)</th>
<th>Copyright © 2021 The Cochrane Collaboration. Published by John Wiley &amp; Sons, Ltd.</th>
<th>RCT for CLE without SLE: Pothinamthong 2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>pimecrolimus cream</td>
<td>Same as above</td>
<td>No RCTs for CLE with SLE; however RCTs for CLE without SLE by Sticherling 2007 and Barikbin 2009</td>
</tr>
<tr>
<td><strong>Calcium channel blockers (oral)</strong></td>
<td>nicardipine</td>
<td>For Raynaud’s phenomenon in SLE: prevents “Ca²⁺ transport across the plasma cell membrane of smooth muscle cells” of blood vessels; inhibits “excitation contraction coupling and muscle constriction” Rupp 1987</td>
</tr>
<tr>
<td>nifedipine</td>
<td>Same as above</td>
<td>Kahan 1985</td>
</tr>
<tr>
<td><strong>Camouflage therapy</strong></td>
<td>cover-up make-up</td>
<td>Relieves suffering from skin lesions causing emotional distress and buys time for other treatments to work; builds confidence in the patient-physician relationship, increasing patient satisfaction and compliance Lanna 2019</td>
</tr>
<tr>
<td><strong>Cereblon inhibitor</strong></td>
<td>CC-220, also known as iberdomite hydrochloride or IBER (oral)</td>
<td>Decreases B-cell subsets and plasmacytoid dendritic cells Werth 2017a</td>
</tr>
<tr>
<td><strong>Chemotherapy</strong></td>
<td>bortezomib (intravenous)</td>
<td>Proteasome inhibitor targeting plasma cells (antibody-producing B-cell line) Ishii 2015</td>
</tr>
<tr>
<td>lenalidomide (oral)</td>
<td>Inhibits TNF-α synthesis</td>
<td>Okon 2014</td>
</tr>
<tr>
<td><strong>Complementary and alternative therapies</strong></td>
<td>acupuncture</td>
<td>Various mechanisms No RCTs for CLE with SLE; however RCTs for SLE reviewed in Greco 2013</td>
</tr>
<tr>
<td>mind-body therapy (cognitive-behavioural therapy (CBT), meditation, interpersonal therapy)</td>
<td>Various mechanisms</td>
<td>No RCTs for CLE with SLE; however RCTs for SLE reviewed in Greco 2013</td>
</tr>
<tr>
<td>supplements (vitamin C, vitamin E, N-acetylcysteine (NAC), turmeric, green tea extracts)</td>
<td>Various mechanisms</td>
<td>No RCTs for CLE with SLE; however green tea extract RCT for CLE without SLE by Shamekhi 2017 and for other supplements for SLE without CLE reviewed by Greco 2013</td>
</tr>
<tr>
<td><strong>Corticosteroids (systemic)</strong></td>
<td>prednisone (oral)</td>
<td>Affect B cells and T cells; lower immunoglobulin production and decreasing TNF-α Tseng 2006</td>
</tr>
<tr>
<td>Interventions for cutaneous disease in systemic lupus erythematosus (Review)</td>
<td>Table 2. Summary of treatments for cutaneous disease in SLE (Continued)</td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td><strong>Corticosteroids</strong> (topical)</td>
<td><strong>Hormonal therapy</strong></td>
<td></td>
</tr>
<tr>
<td>6-methyl-prednisolone (intravenous)</td>
<td>corticotropin (repository injection or gel)</td>
<td></td>
</tr>
<tr>
<td>Same as above</td>
<td>Prolonged-release formulation containing a highly purified porcine ACTH analogue; increases (IL)-10; decreases B lymphocyte and IL-4/CD40 ligand-induced proliferation and immunoglobulin production</td>
<td>Furie 2015a; Furie 2016a</td>
</tr>
<tr>
<td><strong>Corticosteroids (topical)</strong></td>
<td>dehydroepiandrosterone (DHEA) also known as prasterone (oral)</td>
<td></td>
</tr>
<tr>
<td>clobetasol propionate ointment</td>
<td>Adrenal steroid hormone involved in upregulation of IL-2 and downregulation of IL-6</td>
<td>Petri 2004; Van Vollenhoven 1995</td>
</tr>
<tr>
<td>Same as above</td>
<td><strong>Immunomodulatory agents (oral and intravenous)</strong></td>
<td></td>
</tr>
<tr>
<td>fluocinolone ointment</td>
<td>azathioprine</td>
<td>Antimetabolite (purine analogue) cytotoxic agent that depresses T-cell, B-cell, and antigen presenting cell function</td>
</tr>
<tr>
<td>Same as above</td>
<td>cyclophosphamide</td>
<td>Alkylating cytotoxic agent that cross-links DNA leading to cell death by apoptosis; affects proliferating cells preferentially but acts independently of the cell cycle</td>
</tr>
<tr>
<td>diflucortolone valerate</td>
<td>Same as above</td>
<td>methotrexate</td>
</tr>
<tr>
<td>Same as above</td>
<td><strong>Immunomodulatory agents (oral and intravenous)</strong></td>
<td>dapsone</td>
</tr>
<tr>
<td>hydrocortisone acetate</td>
<td>Same as above</td>
<td>methotrexate</td>
</tr>
<tr>
<td>Same as above</td>
<td><strong>Immunomodulatory agents (oral and intravenous)</strong></td>
<td>thalidomide</td>
</tr>
<tr>
<td>betamethasone 17-valerate</td>
<td>Same as above</td>
<td>mycophenolate sodium</td>
</tr>
<tr>
<td>Same as above</td>
<td><strong>Immunomodulatory agents (oral and intravenous)</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hormonal therapy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>corticotropin (repository injection or gel)</td>
<td>Prolonged-release formulation containing a highly purified porcine ACTH analogue; increases (IL)-10; decreases B lymphocyte and IL-4/CD40 ligand-induced proliferation and immunoglobulin production</td>
</tr>
<tr>
<td></td>
<td>dehydroepiandrosterone (DHEA) also known as prasterone (oral)</td>
<td>Adrenal steroid hormone involved in upregulation of IL-2 and downregulation of IL-6</td>
</tr>
<tr>
<td></td>
<td>azathioprine</td>
<td>Antimetabolite (purine analogue) cytotoxic agent that depresses T-cell, B-cell, and antigen presenting cell function</td>
</tr>
<tr>
<td></td>
<td>cyclophosphamide</td>
<td>Alkylating cytotoxic agent that cross-links DNA leading to cell death by apoptosis; affects proliferating cells preferentially but acts independently of the cell cycle</td>
</tr>
<tr>
<td></td>
<td>dapsone</td>
<td>Inhibits myeloperoxidase found in neutrophils, eosinophils, and monocytes</td>
</tr>
<tr>
<td></td>
<td>methotrexate</td>
<td>Anti-TNFα agent that binds to dihydrofolate reductase enzyme, inhibiting cell division in DNA synthesis phase in immune cells, suppressing primary and secondary antibody production</td>
</tr>
<tr>
<td></td>
<td>mycophenolate sodium</td>
<td>Antimetabolite cytotoxic agent that inhibits purine biosynthesis, targeting the lymphocytes most responsible for SLE</td>
</tr>
<tr>
<td></td>
<td>thalidomide</td>
<td>Anti-TNFα agent that inhibits TNFα and UVB induced keratinocyte apoptosis via inhibition of interferon gamma</td>
</tr>
</tbody>
</table>
### JAK inhibitors (oral)
- **baricitinib**: Selective Janus kinase (JAK1 and JAK2) inhibitor that blocks pro-inflammatory cytokines. Wallace 2018

### JAK inhibitors (topical)
- **R932333 ointment 6%** (also known as R333): Same as above. Duleige 2016

### Light therapy
- **Ultraviolet light (UVA-1 defined as 340 to 400 NM)**: Deeply penetrating UVA-1 photons induce an immediate non-transcriptional apoptosis that is localised and non-inflammatory, minimising collateral damage and unwanted "spillover" effects. McGrath 1996; Polderman 2001

### Leukotriene synthesis inhibitors
- **zileuton (oral)**: Leukotriene synthesis inhibitor, specifically an inhibitor of 5-lipoxygenase. Hackshaw 1995

### Monoclonal antibodies (intravenous)
- **anifrolumab**: Anti-IFN-alpha-1a receptor. Furie 2015c

### Monoclonal antibodies (intravenous)
- **belimumab**: Humanised IgG1y monoclonal antibody directed against the B cell-activating factor (BAFF), a soluble ligand of the TNF cytokine family and a prominent factor in B-cell differentiation, homeostasis, and selection. Furie 2011; Navarra 2011; Stohl 2017; Wallace 2009

### Monoclonal antibodies (intravenous)
- **BIIB059**: Fully humanised IgG1 monoclonal antibody targeting blood dendritic cell antigen-2 (BDCA-2) expressed on plasmacytoid dendritic cells. Furie 2016a

### Monoclonal antibodies (intravenous)
- **epratuzumab**: Humanised anti-CD22 monoclonal antibody that modulates B-cell signalling without total B-cell depletion. Clowse 2015; Wallace 2013; Wallace 2014

### Monoclonal antibodies (intravenous)
- **lulizumab pegol (subcutaneous)**: Anti-CD28 domain antagonist. CD28 is a T-cell costimulatory molecule of critical pathogenic T-cell activation. Merrill 2018

### Monoclonal antibodies (intravenous)
- **rituximab**: Chimeric anti-CD20 monoclonal antibody. Andrade-Ortega 2009; Merrill 2010a

### Monoclonal antibodies (intravenous)
- **sifalimumab**: Humanised anti-IFN-alpha. Khamashta 2016; Petri 2013

### Monoclonal antibodies (intravenous)
- **sirukumab**: Anti-IL-6. Szepietowski 2013

### Monoclonal antibodies (intravenous)
- **tabalumab (LY-2127399)**: Fully human IgG subclass 4 (IgG4) monoclonal antibody that binds and neutralises both soluble and membrane-bound BAFF. Merrill 2016

### Monoclonal antibodies (intravenous)
- **ustekinumab**: Antibody against an IL-12 and IL-23 binding protein. Van Vollenhoven 2018

### Retinoid (oral)
- **acitretin**: Affects pathways involved in inflammation, cellular differentiation, and apoptosis. No RCT for CLE with SLE; however RCT for CLE without SLE by Ruzicka 1992
### Table 2. Summary of treatments for cutaneous disease in SLE (Continued)

<table>
<thead>
<tr>
<th>Supplements (oral)</th>
<th>cholecalciferol (vitamin D)</th>
<th>Acts on B-cell regulation and antibody secretion and on dendritic cells and T-cell receptors</th>
<th>Lima 2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>copper</td>
<td></td>
<td>Modulates inflammatory response</td>
<td>Duffy 2004</td>
</tr>
<tr>
<td>fish oil</td>
<td></td>
<td>Reduces autoantibodies and inflammatory cytokines; improves endothelial function</td>
<td>Duffy 2004; Walton 1991; Westberg 1990; Wright 2008</td>
</tr>
<tr>
<td>Traditional Chinese Medicine (TCM)</td>
<td>ginsenosides (ginseng)</td>
<td>Anti-inflammatory, antioxidant, anticancer; relax blood vessels; enhance transactivation of the glucocorticoid receptor</td>
<td>You 2010</td>
</tr>
<tr>
<td>Zi Sen Qing oral herbal formula</td>
<td>Regulates CD4 and CD25</td>
<td></td>
<td>Zhong 2013</td>
</tr>
</tbody>
</table>

ACTH: adrenocorticotrophic hormone.  
BAFF: B cell-activating factor.  
BDCA: blood dendritic cell antigen.  
CLE: cutaneous lupus erythematosus.  
CTLA: cytotoxic T lymphocyte-associated.  
DHEA: dehydroepiandrosterone.  
IgG1: immunoglobulin G1.  
IL-4: interleukin-4.  
JAK: Janus kinase.  
RCT: randomised controlled trial.  
SLE: systemic lupus erythematosus.  
TLR: toll-like receptor.  
TNF: tumour necrosis factor.  
UVA: ultraviolet A light.  
UVB: ultraviolet B light.

### Table 3. Interventions: dose and treatment course

**A**  
Abatacept (intravenous) was studied at a dose of 10 mg/kg on days 1, 15, and 29 and monthly for 12 months (Merrill 2010b)

Anifrolumab (intravenous) was studied at a dose of 300 mg intravenous infusion every 4 weeks for 48 weeks (12 months) (Furie 2015c)

Atacicept (intravenous) was studied at single doses of 3, 9, or 18 mg/kg for 6 weeks, or at multiple doses of 2 × 9 mg/kg for 9 weeks (Pena-Rossi 2009)

Azathioprine (oral) was studied at doses of 0.5 mg/kg/d in 2 divided doses per day increased to a maintenance dose of 2 mg/kg/d with maximum dose of 2.5 mg/kg/d for 12 months (Griffiths 2010). Azathioprine (oral) was also studied at a target dose of 2 mg/kg/d for 24 months (Ordi-Ros 2017)

**B**  
Baricitinib (oral) was studied at doses of 2 mg once daily and 4 mg once daily over 6 months (Wallace 2018)

Belimumab (intravenous) was studied at 2 infusion dosing levels of 1 mg/kg and 10 mg/kg over 1 hour on days 0, 14, and 28, then monthly for 12 months (Navarra 2011), and for 18 months (Furie 2011). It was also studied at the 3 dosing levels of 1 mg/kg, 4 mg/kg, and 10 mg/kg over 2 hours on days 0, 14, and 28, then monthly for 12 months (Wallace 2009). Belimumab (subcutaneous) was studied at doses of 200 mg weekly for 12 months (Stohl 2017)
Cochrane Library

Trusted evidence.
Informed decisions.
Better health.

Cochrane Database of Systematic Reviews

Table 3. Interventions: dose and treatment course (Continued)

<table>
<thead>
<tr>
<th>Interventions for cutaneous disease in systemic lupus erythematosus (Review)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BIIB059</strong> (intravenous) was studied at the dose of 1 single IV administration of 20 mg/kg and was followed for 3 months (Furie 2016b)</td>
</tr>
<tr>
<td><strong>Blisibimod</strong> (intravenous) was studied at 3 dosing levels: 200 mg subcutaneously once each week, 100 mg subcutaneously once each week, and 200 mg subcutaneously once every 4 weeks (month) for up to 52 weeks (12 months) (Furie 2015b)</td>
</tr>
<tr>
<td><strong>Bortezomib</strong> (intravenous) was studied at the dose of 1.3 mg/m² intravenous infusion twice weekly for 8 doses for 4 weeks (1 month) (Ishii 2015)</td>
</tr>
<tr>
<td><strong>CC-220</strong> (oral) was studied at the following doses over 6 months: 0.3 mg every other day; 0.3 mg once each day; 0.6 mg alternating with 0.3 mg each day; 0.6 mg each day (Werth 2017a)</td>
</tr>
<tr>
<td><strong>Cholecalciferol</strong> (oral) was studied at a dose of 50,000 IU each week for 6 months (Lima 2016)</td>
</tr>
<tr>
<td><strong>Chloroquine</strong> (oral) was studied at doses of 150 mg daily for 6 months (Islam 2012), 250 mg daily for 6 months (Bezerra 2005), and 250 mg daily for 12 months (Meinao 1996)</td>
</tr>
<tr>
<td><strong>Clobetasol propionate</strong> (topical) ointment 0.05% was studied for twice-daily application for 2 months (Tzung 2007)</td>
</tr>
<tr>
<td><strong>Clofazimine</strong> (oral) was studied at the dose of 100 mg daily for 6 months (Bezerra 2005)</td>
</tr>
<tr>
<td><strong>Copper</strong> (oral) was studied at the dose of 3 mg per day in the form of copper diglycinate amine acid complex for 6 months (Duffy 2004)</td>
</tr>
<tr>
<td><strong>Corticosteroids</strong> (oral) were studied at doses of prednisone 0.5 mg to 1 mg/kg daily for 12 months, then reduced by 5 mg/d every 2 weeks following clinical remission up to 24 months (Dammacco 2000), or at doses for flares of 30 mg each day for 2 weeks, then 20 mg for 1 week, then 10 mg for 1 week during the 18 month study (Tseng 2006)</td>
</tr>
<tr>
<td><strong>Corticosteroids</strong> (intravenous) were studied at the dose of three 1 gram boluses of 6-methylprednisolone in a 12 month study (Dammacco 2000)</td>
</tr>
<tr>
<td><strong>Corticotropin</strong> (repository injection) was studied at a dose of 40 units a day or 80 units every other day for 4 weeks, then tapered to twice weekly for weeks 5 to 8 during a 2 month study (Furie 2016a); corticotropin (HP repository or acthar gel) was also studied at a dose of 80 units subcutaneous injection every other day for 8 weeks (2 months) (Furie 2015a)</td>
</tr>
<tr>
<td><strong>Cyclophosphamide</strong> (intravenous) was studied at a high dose of 50 mg/kg daily for 4 days, a 1 time dose over a period of 24 months (Petri 2010). This was compared with monthly intravenous cyclophosphamide at 750 mg/m²/body mass index for 6 months followed by maintenance quarterly dosing for a 24 month period (Petri 2010). Intravenous cyclophosphamide was also studied at doses of 750 mg/m² to 1 gram/m² each month for 6 months followed by maintenance quarterly dosing for a 12 month period (Andrade-Ortega 2009)</td>
</tr>
<tr>
<td><strong>Ciclosporin</strong> (oral) was studied at doses of 1 mg/kg/d in 2 divided doses per day increased to the target dose of 2.5 mg/kg/d with maximum of 3.5 mg/kg/d for 12 months (Griffiths 2010). Oral ciclosporin was also studied at doses of less than 5 mg/kg/d for 12 months, then gradually reduced by 0.5 mg/kg/d every 15 to 30 days until complete withdrawal or a minimum maintenance dose until 24 months (Dammacco 2000)</td>
</tr>
<tr>
<td><strong>Dapsone</strong> (oral) was studied in 1 patient at doses that were not stated (Yahya 2013)</td>
</tr>
<tr>
<td><strong>Dehydroepiandrosterone</strong> (DHEA or prasterone) (oral) was studied at a dose of 200 mg daily for 3 months (Van Vollenhoven 1995), and for 12 months (Petri 2004)</td>
</tr>
</tbody>
</table>
### Table 3. Interventions: dose and treatment course (Continued)

| Interventions for cutaneous disease in systemic lupus erythematosus (Review) | Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd. | 273 |

**E**  
Epratuzumab (intravenous) was studied at doses of 600 mg intravenous infusion each week and 1200 mg intravenous infusion every other week for 4 weeks every 3 months for 3 cycles (total of 48 weeks or 12 months) (Clowse 2015). Epratuzumab (intravenous) was also studied at the following doses for 3 months: 200 mg cumulative dose (cd) (100 mg every other week (EOW)); 800 mg cd (400 mg EOW); 2400 mg cd (600 mg weekly); 2400 mg cd (1200 mg EOW); 3600 mg cd (1800 mg EOW) (Wallace 2013). Epratuzumab (intravenous) was also studied at doses of 720 mg/m² each 3 months for 12 months (Wallace 2014)

**F**  
Fish oil (oral) was studied at the dose of 3 grams of MaxEPA fish oil capsule daily for 6 months (Duffy 2004). In Duffy 2004, a 1 gram capsule of MaxEPA contained 18% eicosapentaenoic acid (EPA; 180 mg) and 12% docosahexaenoic acid (DHA; 120 mg). Fish oil was also studied at doses of 20 grams of MaxEPA daily in divided doses for 3 months (Walton 1991). Fish oil was studied at the dose of 0.2 grams MaxEPA/kg body weight per day, corresponding to approximately 10 to 15 grams of MaxEPA fish oil capsules daily for 3 months (Westberg 1990). Fish oil was also studied at the dose of 4 capsules per day of Omacor that provided 1.8 grams of eicosapentaenoic acid (EPA) and 1.2 grams of docosahexaenoic acid (DHA) daily for 6 months (Wright 2008)

**G**  
Ginsenosides (oral) were studied at the dose of 50 mg GS capsules for 3 months (You 2010)

**H**  
Hydroxychloroquine (oral) was studied at doses of 100 mg to 400 mg per day for 6 months (Tsakonas 1991). Hydroxychloroquine was also studied at an oral dose of 200 mg twice per day (400 mg per day) for 12 months (Williams 1994). It was studied in pregnant women at an unspecified dosage during pregnancy until 3 months after delivery (Levy 2001). Hydroxychloroquine was also studied at doses of 100 mg twice per day for 3 months by Zhong 2013 compared with Zi Sen Qing herbal formula. Hydrochloroquine (oral) was studied at an unknown dose for 4 months (Yokogawa 2015)

**L**  
Lulizumab pegol (subcutaneous) was studied at doses of 1.25 mg, 5 mg, and 12.5 mg every other week, and 12.5 mg every week, for 6 months (Merrill 2018)

**M**  
Methotrexate (oral) was studied at doses of 15 mg to 20 mg per week for 6 months (Carneiro 1999), 10 mg each week for 6 months (Islam 2012), and 7.5 mg to 20 mg per week for 12 months (Fortin 2008)

**N**  
Nicardipine (oral) was studied (exact dosage not stated) 3 times a day for 1 month (Rupp 1987)

**R**  
Rituximab (intravenous) was studied at doses of 1 gram for 4 hours in Andrade-Ortega 2009 on days 1 and 15 of the study, and in Merrill 2010a at doses of 1 gram intravenous for a total of 2 doses given 14 days apart on days 1, 15, 168, or 182 of the study

**S**  
Sifalimub (intravenous) was studied at single doses of 0.3, 1, 3, 10, or 30 mg/kg for 12 months (Merrill 2011); at 14 doses of 0.3, 1, 3, or 10 mg/kg for 12.5 months (Petri 2013) and at 200 mg, 600 mg, and 1200 mg monthly doses for 52 weeks (12 months) (Khamashta 2016)

Sirukumab (intravenous) was studied at doses of 1 mg/kg, 4 mg/kg, and 10 mg/kg every 2 weeks for 4 infusions for 4.5 months by Szepietowski 2013
SM101 (intravenous), a human soluble non-glycosylated version of the Fcγ receptor IIb, was studied at doses of 6 mg/kg and 12 mg/kg intravenous infusion once per week for 4 weeks (Tillmanns 2014).

**T**

Tacrolimus (topical) ointment 0.1% was studied for twice-daily application for 2 months by Tzung 2007. Tacrolimus ointment 0.1% was also studied for twice-daily application for 3 months (Kuhn 2011).

Tabalumab (subcutaneous) was studied starting with a loading dose (240 mg) at week 0 and followed by 120 mg every 2 weeks (120 Q2W) for 12 months (Merrill 2016).

**U**

Ustekinumab (intravenous) was studied at the following loading doses based on weight (260 mg for 35 to 55 kg; 390 mg for 56 kg to 85 kg; 530 mg for 86 kg and greater) followed by doses of 90 mg ustekinumab (subcutaneous) every 8 weeks for 6 months (Van Vollenhoven 2018).

UVA-1 phototherapy at 60 kJ/m²/d was studied for 5 days per week for 3 weeks over a 6 week placebo cross-over study (McGrath 1996). In McGrath 1996, the irradiance at body surface was 87 W/m² with duration of 11.5 minutes, and lamps had a spectrum of 340 NM to 450 NM with peak at 365 NM. UVA-1 phototherapy was also studied at doses of 6 J/cm² 5 days per week for 3 weeks with a spectrum of 340 NM to 400 NM (Polderman 2001).

**Z**

Zileuton (oral) was studied at a dose of 600 mg 4 times daily for 2 months (Hackshaw 1995).

Zi Shen Qing herbal formula (an oral Chinese Traditional Medicine) taken as an infusion was studied at a dose of a sachet of 10 grams of granules in 200 mL of hot water twice daily for 3 months by Zhong 2013.

### Table 3. Interventions: dose and treatment course (Continued)

<table>
<thead>
<tr>
<th>Study categorisation</th>
<th>RCT?</th>
<th>SLE?</th>
<th>Cutaneous disease?</th>
</tr>
</thead>
<tbody>
<tr>
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<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Exclusion category 2</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Exclusion category 3</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Included</td>
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<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

### Table 4. Study exclusion criteria

<table>
<thead>
<tr>
<th>Study categorisation</th>
<th>RCT?</th>
<th>SLE?</th>
<th>Cutaneous disease?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exclusion category 1</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Exclusion category 2</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Exclusion category 3</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
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<tr>
<td>Included</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

### APPENDICES

**Appendix 1. CENTRAL (Cochrane Library) search strategy**

```
#1 MeSH descriptor Lupus Erythematosus, Cutaneous explode all trees
#2 MeSH descriptor Lupus Erythematosus, Discoid explode all trees
#3 MeSH descriptor Lupus Erythematosus, Systemic explode all trees
#4 (sle):ti,ab,kw
#5 (lupus)
#6 (#3 OR #4 OR #5)
#7 (cutaneous or skin or discoid)
#8 (#6 AND #7)
#9 (#1 OR #2 OR #8)
```
Appendix 2. MEDLINE (Ovid) search strategy

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab.
4. placebo.ab.
5. clinical trials as topic.sh.
6. randomly.ab.
7. trial.ti.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. exp animals/ not humans.sh.
10. 8 not 9
11. exp Lupus Erythematosus, Cutaneous/
12. exp Lupus Erythematosus, Discoid/
13. exp Lupus Erythematosus, Systemic/
14. sle.ti,ab.
15. lupus.mp.
16. 13 or 14 or 15
17. (cutaneous or skin or discoid).ti,ab.
18. 16 and 19
19. 11 or 12 or 18
20. 10 and 19


Appendix 3. Embase (Ovid) search strategy

1. random$.mp.
2. factorial$.mp.
3. (crossover$ or cross-over$).mp.
4. placebo$.mp. or PLACEBO/
5. (doub$ adj blind$).mp.
7. (assign$ or allocat$).mp.
8. volunteer$.mp. or VOLUNTEER/
9. Crossover Procedure/
10. Double Blind Procedure/
11. Randomized Controlled Trial/
12. Single Blind Procedure/
13. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14. exp skin lupus erythematosus/
15. exp discoid lupus erythematosus/
16. exp systemic lupus erythematosus/
18. sle.ti,ab.
19. lupus.ti,ab.
20. (cutaneous or skin or discoid).ti,ab.
21. 19 and 20
22. 14 or 15 or 21
23. 13 and 22


Appendix 4. Wiley online search

(systemic lupus erythematosus) AND (randomised controlled trial) AND (cutaneous)
Appendix 5. Virtual Health Library search strategy

'systemic lupus erythematosus' limited to "clinical_trials", "therapy" "humans"

HISTORY

Review first published: Issue 3, 2021

CONTRIBUTIONS OF AUTHORS

CWH was the main contact person with the editorial base.
CWH coordinated contributions from co-authors and wrote the final draft of the review.
CWH, CM, and CB screened papers against eligibility criteria.
CWH and CM obtained data on ongoing and unpublished studies.
CWH, CM, and CB appraised the quality of papers.
CWH and CM extracted data for the review and sought additional information about papers.
CWH and CB entered data into RevMan.
CWH and CB analysed and interpreted data.
CWH and CB worked on the methods, results, and discussion sections.
CWH drafted clinical sections of the background and responded to the clinical comments of referees.
CWH and CB responded to the methodological and statistics comments of referees.

Disclaimer

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DECLARATIONS OF INTEREST

Cora W Hannon: has declared that they have no conflict of interest.
Collette McCourt: reports consultancy fees from Janssen Pharmaceuticals (paid as a panel member to consult on a medical education steering committee [no relation to SLE/cutaneous lupus or medication]); Janssen manufacture STELARA, which is in phase 3 trials for SLE); personal payment. CM reports personal payment to prepare and deliver a lecture on biologic drugs in psoriasis from Janssen Pharmaceuticals. CM reports personal payment from AbbVie (virtual meeting sponsorship for American Academy of Dermatology [AAD] 2020, and meeting travel, accommodation, and attendance for AAD Florida 2017); Janssen Pharmaceuticals [meeting travel, accommodation, and attendance for European Academy of Dermatology and Venereology (EADV) Madrid 2019, AAD Washington 2019, and AAD San Diego 2018]; and Celgene (meeting travel, accommodation, and attendance for EADV Paris 2018). CM is currently a co-author of the British Association of Dermatologists Guideline Group for Cutaneous Lupus Erythematosus (from 2016 to present). This is not financially reimbursed. CM has received financial support for travel, accommodation, and conference attendance by Almirall and UCB; she has received consultancy and guest speaker honorarium from AbbVie and Janssen Pharmaceuticals. She reports that none of these are directly relevant to her role as co-author of this Cochrane Review.
Hermenio C Lima: reports consultancy fees from AbbVie (Abbott), Amgen, AstraZeneca, Bristol-Myers Squibb, Celgene, Dermira, Eli Lilly, Janssen, La Roche-Posay, Merck Sharp & Dohme, Novartis, Pfizer, Regeneron, and Sanofi; personal payment. HL reports grants/grants pending for clinical trials from AbbVie (Abbott), Amgen, AstraZeneca, Bristol-Myers Squibb, Celgene, Dermira, Eli Lilly, Janssen, La Roche-Posay, Merck Sharp & Dohme, Novartis, Pfizer, Regeneron, and Sanofi; personal payment. HL reports payment for lectures from AbbVie, Novartis, Sanofi, and Bausch Health; personal payment. HL reports payment for development of educational presentations from AbbVie (Abbott), Celgene, Janssen, Leo Pharmaceutics, Novartis, Sanofi, and Pediapharma. "I, Hermenio Lima, have received grants, speaker honorarium, consulting fees, and/or advisory boards from the companies listed above. None of these were related to this review or its subject."
Suphy Chen: has declared that they have no conflict of interest.
Cathy Bennett: reports consultancy fees paid to her own company, Systematic Research Ltd. "I am the proprietor of Systematic Research Ltd. My company received a consultancy fee to enable me to work as a co-author of this review. This included drafting text, extracting data, screening searches, co-ordinating work and producing reports and summaries. Since I am the sole employee of Systematic Research Ltd, the consultancy fees from this and other work are paid to me in the form of a salary and company dividends. I have business relationships with other clients who may provide consultancy fees for evidence-based medicine reviews, projects, and reports."

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Internal sources

- Harvard School of Public Health, USA
External sources

- National Institute for Health Research (NIHR), UK

  The NIHR, UK, is the largest single funder of the Cochrane Skin Group.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

There are some significant differences between the protocol and the review. In addition, we added the following clarifications when the protocol was not specific.

Changes to authors

Two new authors have been added to the review since the time the protocol was prepared (CM, CB), and Dr Carlos Cesar Cusmanich, an author on the protocol, did not co-author the review.

Three review authors (CWH, CM, CB) worked on selection of studies. Two review authors (CWH, CM) completed double data extraction and assessment of risk of bias. Agreement between review authors (CWH, CM, CB) was good.

Clarification of inclusion and exclusion criteria

We included participants of any age (including child-onset lupus), gender, or race who met the following criteria.

- Diagnosis of SLE based on criteria of the American College of Rheumatology for the classification of SLE (Cohen 1971 Hochberg 1997; Tan 1982), or of SLICC (Petri 2012), or based on Traditional Chinese Medicine (Li 2012).

  AND

- Clinical diagnosis of cutaneous lupus erythematosus.

  OR

- Diagnosis of Raynaud’s phenomenon based on 1971 criteria of the American College of Rheumatology (Cohen 1971).

We excluded:

- CLE patients without a diagnosis of SLE by ACR criteria (Cohen 1971; Hochberg 1997; Tan 1982), or by SLICC criteria (Petri 2012), or based on Traditional Chinese Medicine (Li 2012);

- SCLE patients without a diagnosis of SLE by ACR criteria (Cohen 1971; Hochberg 1997; Tan 1982), or by SLICC criteria (Petri 2012), or based on Traditional Chinese Medicine (Li 2012);

- patients with drug-induced lupus erythematosus; and

- patients with neonatal lupus erythematosus.

Clarification of outcomes

We clarified primary outcome measures as follows.

- Complete clinical response, defined as the percentage of participants with SLE with complete resolution of cutaneous disease based on the Gilliam 1981 classification (lupus-specific or lupus-non-specific) (i.e. “absence of (cutaneous) rash.”

  - Lupus-specific cutaneous disease was defined as:
    - malar rash (classic butterfly rash across cheeks) or other form of acute cutaneous lupus erythematosus (ACLE);
    - subacute cutaneous lupus erythematosus (SCLE); and
    - discoid rash (coin-shaped rash) or other form of chronic cutaneous lupus erythematosus (CCLE).

  ***We also accepted other less common manifestations of lupus as described in Description of the condition under “Other lupus-non-specific skin symptoms” (Chong 2019), as well as standardised definitions of lupus by Traditional Chinese Medicine, as acceptable equivalents (Li 2012).

- Partial clinical response, defined as the percentage of participants with at least 50% improvement in cutaneous disease (lupus-specific or lupus-non-specific).

We clarified secondary outcome measures as follows.
• Reduction (or change) in the number (or percentage) of SLE participants with clinical flares in cutaneous disease (lupus-specific or lupus-non-specific);
• Increase (or change) in time to flare in cutaneous disease (lupus-specific or lupus-non-specific) in SLE participants;
• Relapse rate (or percentage of SLE participants with relapse) in cutaneous disease (lupus-specific or lupus-non-specific) when medications are stopped or reduced;
• Skin-specific measures of SLE disease activity such as:
  o Cutaneous Lupus Disease Area and Severity Index (CLASI) (Albrecht 2007);
  o Integument domain of the Systemic Lupus Activity Measurement (SLAM) (American College of Rheumatology 2004);
  o Mucocutaneous domain of the British Isles Lupus Assessment Group (BILAG) disease activity index (Hay 1993);
  o Mucocutaneous domain of the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) (Bombardier 1992); and
  o Mucocutaneous domain of the SLE Responder Index (SRI) (Furie 2009); and
• Dermatology Quality of Life Measures (DLQI) in SLE patients.

We clarified adverse outcomes as follows.

• Severe events defined as:
  o discontinuation or withdrawal from the study; or
  o resulting in significant morbidity or mortality.
• Minor events were defined as:
  o bothersome to participants but not leading to withdrawal from the studies.

In addition, the primary outcome of complete clearance was chosen initially at the protocol stage as the most clinically relevant outcome to the clinician in practice due to its patient-centred-ness. However, relatively few studies have reported this primary outcome directly without the need for data transformation. More studies have reported the number or percentage of participants with the cutaneous lupus manifestation present at a given endpoint in the study. We have transformed data on the presence of skin lesions as follows: ‘present’ is equivalent to ‘NOT complete clearance’ or ‘NOT complete absence’. Similarly, ‘NOT present’ is equivalent to ‘complete clearance’ or ‘complete absence’. By knowing the total N in the group, we transformed available ‘presence’ data to the ‘complete clearance’ outcome as needed. The final review does encompass a broader scope of primary outcomes than was initially predicted in the protocol, especially in the semantic sense. This semantic broadening of the criteria does not lead to any methodological issues or serious protocol violations. Details about any data transformations that were performed on raw data from clinical trials are given in the appropriate sections.

We clarified which of the primary and secondary outcomes are lupus-specific and lupus-non-specific. Lupus-specific outcomes are defined as malar rash (classic butterfly rash across the cheeks) orACLE rash, SCLE rash, discoid rash, or CCLE rash; lupus-non-specific outcomes are defined as photosensitivity (excessive sensitivity to sunlight), mouth ulcers, alopecia, Raynaud’s attacks, vasculitis, or other (such as oedema). Rashes were categorised as lupus-specific or lupus-non-specific only if they were clearly described by study authors to meet the criteria of photosensitivity, alopecia, mouth ulcers, Raynaud’s, vasculitis, or other clearly defined non-specific categories.

Changes to search methods

We planned in our protocol to search Google Scholar, but our search retrieved over 2000 citations. As few seemed relevant for the effort required to review them, we excluded this source from searches undertaken for the final review.

We initially characterised Natural Medicine and Natural Standard as two separate databases. These web-based resources are better characterised as detailed online updated review articles containing useful references to controlled trials including RCTs. We conducted bibliographic searches on these two resources. As of 2016, they were combined into one website.

We stated in the protocol that we would search the Cochrane Musculoskeletal Register, AMED, and two additional trials registers; obtain unpublished trials via correspondence with study authors; examine key rheumatology and dermatology textbooks to identify additional trials; do a separate search for adverse events; and check drug reference books and databases for relevant adverse event information. We decided not to perform these tasks as they were later thought to be low yield for the effort required.

PubMed and Ovid HealthStar were searched in 2008 using the strategy presented in Appendix 2. Given that MEDLINE, PubMed, and OVID HealthStar are very similar in content, we used MEDLINE alone for all searches after 2008.

Clarification of data analysis and reporting methods

We clarified methods used to report and analyse omitted, missing, unavailable, or combined data.

If studies had subsets of data that could not be included in the meta-analysis, this information was reported narratively. For example, if full quantitative analysis was not possible because key quantitative information was omitted, missing, or unavailable (such as values of "n" or standard deviation), then available data were reported narratively along with an explanation of the additional information that would be needed for full analysis. Also, in some cases, data from SLE patients with cutaneous disease were combined with data from...
excluded groups. If it was not possible to fully separate the data, this was reported narratively, and the nature of the combined data was fully discussed. Any combined data were excluded from quantitative analysis and meta-analysis.

**Changes to analysis**

During the initial design of the protocol, it was proposed that differences between review authors would be calculated using Cohen’s kappa. However, after publication of the protocol, the lead author (CWH) found information in the Cochrane Style Manual indicating that this type of analysis is not typically conducted for Cochrane Reviews. In addition, upon examination of outcome data, the lead review author (CWH) concluded that a qualitative analysis would be challenging to carry out due to data format and would be of only questionable usefulness beyond the quantitative summary already performed.

There were no time-to-event or hazard ratio data to be analysed, so this was not included in the final review.

Unit of analysis issues were slightly different than anticipated in the protocol, and how these differences were handled is explained in the appropriate section. For example, we added details about the method used for analysis of cross-over studies and multi-arm studies.

We clarified in greater detail the subgroup analysis conducted to explore treatment effect size differences as follows: by more specific type of CLE (by lupus-specific (acute, subacute, or chronic) or lupus-non-specific subtypes (such as photosensitivity, oral ulcers, vasculitis, alopecia, or other)) and by timing of short-term (less than 12 months) and long-term (12 months or longer) treatment.

We had planned to obtain missing data directly from the original researchers; however, we did not do this.

We planned to calculate the number needed to treat for an additional harmful outcome; however, we have not done so yet, as we found insufficient data to report meaningful conclusions.

**INDEX TERMS**

**Medical Subject Headings (MeSH)**

Age of Onset; Azathioprine [therapeutic use]; Bias; Biological Factors [therapeutic use]; Chloroquine [adverse effects] [therapeutic use]; Cosmetic Techniques; Cyclosporine [therapeutic use]; Dermatologic Agents [adverse effects] [*therapeutic use]; Exanthema; Hydroxychloroquine [adverse effects] [therapeutic use]; Immunosuppressive Agents [*therapeutic use]; Lupus Erythematosus, Cutaneous [classification] [diagnosis] [therapy]; Lupus Erythematosus, Systemic [classification] [complications] [*therapy]; Medicine, Chinese Traditional; Methotrexate [adverse effects] [therapeutic use]; Placebos [therapeutic use]; Quality of Life; Randomized Controlled Trials as Topic; Skin Diseases [etiology] [*therapy]; Symptom Flare Up

**MeSH check words**

Female; Humans; Male