Association of antieosinophil therapy with decreased body mass index in patients with severe asthma: A preliminary retrospective analysis

Merin Kuruvilla, Emory University
Meera Patrawala, Emory University
Joshua Levy, Emory University
Jennifer Shih, Emory University
Frances Lee, Emory University

Journal Title: Annals of Allergy, Asthma & Immunology
Volume: Volume 122, Number 6
Publisher: Elsevier Science Inc. | 2019-06-01, Pages 649-650
Type of Work: Article | Post-print: After Peer Review
Publisher DOI: 10.1016/j.anai.2019.03.031
Permanent URL: https://pid.emory.edu/ark:/25593/vnhnb

Final published version: http://dx.doi.org/10.1016/j.anai.2019.03.031

Copyright information:

© 2019 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc. All rights reserved.

This is an Open Access work distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License (https://creativecommons.org/licenses/by-nc-nd/4.0/).

Accessed December 3, 2022 9:47 AM EST
Association of antieosinophil therapy with decreased body mass index in patients with severe asthma: A preliminary retrospective analysis

Merin Kuruvilla, MD, Meera Patrawala, MD, Joshua M. Levy, MD, Jennifer Shih, MD, and Frances E. Lee, MD

Division of Pulmonary, Allergy, and Critical Care, Emory University School of Medicine, Atlanta, Georgia

Department of Otolaryngology–Head and Neck Surgery, Emory University School of Medicine, Atlanta, Georgia

The type 2 high endotype of asthma with adult onset is often characterized by severe, persistent, steroid-refractory eosinophilic inflammation. Interleukin 5 (IL-5) is a pivotal cytokine for eosinophil survival. The amelioration of eosinophilic inflammation through anti—IL-5 therapies (mepolizumab, reslizumab, and ben-ralizumab) reduces exacerbations and improves control is and well tolerated overall.

Eosinophils have recently been implicated in adipose tissue (AT) homeostasis. A threshold number of eosinophils appear critical for weight loss and glucose tolerance. Wu et al. first reported the residence of eosinophils in AT with weight gain and insulin resistance in an eosinophil-deficient murine model, in contrast to hypereosinophilic mice that demonstrated weight loss and improved glucose tolerance. An accumulating body of evidence has since supported these findings and implicated eosinophils in browning of AT, which decreases weight while enhancing insulin sensitivity. Eosinophils induce polarization of AT macrophages into M2-like macrophages, which enhances catecholamine import into the local environment thereby improving glucose tolerance. Obese individuals have fewer eosinophils and type 2 cytokines in their AT.

The literature suggests a critical mass of eosinophils is necessary for AT homeostasis, but increasing eosinophil levels alone does not appear sufficient to confer metabolic benefits. The effect of depleting eosinophils on individual weight is a potentially important area of AT biology. Although patients with asthma treated with anti—IL-5 therapies are theoretically an ideal population for evaluation, in reality multiple confounding factors may preclude this population from evaluation. These factors include concomitant use of steroids in patients with severe asthma as well as the underlying association of tissue eosinophilia with obesity in severe asthma. In a cohort of patients with severe asthma stratified by weight, those with a higher body mass index (BMI; calculated as weight in kilograms divided by square of height in meters) had higher sputum IL-5 and eosinophils in lung tissue but not in the lumen. The

Disclosures: None.
redistribution of eosinophils from AT to lungs has been postulated to determine disease severity.\textsuperscript{6}

This retrospective analysis used a cohort of adults with asthma who were receiving anti—IL-5 therapies between January 2016 and September 2018 at a single institution. Inclusion criteria were adult-onset asthma with severe persistent disease and treatment with anti—IL-5 therapy for 6 consecutive months. The primary objective was to determine the long-term effect of antieosinophil agents in patients with severe asthma on BMI trajectories.

During the study period, 58 patients were prescribed anti—IL-5 agents. Of these patients, 51 (15 [29.4%] male; mean [SD] age, 56.7 [13.4] years) met the inclusion criteria and were included in the analysis. A total of 29 patients were prescribed mepolizumab, 16 reslizumab, and 6 benralizumab. All 3 groups were broadly similar without a significant difference in baseline BMI. The median age of asthma diagnosis was 38.5 years (range, 18–62 years). Peak documented blood eosinophil counts ranged from 110 to 1360/μL (mean, 550/μL). The large variance in eosinophils may be secondary to the fact that 19 patients were treated with maintenance oral corticosteroids (OCSs), with a median maximal daily prednisone dose of 20 mg (range, 5–80 mg). A total of 23 patients had a baseline BMI greater than 30 before anti—IL-5 therapy. Similar frequency of maintenance OCSs was found between obese and nonobese cohorts: 11 of 20 obese patients (55%) and 9 of 23 nonobese patients (39%) (\( P = .30 \)).

Table 1 stratifies weight change by baseline BMI and anti—IL-5 agent. The mean BMI change during 6 months among the entire cohort showed a decrease by 1 point (\( P = .03 \)) and was within 1 point of each other for all 3 agents used: −1.3 for mepolizumab, −1.1 for reslizumab, and 0.3 among benralizumab users. The largest apparent effect was among mepolizumab users; however, this group also accounted for the most patients. There was also significant variability in BMI fluctuations among the mepolizumab subgroup mepolizumab (range, −5.9 to 5.4; \( P = .03 \)), which was not observed for the other 2 agents (−3.0 to 1.6 for reslizumab [\( P = .34 \)] and −2.5 to 3.3 for benralizumab [\( P = .71 \)]). Obese patients with a baseline BMI greater than 30 had a mean BMI decrease of 1.7 across all 3 agents, which was significant compared with the remainder of the cohort (\( P = .04 \)). When analyzed within the obese category, the mean BMI change for each agent was not significantly different.

An unexpected role for eosinophils has been in AT homeostasis, potentially influencing whole-body metabolic fitness. Murine models have attempted the use of recombinant IL-5 in genetically modified mice that lack eosinophils to ameliorate obesity.\textsuperscript{7} Conversely, eosinophil depletion may predispose individuals to obesity. However, none of the eosinophil depletion models have been conducted in nonmodified mice. Homeostatic eosinophils have different response patterns and functions, depending on their localization; however, AT eosinophils depend on IL-5 for survival. Theoretically, patients with severe asthma receiving anti—IL-5 —targeted therapy provide an ideal population to study the effect of eosinophil depletion. We were unable to find any data evaluating the effect of anti—IL-5 mediated eosinophil depletion on BMI.
We observed a statistically significant decrease in BMI across all 3 anti—IL-5 therapies at 6 months; however, the clinical relevance is unclear in the setting of marginal change and low sample size. This effect appears to have been most pronounced in those with a baseline BMI greater than 30 and may have been expected based on maintenance OCS wean rates as well as decrease in acute flares that required systemic steroids.

The major weakness of this study was the retrospective design and consequent limitations in parameters assessed. Our study is not randomized or placebo controlled and is confounded by prior and intercurrent steroid prescriptions. We did not measure other parameters, such as body fat or glucose tolerance. Our lack of a more substantial association between eosinophil depletion and BMI may also have been attributable to relatively small sample size. In addition, the effects of anti—IL-5 agents on tissue eosinophils are more prominent than in peripheral blood, which may be explained by restricted tissue access and contribution of other mediators to eosinophil survival. There may also be a distinct resident homeostatic population of tissue eosinophils within the visceral fat, whereas bone marrow—derived eosinophils are important during inflammation.

In conclusion, anti—IL-5 therapy was associated with mild but significant overall decrease in BMI for the study duration. Higher baseline BMI was associated with more pronounced weight loss. Although the exact biological effects of eosinophil depletion cannot be deduced from this limited retrospective series, it appears that any obesity-promoting effect of IL-5 blockade is offset by improvement in asthma and presumable decrease in systemic steroid burden. Given the emerging paradigms associating eosinophils with AT function and the potential effects of eosinophil- depleting therapies, future larger studies should clarify the true implications of eosinophil depletion. We hope our preliminary data will stimulate prospective trials to elucidate this association.

References

Table 1

Stratification of BMI Change by Anti–IL-5 Agent

<table>
<thead>
<tr>
<th>Type of medication and obesity category</th>
<th>Change in BMI (pretreatment vs posttreatment)</th>
<th>Mean (SD)</th>
<th>Median</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entire cohort (N = 51)</td>
<td>−1 (3.4)</td>
<td>−1</td>
<td>.03</td>
<td></td>
</tr>
<tr>
<td>Nonobese BMI (n = 28)</td>
<td>−0.6 (2.9)</td>
<td>−0.2</td>
<td>.0</td>
<td></td>
</tr>
<tr>
<td>Obese BMI (n = 23)</td>
<td>−1.7 (3.8)</td>
<td>−2.3</td>
<td>.047</td>
<td></td>
</tr>
<tr>
<td>Mepolizumab (n = 29)</td>
<td>−1.3 (3.0)</td>
<td>−1.7</td>
<td>.0</td>
<td></td>
</tr>
<tr>
<td>Nonobese BMI (n = 14)</td>
<td>−1.4 (2.7)</td>
<td>−1.8</td>
<td>.06</td>
<td></td>
</tr>
<tr>
<td>Obese BMI (n = 15)</td>
<td>−1.2 (3.4)</td>
<td>−1.7</td>
<td>.18</td>
<td></td>
</tr>
<tr>
<td>Reslizumab (n = 16)</td>
<td>−1.1 (4.3)</td>
<td>−0.4</td>
<td>.34</td>
<td></td>
</tr>
<tr>
<td>Nonobese BMI (n = 9)</td>
<td>0.7 (3.4)</td>
<td>2.4</td>
<td>.55</td>
<td></td>
</tr>
<tr>
<td>Obese BMI (n = 7)</td>
<td>−3.3 (4.4)</td>
<td>−3.9</td>
<td>.09</td>
<td></td>
</tr>
<tr>
<td>Benralizumab (n = 6)</td>
<td>0.3 (2.1)</td>
<td>0</td>
<td>NC</td>
<td></td>
</tr>
<tr>
<td>Nonobese BMI (n = 5)</td>
<td>−0.3 (1.7)</td>
<td>−0.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obese BMI (n = 1)</td>
<td>3.3</td>
<td>3.3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; IL, interleukin; NC, statistical test not conducted (because of small sample size).