Methylprednisolone for Coronavirus Disease 2019 (COVID-19): Was Benjamin Rush Prescient?

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To excel in the practice of medicine is to master the skill of swimming through waves of uncertainty. When treating a patient how certain is the diagnosis? If the diagnosis is certain, is there a treatment that is better than all others? If there is a proven treatment, was it studied in this population, with this patient’s comorbidities? Add to these typical factors a unique viral pandemic, and the size and frequency of the uncertainty waves become magnified. Physicians in 2020 must decide whether to try treatments that may have been tested against other viral pathogens, including the other two coronaviruses that have appeared in the two decades. Until clinical trials of therapies for Covid-19 are complete, navigating these choices feels somewhat like swimming in the dark.

The first light to break through this darkness was the results of the Adaptive Covid-19 Treatment Trial (ACTT-1).(1) This trial tested remdesivir, an antiviral that was shown to be beneficial in a non-human primate model of MERS-CoV. In ACTT-1 the median time to recovery was 11 days in those who received remdesivir versus 15 days in those who received placebo. There was no mortality benefit in the remdesivir arm. Subgroup analysis indicated that the greatest clinical benefit was in those who required supplemental oxygen but who did not require high flow oxygen, or non-invasive or invasive mechanical ventilation. Based on these results the National Institutes of Health (NIH) Covid-19 Treatment Guidelines panel recommended that remdesivir be prioritized to treat patients who require oxygen but who do not require more aggressive respiratory support.(2)

There is a long history of clinical trials of corticosteroid treatment producing conflicting results for efficacy in the setting of severe pneumonia, and in particular for influenza. In the two earlier outbreaks of coronavirus infection there was a delayed viral clearance in patients with MERS who were treated with corticosteroids, and insufficient evidence to determine whether corticosteroids were beneficial or harmful in SARS.(3,4) Based on this limited data, corticosteroids were frequently employed empirically for Covid-19, and many retrospective case series of this strategy have been published. The results have been variable, with a recent meta-analysis showing a potential increased risk of mortality with corticosteroid treatment in severe coronavirus related disease.(5)

The first published randomized trial of corticosteroid treatment for Covid-19 was the RECOVERY study.(6) In this randomized, open label study 6,425 subjects were assigned to receive up to 10 days of dexamethasone or non-corticosteroid containing treatment. Mortality at Day 28 was 25.7% in the non-corticosteroid treated group and 22.9% in the dexamethasone group. For those who received mechanical ventilation the non-corticosteroid treated group had a 41.4% mortality and the treated group a 29.3% mortality. Therefore, based on the results of this single randomized trial, the NIH Guidelines Panel recommended that subjects with COVID-19 who are either mechanically ventilated
or receiving supplemental oxygen in the hospital should be treated with dexamethasone 6 mg per day for up to 10 days.

Since dexamethasone may have adverse effects such as worsening of diabetes, neuropsychiatric illnesses, and reactivation of latent infections, there are reasons to be cautious about basing practice on a single open label study. In this issue of *Clinical Infectious Diseases* the first double-blind, randomized, placebo-controlled trial of corticosteroid treatment for Covid-19, the METCOVID study, is presented.(7) This study differs in many aspects, other than its blinded nature, from the RECOVERY trial. For example, the population is approximately 1/10 the size that in the RECOVERY trial, the study was done at a single institution, and dexamethasone was replaced by methylprednisolone. The dose of methylprednisolone is, for a 70 kg person, the equivalent dose of dexamethasone used in RECOVERY given intravenously twice daily. The duration of corticosteroid treatment, five days, was also half the maximum duration as that in the RECOVERY study. The results of METCOVID showed no benefit of methylprednisolone treatment to prevent the primary objective of 28 day mortality. In addition, in the two sub groups that were shown to have the greatest benefit in the RECOVERY trial, METCOVID showed no evidence of a benefit of methylprednisolone.

How are we to reconcile the different outcomes between RECOVERY and METCOVID? In the METCOVID study the average age was 55, which is a decade less than the average age in the RECOVERY study. In addition, the time between diagnosis and randomization was 13 days in the METCOVID study, versus 8-9 days in the RECOVERY study. The percentage of persons who were intubated in the METCOVID study was more than twice the percentage who were intubated in the RECOVERY study, and there was a correspondingly lower percentage of patients in the METCOVID study who did not require supplemental oxygen treatment. In addition, patients in METCOVID universally received azithromycin versus only about 25% in RECOVERY. Other secondary conditions such as diabetes appear to be roughly the same between the two studies. Therefore, in the METCOVID study patients were treated later in the course of the infection, were more severely ill at the start of corticosteroid treatment, were given a different corticosteroid for a shorter course, and were treated with different concomitant medications.

So should we discard the results of one or the other of these trials? The survival benefit in the RECOVERY study, which included a much larger population, indicates that up to 10 days of dexamethasone treatment is beneficial for hospitalized patients requiring supplemental oxygen. The technically superior METCOVID study indicates that corticosteroid treatment is not beneficial if treatment is delayed until about 2 weeks into illness, and that shorter course methylprednisolone may not be equivalent to dexamethasone. Physicians treating Covid-19 infected patients will therefore have to carefully practice timing remedies. A five day course of remdesivir should be prioritized for those requiring oxygen but not needing other respiratory support. Dexamethasone, if it is to be used, should be started by about day 8 of illness. Many patients will therefore receive treatment with both remdesivir and dexamethasone, a combination that was not tested in the ACTT-1, RECOVERY, or METCOVID trials. Deep, dark waves of uncertainty indeed!
The author has no potential conflicts to disclose.
References