Brief on “Dexamethasone in Hospitalized Patients with COVID-19 – Preliminary Report”

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This article is a preliminary report from the larger RECOVERY clinical trial (Randomized Evaluation of COVid-19 thERapY) in the United Kingdom investigating whether treatment with either lopinavir-ritonavir, hydroxychloroquine, corticosteroids, azithromycin, convalescent plasma or tocilizumab prevents death in patients with COVID-19. The low-dose dexamethasone arm was halted based on the trial Steering Committee assessment that a sufficient number of patients were enrolled to establish whether or not the drug had meaningful benefit. We previously reported on this preprint that has since been published in the New England Journal of Medicine, July 17th, 2020. Based on this preliminary data, the National Health Service in the UK included dexamethasone in national recommendations and NIH added dexamethasone to the COVID-19 Treatment Guidelines.

In brief, 2,104 patients randomly allocated to receive usual care plus dexamethasone 6 mg once daily (PO or IV) for up to 10 days (or discharge if sooner, median treatment was 7 days) were compared to 4,321 patients concurrently allocated to usual care. Overall, 22.9% of the patients receiving dexamethasone and 25.7% allocated to the usual care died within 28 days (age-adjusted rate ratio [RR] 0.83; 95% CI 0.75-0.93; p<0.001). The largest benefit was seen in the patients receiving invasive mechanical ventilation, where mortality in the dexamethasone group was 29.3% vs 41.4% in the usual care group (RR 0.64, 95% CI 0.51-0.81). There was also a benefit in the group receiving oxygen supplementation (which included non-invasive ventilation) compared to the usual care group where the mortality in the dexamethasone group was 23.3% vs 26.2% (RR 0.82, 95% CI 0.72-0.94). This benefit was not seen in the patients who were not requiring oxygen supplementation.

It is important to consider the following information when evaluating how to apply the findings of this study moving forward:

First, patients were excluded from the trial if the treating clinician considered dexamethasone to be “definitely indicated” or “definitely contraindicated.” Further demographic details are not available regarding these excluded patients. Therefore, before starting dexamethasone, clinicians should review the patient’s medical history and assess the potential risks and benefits of administering corticosteroids to the patient.

A second note is that 83% of the mechanical ventilation group were under 70 years old, compared to 55% in the oxygen only group and 43% in the no oxygen group. Another way to describe the difference, patients in the mechanical ventilation group were, on average, ten years younger. In the supplemental material, the investigators also showed an analysis of the effect of dexamethasone on mortality by age. There was a significant benefit in those patients <70 years (RR 0.64; 95% CI 0.53-0.78) but not in those ≥70 years. While the primary analysis between respiratory support groups was age-adjusted, these age effects are important to note before we generalize to our population in the ICU in the US. We know that age ≥65 is a risk factor for more severe disease. As highlighted in the NIH treatment guidelines, complete analysis is needed to determine the effect of dexamethasone in particular age groups.

Reviewed on 8/7/20.
Thirdly, we know there are two clinical phases of COVID-19, the first primarily driven by the viral infection and the second driven by the host immune response (see Figure). It is in this second phase where we think immunomodulators such as corticosteroids may have a beneficial impact. In this study they showed a significant benefit when the steroids were given >7 days since symptom onset (RR 0.69, 95% CI 0.59-0.80) and no benefit if given earlier, reinforcing this idea that immunomodulators may have greatest benefit in this second phase of the illness. The mechanical ventilation group also had symptoms for seven days longer than the no oxygen group, with dexamethasone started at a median of 13 days from symptom onset. These findings should help us as we think about timing and patient-related factors for immunomodulator administration in COVID.

Recently, the NIH COVID-19 Treatment guidelines updated their recommendations to allow alternative corticosteroids, such as prednisone, methylprednisolone, or hydrocortisone, in situations where dexamethasone may not be available. These guidelines also comment on the safety of dexamethasone in pregnant women with COVID-19, given the potential benefit of decreased maternal mortality and the low risk of fetal adverse effects for this short course. Based on preliminary data available, there is clearly a role for dexamethasone in some COVID-19 infected patients. As the data are further analyzed and reviewed, details will emerge regarding the ideal patient population and timing of administration. The ongoing work will also provide information on toxicities.

References:

**Effect of Dexamethasone in Hospitalized Patients**

Clinical Trials.gov: NCT04381936

**NIH COVID-19 Treatment Guidelines**