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Steroids in COVID-19: An overview

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ABSTRACT

Most antiviral or immunomodulatory therapies investigated for use in patients with COVID-19 have failed to show any mortality benefit. Similar to the previous pandemics caused by respiratory viruses, the role and benefit of corticosteroids has been under debate in COVID-19–related pulmonary disease. In this consult, we discuss the evidence regarding the efficacy of corticosteroid use in hospitalized patients with COVID-19, including data from the first randomized controlled trial on this subject.

INTRODUCTION

As of July 19, 2020, coronavirus disease 2019 (COVID-19)—caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)—has infected more than 14 million people worldwide, with more than 600,000 deaths globally.[1] Several pharmacologic therapies have been investigated in randomized trials but did not improve mortality. These include hydroxychloroquine (with or without azithromycin), antivirals such as remdesivir, and IL-6 inhibitors such as tocilizumab.

The effect of corticosteroids in COVID-19 has been of great interest, based on evidence from prior pandemics caused by respiratory viruses and their association with the acute respiratory distress syndrome (ARDS). In this article, we discuss the evidence on the efficacy of corticosteroids among patients hospitalized with COVID-19, including recently released data from the first randomized controlled trial on this subject.[2]

STEROIDS IN ARDS AND VIRAL RESPIRATORY ILLNESS

Conflicting data exist regarding the efficacy of corticosteroid therapy in patients with ARDS. A significant challenge in interpreting the studies has been the marked heterogeneity of underlying processes causing ARDS, steroid dosing and duration, and patient selection. More recent evidence suggests that steroid therapy decreases mortality and the duration of intermittent mandatory ventilation (IMV) in patients with ARDS.[3-5]

Much of the initial guidance issued by medical societies concerning steroid use in COVID-19 was extrapolated from studies that used steroids to treat severe acute respiratory syndrome (due to SARS-CoV-1)[6] and Middle East respiratory syndrome (due to MERS-CoV).[7] In both diseases, steroids failed to consistently show any benefit and were associated with delayed viral clearance.[6,7] However, a study of patients infected with SARS-CoV-2 showed no effect of methylprednisolone on viral clearance using pharyngeal polymerase chain reaction testing.[8] This difference can possibly be explained by delayed administration of steroids in this study, as patients were hospitalized at a median 7 days after symptom onset.

Previous trials and meta-analysis have shown that low-dose corticosteroids are well tolerated; common adverse effects include hyperglycemia and hypernatremia.[4,9,10] Dexamethasone has minimal mineralocorticoid activity, which could be potentially beneficial in limiting sodium and fluid retention—a key problem in ARDS.

RETROSPECTIVE STUDIES OF STEROIDS IN COVID-19

Several retrospective analyses have been published on the use of corticosteroids in patients with COVID-19:

- A cohort study by Wu et al. found that among a subgroup of 84 patients with COVID-19 and ARDS in Wuhan, China, treatment with methylprednisolone was associated with a lower risk of death (hazard ratio [HR] 0.38, 95% confidence interval [CI], 0.20 – 0.72).[11]

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- Another study from Wuhan in patients requiring supplemental oxygen showed a significant reduction in the duration of oxygen among those treated with methylprednisolone (8 days vs 14 days).[12]
- Cruz et al., in their study of patients in Spain with ARDS or hyperinflammatory syndrome (based on cytokine elevation profile), found that treatment with methylprednisolone was associated with decreased mortality (odds ratio 0.51, 95% CI, 0.27 – 0.96).[13] Of note, the median time to steroid administration from symptom onset was 10 days.
- An Italian study reported a reduction in the composite end-point of 28-day mortality, intensive care unit transfer, or need for IMV among patients with ARDS treated with methylprednisolone.[14]
- A before-after study in the United States demonstrated that among patients requiring supplemental oxygen or IMV, a course of methylprednisolone (0.5 – 1 mg/kg/day for 3 days) was associated with decreased risk of a similar composite end-point compared with the standard of care.[15]

In contrast to above studies, a retrospective study from Wuhan by Yuan et al. demonstrated that in patients with non-severe COVID-19 (resting O2 saturation > 93%, PaO2/FiO2 > 300, respiratory rate < 30), treatment with corticosteroids was associated with a higher risk of progression of severity and prolonged hospital stay, although the results were not statistically significanct.[16] Finally, it is unclear if there is an increased risk of superinfection in patients with COVID-19 receiving steroids as is seen in influenza pneumonia.[17]

THE RECOVERY TRIAL

The Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial is a multicenter, randomized, controlled, open-label, adaptive platform trial for evaluating potential treatments among hospitalized patients with COVID-19 in the UK. Preliminary findings showed that dexamethasone 6 mg once daily (intravenous or by mouth) for up to 10 days reduced 28-day mortality (rate ratio [RR] 0.83, 95% CI 0.75 – 0.93) in hospitalized patients with COVID-19.[2] The maximum effect was observed in the sub-group of patients on IMV at randomization (RR 0.64, 95% CI 0.51 – 0.81), with benefit also seen among those receiving supplemental oxygen without IMV at randomization (RR 0.82, 95% CI 0.72 – 0.94). Those who were treated more than 7 days after symptom onset were also less likely to die (RR 0.69, 95% CI 0.59 – 0.80). Importantly, there was no benefit in patients who did not require any oxygen at randomization, and there was a signal towards increased mortality in this group of patients (RR 1.19, 95% CI 0.91 – 1.55).

Dexamethasone was also associated with a higher likelihood of discharge at 28 days among those receiving oxygen or IMV. Lastly, among those receiving oxygen, the risk of progression to IMV or death was lower in the dexamethasone group (RR 0.87, 95% CI, 0.79 – 0.96). Neither of these benefits were observed among the patients who were not receiving supplemental oxygen at randomization.

These findings could be explained by the proposed temporal pathophysiology of COVID-19.[18] During the first few days of illness, the viral replicative phase is predominant, and peak viral shedding occurs early in the illness and declines thereafter as compared to SARS-CoV-1 where peak viral replication occurs in week 2.[19] In COVID-19, usually around the second week, the host inflammatory response is the predominant driver of symptoms resulting in ARDS, cytokine storm, coagulation disorders, and multi-organ failure.[20,21] Thus, in our opinion, steroids given during the suspected hyperinflammatory state, when viral replication has decreased, may be optimal. This is a plausible pathophysiological explanation for the benefit of steroids for SARS-CoV-2 infection in the RECOVERY trial compared with other respiratory viruses in previous studies.

Those enrolled in RECOVERY trial were similar to patients described among various series of COVID-19 hospitalizations from different countries.[13-15] The mean age of patients enrolled in the study was 66 years, with 56% patients having at least one major comorbidity, including 21% of patients with preexisting chronic lung disease and 24% with diabetes. Sixty percent of patients were receiving supplemental oxygen at randomization and 16% were on IMV or extracorporeal membrane oxygenation. These characteristics make the study findings reasonably generalizable. However, there are some limitations of the RECOVERY trial that must be noted: it is a non-blinded study introducing the possibility of bias, and about 17% of patients were excluded due to the non-availability of dexamethasone at the treating facility or an absolute indication or contraindication to dexamethasone as decided by the treating physician.

Overall, the findings from the RECOVERY trial are similar to the retrospective studies of steroids in COVID-19 mentioned above in terms of effect size,

TABLE 1

Society recommendations on the use of corticosteroids in patients with COVID-19–related respiratory illness (as of 7/19/2020)

Surviving Sepsis Campaign[22] (3/28/2020

- In mechanically ventilated adults with COVID-19 and respiratory failure (without ARDS), we suggest against the routine use of systemic corticosteroids. (Weak recommendation, low-quality of evidence)
- In mechanically ventilated adults with COVID-19 and ARDS, we suggest using systemic corticosteroids over not using corticosteroids. (Weak recommendation, low-quality of evidence)

American Thoracic Society COVID-19: Interim Guidance[23] (4/3/2020)

- For hospitalized patients with COVID-19 who have evidence of pneumonia, we make no suggestion either for or against treatment with systemic corticosteroids: 15% for intervention; 18% no suggestion; 67% against intervention. (Evidence not available)

Infectious Diseases Society of America[24] (6/25/2020)

- Among hospitalized patients with severe[a] COVID-19, suggests glucocorticoid rather than no glucocorticoids. (Conditional recommendation, moderate certainty of evidence)
- Among hospitalized patients with COVID-19 without hypoxemia requiring supplemental oxygen, suggests against the use of glucocorticoid. (Conditional recommendation, low certainty of evidence)

[a]Severe illness is defined as patients with 94% or less SpO_2 on room air, and those who require supplemental oxygen, mechanical ventilation, or ECMO

National Institutes of Health[25] (6/25/2020)

- The COVID-19 Treatment Guidelines Panel recommends using dexamethasone (at a dose of 6 mg per day for up to 10 days) for the treatment of COVID-19 in patients who are mechanically ventilated (Strong recommendation) and in patients who require supplemental oxygen but who are not mechanically ventilated (Moderate recommendation).
- The Panel recommends against using dexamethasone for the treatment of COVID-19 in patients who do not require supplemental oxygen. (Strong recommendation)

World Health Organization Interim Guidance[26] (5/27/2020)

- Recommends against the routine use of systemic corticosteroids for treatment of viral pneumonia. (Evidence not available)

ARDS = acute respiratory syndrome; ECMO = extracorporeal membrane oxygenation; SpO_2 = peripheral oxygen saturation

benefit among sicker patients, and lack of benefit—and potential for harm—among patients who are less sick or very early in the disease course (e.g. not requiring supplemental oxygen). **Table 1**.[22-26] summarizes current society recommendations for the use of steroids in patients with COVID-19.

CONCLUSION

Hypoxemic COVID-19 patients should receive dexamethasone based on current evidence, given the reduced risk of death and increased likelihood of hospital discharge. Corticosteroid use is also associated with reduced length of oxygen therapy and risk of progression to invasive mechanical ventilation among those on supplemental oxygen. There is no benefit of using dexamethasone among patients who do not require supplemental oxygen, and it may even lead to harm. Further studies are needed to evaluate the impact of corticosteroids within different subtypes of COVID-19–associated ARDS, risk of superinfections, and long-term outcomes.

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