EDITOREAL

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Corticosteroids for non-severe COVID-19 infections? Too early to conclude

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Corticosteroids are potent anti-inflammatory agents that can mitigate the risk of acute respiratory distress syndrome (ARDS) and extrapulmonary organ dysfunctions. However, contrary to bacterial ARDS or septic shock, corticosteroids were associated with increased mortality in influenza-associated ARDS and more complications or delayed viral clearance in previous coronavirus outbreaks (i.e., severe acute respiratory syndrome [SARS] and middle east respiratory syndrome [MERS]). Accordingly, during the early period of coronavirus disease 2019 (COVID-19) outbreak, the World Health Organization (WHO) suggested against the routine use of corticosteroids, and the Survival Sepsis Campaign guidelines group gave a weak recommendation for the use of corticosteroids only in mechanically ventilated patients with ARDS (not those without ARDS). However, recently, the Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial, the world's largest randomized controlled trial (RCT) of COVID-19 treatments, showed beneficial effects from low dose dexamethasone therapy in COVID-19 [1]. Dexamethasone therapy resulted in lower 28-day mortality in patients who required oxygen supplementation or mechanical ventilation. Interestingly, the benefit was shown in those aged < 70 years (not in those ≥ 70 years) and those with symptoms > 7 days prior to randomization (not in those with symptoms ≤ 7 days). Despite several methodological problems (e.g., open-label trial, withdrawals, and crossovers), this study added some important information to the current knowledge of the role of corticosteroids in COVID-19 patients with ARDS. First, when deciding to start corticosteroids, careful reconsideration should be given to older patients. This might be the case given the higher viral loads or delayed viral clearance in older patients (i.e., immune senescence). Second, timing of corticosteroid administration may be critical. In previous studies of SARS or MERS, failure to show mortality benefits from corticosteroids might have been associated with its initiation time when viral shedding was still increasing or has not been on decline. Third, lower dose corticosteroids may strike a balance between anti-inflammatory and immunosuppressive action. Especially, based on the results of the RECOVERY trial, a low-dose dexamethasone, with no mineralocorticoid effects, may provide the greatest benefit [1]. Fourth, however, corticosteroids could be risky, or at least not beneficial, for mild COVID-19 infections. In the RECOVERY trial, an increasing tendency for 28-day mortality was found among patients who did not require respiratory supports.

Issak and Amin [2] published interesting results from their open label RCT. In their study, methylprednisolone therapy was associated with lower rates of 28-day mortality,

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need for oxygen supplement, and need for hospitalization. The methylprednisolone dose used was 30 mg/day for moderate cases (i.e., positive computed tomography [CT] findings and SpO_2 > 92%) and 15 mg/day for mild cases (i.e., mild symptoms, normal CT findings, and SpO_2 > 92%). Contrary to other retrospective studies of non-severe COVID-19 pneumonia where corticosteroid therapy was associated with development of more severe disease [3,4], their positive results could appeal to the proponents of corticosteroids. However, some caution should be exercised when interpreting the results. Despite the relatively large sample size, the treatment was not blinded (i.e., no placebo arm), and contrary to other large-sized multicenter trials, there was no mention of any programs about data audit or safety. Besides, many important clinical data were missing in their study; that is, data on vaccination history, time intervals from symptom onset to randomization (or to corticosteroid therapy), various clinical symptoms, detailed comorbidities, organ dysfunctions (e.g., sequential organ failure score) at randomization, and duration of corticosteroids were absent. Because these factors could be significantly associated with treatment outcomes, some readers may cast doubt on the study's reliability. Similarly, in a study by Almas et al. [5], corticosteroids were associated with lower mortality in non-severe COVID-19 infections. However, this was also a small-sized, retrospective study.

Recently, the WHO living guidelines, as well as the Surviving Sepsis Campaign group, gave a strong recommendation for the use of corticosteroids for patients with severe or critical COVID-19 [6,7]. In a recent meta-analysis by the Cochrane Collaboration group where 10 RCTs were included, systemic corticosteroids were also effective in reducing mortality [8]. It seems that the results of the RECOVERY study had a great deal of influence on the decisions or recommendations of the recent guidelines or meta-analyses. On contrary, for non-severe COVID-19, the WHO living guidelines suggested not to use systemic corticosteroids (a conditional recommendation) [6], and the National Institutes of Health (NIH) guidelines also indicated that there were no sufficient data to support the use of systemic corticosteroids in those mild patients [9]. Besides the two aforementioned retrospective studies showing negative results [3,4], the WHO panel members noted a tendency for higher mortality rate with corticosteroids in non-severe COVID-19 infections from their systematic review (using the WHO SOLIDARITY trial) [6]. Although current evidence cannot rule out a potential benefit in this population, the safety and efficacy of using systemic corticosteroids have not been well established. Another problem for corticosteroids in non-hospitalized patients is that adverse events may be difficult to detect and monitor in outpatient settings.

Inhaled corticosteroids are well established agents for the treatment of inflammatory airway diseases, and some agents inhibited viral replication of SARS-CoV-2 and down-regulated the expression of the viral entry receptor angiotensin-converting enzyme-2 (ACE-2) *in vitro* and *in vivo* (animal) models. Unfortunately, however, several RCTs of the efficacy of inhaled corticosteroids (budesonide or ciclesonide) in non-hospitalized patients with COVID-19 have shown inconsistent results in terms of hospitalization or time to symptom resolution [10,11]. Although a recent meta-analysis by the Cochrane Collaboration group demonstrated potential benefit of inhaled corticosteroids in improving outcomes, evidence is still insufficient to make any clear decisions.

Taken together, based on the available evidence, systemic corticosteroids, especially low dose dexamethasone, seem to be best suited for severe COVID-19 infections. Although hydrocortisone or methylprednisolone can be used, the evidence supporting their use is not as strong as the evidence supporting the use of dexamethasone in severe COVID-19 infections. Timing of corticosteroids also seems to be important, but symptom onset is frequently obscure, and a collinearity between timing and severity must be considered [6]. However, at present, it seems too early to recommend corticosteroids for non-severe (or non-hospitalized) COVID-19 infections. Some physicians may claim that corticosteroids are not associated with increased risk of adverse effects except for hyperglycemia or hypernatremia and that they already have wide experience on the use of the agents. However, until more evidence is provided, the routine use of corticosteroids should be discouraged in non-severe COVID-19 infections.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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