Intensive Care Med (2021) 47:355–356
https://doi.org/10.1007/s00134-020-06330-w

CORRESPONDENCE

Ten reasons why corticosteroid therapy reduces mortality in severe COVID-19

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We have read with interest the recent article by Arabi et al. [1] published in Intensive Care Medicine where the authors provided 10 reasons why corticosteroid therapy reduces mortality in severe coronavirus disease 2019 (COVID-19). The authors stated that the best available evidence to support the use of corticosteroids in COVID-19 is based on the results of the RECOVERY trial [2] and the WHO REACT prospective meta-analysis [3]. They mentioned the DEXA-ARDS trial [4] where dexamethasone, (20 mg and 10 mg for 5 days each) markedly decreased 60-day mortality in mechanically ventilated patients with persistent moderate-to-severe acute respiratory distress syndrome (ARDS).

Several comments can be made regarding these statements. In the RECOVERY trial [2], patients allocated to dexamethasone received 6 mg/day for 10 days. It is unclear why a dose of 6 mg was selected. RECOVERY [2] investigators postulated that higher doses could be harmful. A subgroup analysis of the DEXA-ARDS trial [4] revealed (data unpublished) that 62 patients had H1N1-ARDS and the number of deaths at 60-days was lower in the dexamethasone arm [3/31 (9.7%) vs 8/31 (25.8%)]. Although this difference was not statistically significant ($p = 0.182$) probably due to reduced statistical power, it suggests that higher doses of dexamethasone could be more beneficial in COVID-19-related acute respiratory distress syndrome (ARDS).

In the WHO REACT meta-analysis [3], data from 7 trials were pooled. Five trials reported mortality at 28 days, one trial at 21 days, and one trial at 30 days. The corticosteroid groups included dexamethasone at low and high doses, low-dose hydrocortisone, and high-dose methylprednisolone. The larger number of patients in the meta-analysis were those mechanically ventilated in the RECOVERY trial [2] (59.1% patients). Of note, the other trials also included patients who did not receive mechanical ventilation. Due to these and other limitations recognized by the authors, it is difficult to draw strong conclusions for COVID-19-related ARDS.

However, we postulate that the most important weakness of available evidence is that the primary outcome in the RECOVERY trial [2] and in the WHO REACT meta-analysis [3] was 28-day mortality. Assessing 28-day mortality may not be the optimal outcome in a trial. Since patients with severe COVID-19 often require prolonged intensive care unit (ICU) and hospital stays (beyond day-28), especially when receiving mechanical ventilation, it is unfortunate that long-term mortality (ICU, 60-day, or hospital mortality) was not reported in those two major studies. Recent data on corticosteroid therapy in the management of COVID-19 are also important, but far to represent a "milestone" precluding definitive conclusions. More studies are needed to evaluate issues such as type of corticosteroid, timing of initiation [5], optimum dose, duration of treatment, and "mandatory" long-term mortality. Although the preliminary results of the RECOVERY trial [2] represented a gigantic optimism for this pandemic, it is time to know their final, long-term outcome data. Beneficial effects of 6 mg/day of dexamethasone at 28-day might not translate into longer-term benefit.

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Compliance with ethical standards

Conflicts of interest
The authors have disclosed that they do not have any potential conflicts of interest.

Publisher's Note

Accepted: 2 December 2020
Published online: 2 January 2021

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