Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Steroids for sepsis and ARDS: this eternal controversy remains with COVID-19

In the past 50 years, the potential benefit of corticosteroids in treating sepsis or acute respiratory distress syndrome (ARDS) has been evaluated in many randomised controlled trials (RCTs). Corticosteroids have contradictory effects on mortality, leading to a profound and still active controversy. Low doses of corticosteroids have been shown to decrease mortality from septic shock in patients who also receive mineralocorticoids.[1] However, the effect of corticosteroids has been negative in other studies.[2] In one RCT,[3] corticosteroids were efficacious for ARDS of various origin. This modest hope for corticosteroids has been heightened from findings in patients with severe COVID-19.

Most of the initial therapeutic studies of corticosteroids for COVID-19 have been of very poor quality. The RECOVERY trial was one of the most robust studies.[4] In this large, open-labelled RCT, 2104 patients treated with corticosteroids were compared with 4321 patients receiving standard therapy. The study used different compounds, at different time courses, and in patients with COVID-19 symptoms of varying severity. Corticosteroids (dexamethasone, 6 mg per day) caused a moderate but significant 11% reduction in mortality. Mortality was significantly reduced in patients who were mechanically ventilated (29%) or received oxygen (11%), but not in patients without any respiratory failure. These results were considered credible proof of corticosteroid efficacy, particularly by WHO, which announced prematurely that corticosteroid was the gold standard for treating severe COVID-19.[5] However, the methodology in this study was very questionable, in particular (but not only) because no severity markers were recorded, making highly questionable the comparability of the two treatment groups at the time of study inclusion.

Results of four additional studies have since been published,[6–9] one of which was a meta-analysis promoted by WHO.[6] In this meta-analysis of pooled data from seven studies, corticosteroids were associated with a decrease in mortality from severe COVID-19. However, this effect disappeared when data from the RECOVERY trial[4] were excluded from the meta-analysis, suggesting an overweight of these data in the meta-analysis. The substantial heterogeneity within the remaining six trials limits the validity of the interpretation of the meta-analysis results. Furthermore, in the RECOVERY trial,[4] various compounds and dosages of corticosteroids were used.

Among the three other studies,[7–9] the CAPE COVID study[7] was stopped after publication of the RECOVERY trial[4] results. In CAPE COVID,[7] a well designed study that enrolled 149 patients with severe COVID-19, no benefit of corticosteroids was found. In the REMAP trial,[8] which included 903 treated patients, hydrocortisone (40 mg intravenous every 6 h) significantly reduced mortality from severe COVID-19 by 26%. Although not double-blinded, REMAP was the first robust trial to show a very clear-cut positive effect on mortality. The CoDEX trial,[9] with an excellent methodology, included 299 patients with mild or severe ARDS. Corticosteroids significantly increased ventilator-free days during the first 28 days, but there was no benefit on 28-day mortality or length of stay in intensive care units, both tested as secondary endpoints. Finally, in Metcovid,[10] a large phase 2b double-blind RCT with 416 patients with COVID-19, corticosteroids had no effect on mortality.

The above scientific limits and the contradicting results of the various studies ought to impose caution before adoption of corticosteroids as the master drug to save lives from COVID-19 (appendix). Although the medical community and citizens worldwide are impatient for efficient therapies, enthusiasm after the first positive results should be tempered until studies with a better design are completed, demonstrating clearly the efficacy of corticosteroids. We do not think there is any equipoise or ethical problem in planning further double-blind RCTs.

We declare no competing interests.

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See **Online** for appendix

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