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.

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CHEST

Editor's Note: Authors are invited to respond to Correspondence that cites their previously published work. Those responses appear after the related letter. In cases where there is no response, the author of the original article declined to respond or did not reply to our invitation.

Caution When Comparing the Impact of Corticosteroids in COVID-19

To the Editor:

Meta-analyses have the advantage of providing a summary effect estimate when there are a number of methodologically homogenous studies that examine the same intervention in the same study populations. Forty-five days after the publication of the Recovery trial,[1] a meta-analysis of eight randomized trials (7,184 participants) was published,[2] and a corresponding WHO guideline panel subsequently recommended systemic corticosteroids in patients with severe and critical COVID-19 (strong recommendation, based on moderate certainty evidence).[3]

In contrast, the systematic review and metanalysis published in *CHEST* (March 2021) by Cano et al[4] includes only one randomized controlled trial[1] and 72 observational studies, analyzed together, with a search end date of July 22, 2020. Of the observational studies, only four reported outcomes of propensity score-matched populations. Even with adjustment or propensity-matching, observational studies are subjected to residual cofounding (imbalances in baseline characteristics and post-baseline time-dependent patient differences that influence the decision to prescribe corticosteroids) and other sources of bias. Given this, the Cochrane handbook specifically discourages meta-analysts from pooling randomized controlled trials and observational studies together given, the method heterogeneity. Based on their analysis, the authors of this review concluded that "the potential role for corticosteroids as an immunomodulatory agent in COVID-19 needs to be explored further in clinical trials."

The authors also combined studies without a predefined treatment protocol with preregistered trials that used an established and explicit corticosteroid protocol. Unsurprisingly, Cano et al[4] were unable to generate conclusions around optimal dosing, indication, and timing of corticosteroids across studies.

Nevertheless, despite the limitations in their analysis, we agree with Cano et al[4] that there is a need for further studies that will examine corticosteroids in COVID-19. Specifically, more data are needed that evaluate the impact of type of corticosteroid, timing of initiation, dose, mode of administration, duration, and dose tapering on patient-important outcomes.[5] Further exploration of laboratory parameters of oxygenation and inflammation and how they may be incorporated into corticosteroid treatment protocols would also be important. The MEDEAS trial (Methylprednisolone vs. Dexamethasone in COVID-19 Pneumonia trial, ClinicalTrials.gov Identifier: NCT04636671) will address this issue by comparing the RECOVERY randomized controlled trial protocol to a protocol similar to the one investigated in an Italian prospective observational study.[6]

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Response

To the Editor:

We appreciate the interest in our article[1] by Confalonieri et al. The authors emphasize caution when combining retrospective and prospective studies into a meta-analytic synthesis. We agree with the authors that confounders often hinder observational studies; however, we also have firsthand experience during this pandemic that high-quality evidence often lags the clinical demand to treat patients.

The role of corticosteroids was challenged early in the pandemic, and several randomized controlled trials were set up to explore clinically relevant outcomes. However, rigorously controlled studies demand a longer timeline from planning to results than observational reports; thus, retrospective studies represent a precious source of information during a global health crisis when high-quality data is forthcoming.

Although the Cochrane handbook discourages the combination of prospective and retrospective studies, it also leaves the decision to include nonrandomized studies based on study designs and the availability of studies when such controlled studies do not exist.[2] When we performed our synthesis, there was no such information from controlled studies, there was only one exception, which left retrospective data as the most important source of information to shed light on a critical question.

Meta-analyses combining controlled and observational studies are commonplace in contemporary literature. The potential advantages have been well-recognized from pragmatic and methodologic perspectives.[3] As measured by the effect size estimates, the efficacy of several interventions that were reported from controlled trials has been found similar to effect size estimates that were generated from observational studies with rigorous methodologic assessments. Whether these assumptions hold true to corticosteroids in COVID-19 is yet unknown.

In our study, the mortality benefit that was observed in critically ill patients remains the most clinically relevant and statically valid result ($P = .0006$; $I^2 = 26\%$, low heterogeneity). Moreover, our findings in this population were corroborated by results of a prospective meta-analysis[4] (which was published when our manuscript was under revision) that represents the highest-quality evidence on this topic at present.

At this point in the pandemic, corticosteroids has been embraced as the intervention of choice for the most ill COVID-19 cases[5] and persists as the frontrunner intervention with chances to improve survival. Caution should be exercised continuously when one is interpreting clinical data as the literature continues to expand. This growth is evident today (April 9, 2021) when a repeat PubMed database search, using the original search terms, returns 2,885 references, which represents an opportunity to revise this topic further and address unanswered questions.

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