Higher, but Not Too High, Dose Is Only One Determinant of Corticosteroid Treatment Success in Severe COVID-19

To the Editor:

We read with interest the study from Pitre and colleagues, who systematically reviewed 20 randomized controlled trials published through August 2022, concluding that higher doses of corticosteroids (CSs) probably reduce mortality (relative risk, 0.92; 95% confidence interval [CI], 0.85–0.98) and the need for mechanical ventilation (relative risk, 0.91; 95% CI, 0.87–1.03) compared with lower doses in severe-to-critical coronavirus disease (COVID-19), without significantly impacting either the duration of hospitalization or the incidence of nosocomial infections (1).

These results are mostly aligned with those of our recent randomized controlled trial investigating methylprednisolone 80 mg as a continuous daily infusion for 8 days followed by slow tapering, versus dexamethasone 6 mg daily for 10 days in a similar population (2). However, their results need to be interpreted comprehensively before being transferred into clinical practice, as possible misinterpretations may lead to hazardous conclusions.

First, the authors defined "higher" and "lower" doses in a comparative fashion, referring to 12 mg of dexamethasone equivalent daily for 10 days as the former and to 6 mg of dexamethasone equivalent daily for 10 days as the latter. However, both these dosages and administration schedules fall within the prolonged, paraphysiological, low-to-intermediate dose (i.e., ⩽1 mg of prednisone equivalent/kg/d for at least 8–10 d) CS treatment conception that has shown the greatest efficacy in acute respiratory distress syndrome (ARDS) (3). On the contrary, short courses (⩽3 d) of truly high doses (10–30 mg of prednisone equivalent/kg/d) of CSs have proven detrimental in both septic shock and ARDS—including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-related ARDS—because of inflammatory rebound after discontinuation (4).

Second, there is now substantial evidence of a proportional benefit of CSs for patients requiring higher-intensity respiratory support modalities (i.e., mechanical ventilation and high-flow nasal cannula) rather than lower-intensity ones (i.e., low-flow oxygen therapy), as opposed to the increased mortality observed among patients not requiring any respiratory support (5). Therefore, we highlight that the findings of this study can only be generalized to patients affected by moderate-to-severe COVID-19 and not by COVID-19 of any severity.

Third, different patients receiving the same CS protocol may experience different disease progression and outcomes. This provides a rationale for dose and duration adjustments based on clinical and laboratory responses, as a higher dose may overcome a decreased sensitivity to CSs in the most critically ill patients (3). Indeed, both traditional and Bayesian analyses conducted within the COVID STEROID 2 trial suggest that 12 mg of dexamethasone/d might benefit patients who require high levels of respiratory support more than 6 mg of dexamethasone/d (6). Therefore, some clinicians might choose to titrate CS treatment, increasing its dose and/or duration when patients require endotracheal intubation as a result of noninvasive respiratory support strategy failure. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

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