Glucocorticoid Dose in COVID-19
Lessons for Clinical Trials During a Pandemic
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The ongoing COVID-19 pandemic necessitates an urgent need for rapid and yet methodologically rigorous clinical trials to identify the optimal combination of safe and effective treatments as well as rapid identification of candidate treatments that are harmful or ineffective. This need is particularly acute for treatments suitable for use in resource-limited settings, which require interventions that are widely available and inexpensive.

To date, few COVID-19 treatments have been shown to be effective in improving outcomes. Systemic glucocorticoids have been demonstrated to improve survival when administered to patients who are moderately or severely ill, and are recommended in both the World Health Organization (WHO) guidance for the clinical management of COVID-19 and the National Institutes of Health COVID-19 treatment guidelines.

Although the WHO guidance does not recommend a particular glucocorticoid dose, the National Institutes of Health guidelines recommend 6 mg of dexamethasone once daily for 10 days or until hospital discharge for hospitalized adults requiring supplemental oxygen or mechanical ventilation.

The prospective meta-analysis of systemic glucocorticoids from the WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group found that administration of systemic glucocorticoids was associated with lower 28-day all-cause mortality. The included trials, which enrolled patients who were severely ill and reported a broadly consistent treatment effect, evaluated daily glucocorticoid equivalent doses that ranged from 6 mg to 20 mg of dexamethasone. The treatment effects were similar with low-dose vs high-dose regimens. No determination could be made regarding dosage, and further evidence is needed to answer the question of optimal glucocorticoid dose. A more recent Cochrane review found no completed studies enabling a comparison of different doses of glucocorticoids for COVID-19.

In this issue of JAMA, the COVID STEROID 2 Trial Group reports the results of an international, multicenter randomized clinical trial that compared 2 alternative doses of glucocorticoids in critically ill patients with COVID-19. The investigators randomly assigned 1000 patients with confirmed SARS-CoV-2 infection who were receiving supplemental oxygen at a flow rate of at least 10 L/min or mechanical ventilation to receive, as blinded study medication, either 12 mg/d of dexamethasone or 6 mg/d of dexamethasone. The median duration of prior treatment with dexamethasone was 1 day. The primary outcome was the number of days alive without life support (defined as invasive mechanical ventilation, circulatory support, or kidney replacement therapy) censored at 28 days following randomization. The study had 85% power to demonstrate a relative reduction of 15% in 28-day mortality (from 30.0% to 25.5%) combined with a reduction of 10% in time receiving life support.

The median number of days alive without life support was 22.0 days (IQR, 6-28 days) in the 12 mg of dexamethasone group and 20.5 days (IQR, 4-28 days) in the 6 mg of dexamethasone group (adjusted mean difference, 1.3 days [95% CI, 0.2-6.0 days]; P = .07). Mortality at 28 days after randomization was 27.1% for patients in the 12-mg/d group and 32.3% for patients in the 6-mg/d group. This mortality difference, if real, would be of substantial clinical importance, but there is a possibility that the difference may have arisen due to chance (adjusted relative risk, 0.86 [99% CI, 0.68-1.08]). Importantly, the occurrence of serious adverse events was not different between the 2 doses, with serious adverse events reported in 11.3% of patients receiving 12 mg/d and in 13.4% of those receiving 6 mg/d.

Other immune modulators, including IL-6 receptor antagonists, such as tocilizumab and sarilumab, and the Janus kinase inhibitor baricitinib, have been demonstrated to improve outcomes when administered to patients with COVID-19 who are moderately or severely ill. There is evidence that the beneficial effects of IL-6 receptor antagonists are additive to glucocorticoids, at least for lower doses of glucocorticoids (ie, 6-7.5 mg/d of dexamethasone). The reported improvement in outcomes for patients treated with baricitinib was in a study in which a high proportion of patients received glucocorticoids. In the current trial by the COVID STEROID 2 Trial Group, the 12-mg/d dose of dexamethasone significantly increased the number of days alive without life support to day 28 in the prespecified subgroup of patients who were not receiving IL-6 receptor antagonists at baseline, comprising about 90% of patients.

How should clinicians interpret the study by the COVID STEROID 2 Trial Group? The results are supportive of improved outcomes with 12 mg/d of dexamethasone, but not definitive, and do not satisfy the usual criteria to support change in practice. However, clinicians will wonder if there is a risk of a type II error, with insufficient power to confirm a real difference of major importance to clinical practice and public health. In this regard, the consequences of a type II error are of greater importance than a type I error, particularly in resource-limited settings with widespread availability of glucocorticoids and limited access to other immune modulators. Additional trials, which are underway (NCT04381936, NCT04726098, NCT04663555), are needed to clarify this important clinical question, with the results ideally combined in a prospective meta-analysis.
Research published over the course of the pandemic provides lessons for trialists who seek to identify the optimal combination of effective treatments for patients with COVID-19. First, unlike the report by the COVID STEROID 2 Trial Group, much of the research conducted during the pandemic has been inefficient at a time when there is an urgent need for rapid generation of clinically useful evidence. Platform and adaptive trials have demonstrated their value to quickly generate results during the pandemic, 1,9,13-15 but this time-critical evidence was needed even more expeditiously. It is estimated that less than 5% of patients diagnosed with COVID-19 have been enrolled in a randomized clinical trial, 16 although countries with well-developed infrastructure for clinical research have done notably better. 17

Second, trials that use traditional frequentist statistics must prespecify the size of the treatment effect that the trial is designed to detect. This creates the possibility of a trial that reports a difference, in a favorable direction, that is not statistically significant but may still represent a clinically meaningful difference. This has not been problematic for trials with access to large sample sizes that have conducted frequent interim analyses, such as the Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial. However, in the absence of large sample sizes, the use of frequentist statistics leads to answering a narrow question regarding the prespecified size of the treatment effect, not whether there is a potentially useful treatment effect. An alternative approach, using bayesian statistics, is to prespecify the statistical confidence necessary to draw inference that a treatment is effective or futile, recruit to that level of confidence using regular adaptive analyses, and report the result as rapidly as possible. 9,13,14,18

Third, ideally, trials are multifactorial so that inference can be drawn regarding combinations of therapies. If 12 mg/d of dexamethasone (or some other dose) is demonstrated to be more effective than a lower dose, this raises the possibility that benefit from IL-6 receptor antagonists, or baricitinib, may be less substantial when coadministered with this optimal dose of glucocorticoids. Such a finding would be of major importance for clinical care and public health, especially in resource-limited settings without access to more expensive therapies. An understanding of treatment-treatment interactions is best achieved using a multifactorial design in which exposure to different treatment domains is evaluated within a single (bayesian) statistical model.

The report by the COVID STEROID 2 Trial Group6 in this issue of JAMA adds important data to the evidence base of therapies for COVID-19, based on a well-executed trial conducted in multiple locations during the pandemic. The results raise the strong possibility that treatment outcomes for COVID-19 may be improved further by the use of higher doses of glucocorticoids; however, additional trials are needed to confirm this and determine what dose is optimal.

ARTICLE INFORMATION

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