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Steroid Stewardship in COVID-19

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ABSTRACT

Corticosteroids have transformed clinical practice in COVID-19 following the publication of the results of the RECOVERY trial. Despite available evidence, there is considerable disparity among physicians in the dose and duration of steroids they prescribe. Steroids have a fragile affiliation in clinical practice with the benefits frequently accompanied by distressing adverse effects. An institutional steroid stewardship program can help all physicians take advantage of what is the only proven therapy of benefit in this global crisis while avoiding its overuse and the numerous adverse effects associated with it.

Keywords: COVID-19; corticosteroids; RECOVERY trial; steroid stewardship

INTRODUCTION

SARS-CoV-2 induces a dysregulated host response with widespread immune-inflammatory derangements.[1] The occurrence of an apparent cytokine storm is peculiar with respect to the scale of the response and the mediators involved.[2] Many drugs have been repurposed from previous similar viral illnesses and other medications such as Interleukin (IL) - 6 inhibitors and Janus Kinase (JAK) inhibitors have been employed assuming their potential benefit with progressive understanding of the pathophysiological mechanisms involved.[3]

AVAILABLE EVIDENCE

Corticosteroids seemed a reasonable therapeutic candidate in view of the multisystem inflammatory response induced by SARS-CoV-2. The RECOVERY trial in hospitalized patients with COVID-19, established that a moderated dose Dexamethasone (6 mg daily for 10 days) reduced mortality in patients with respiratory failure who required supplemental oxygen or mechanical ventilation.[4] However, mortality was increased in patients not receiving oxygen therapy. This landmark trial has subsequently changed clinical practice.

The CODEX randomized controlled trial from Brazil, with a substantially lower sample size, used a higher dose of Dexamethasone as compared to the RECOVERY trial: 20 mg daily for 5 days followed by 10 mg daily for 5 days or until discharge from the ICU.[5] Although the results elicited significantly higher ventilator-free days at 28 days in the Dexamethasone group, all-cause mortality and ICU-free days were not different as compared to placebo.

The REMAP-CAP trial assessed intravenous Hydrocortisone in patients with severe COVID-19 in comparison to standard care to identify 21-day organ support free days.[6] The trial ceased recruitment following the publication of the RECOVERY results, due to a lack of equipoise. Hydrocortisone was either administered as a fixed dose of 50 mg 6 hourly for 7 days or for shock-reversal in patients requiring vasopressors due to COVID-19 at a dose of 50 mg 6 hourly whilst in shock. Termination of the trial earlier than what was planned made it impossible to reach pre-defined statistical triggers and thus arrive at definitive conclusions. Bayesian results from the data collected revealed fixed-dose Hydrocortisone and Hydrocortisone for shock reversal resulted in 93% and 80% probabilities of superiority in terms of improvement in organ support free days at 21 days.

The CAPE COVID trial was a multicenter, randomized, placebo controlled trial from 9 ICUs in France where 149 adult patients with COVID-19 with acute respiratory failure were given a continuous infusion of low dose Hydrocortisone (200 mg/day for 7 days followed by 100mg/day for 4 days and 50 mg/day for 3 days) compared to placebo.[7] Much like the CODEX trial, there was no statistically significant difference in mortality. Considering the trend towards benefit, a much larger trail may have found statistical significance.

Investigators have evaluated the use of both low-dose as well as high dose Methylprednisolone. Jeronimo et al. administered 0.5 mg/kg of Methylprednisolone twice daily for 5 days in patients with clinical or radiological

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suspicion of COVID-19 with SpO2 ≤ 94% in room air or requiring respiratory assistance with supplemental oxygen or invasive mechanical ventilation.[8] In the modified intention to treat analysis, no difference in the 28-day mortality was seen in between the intervention group and the placebo group.

American investigators gave high dose of Methylprednisolone (range 120-180 mg) daily for a median duration of 5 days in 153 patients as compared to 294 who did not receive corticosteroids in a randomized trial among patients with COVID-19 pneumonia with severe respiratory distress with SpO2 <93% in room air and requiring high flow oxygen or non-invasive ventilation.[9] There was no difference in mortality compared to the control group at 28 days, but the study did show a lower requirement for mechanical ventilation in the group of patients receiving high dose Methylprednisolone. Investigators have also attempted to see the effect of pulse-dose Methylprednisolone of 250 mg/day for 3 days. They compared it to standard care in a small number of patients with primary outcomes of time to discharge or death. A definitive conclusion would be unwise due to the limited sample size with the endpoint a composite of a positive and a negative event.[10]

A meta-analysis of 7 randomized controlled trials of corticosteroid treatment among 1703 critically ill patients with COVID-19 assessed the different types and doses of corticosteroids.[11] The RECOVERY trial contributed to 57% of the weightage and it concluded that as compared to usual care of placebo, systemic corticosteroids resulted in a lower 28-day all-cause mortality.

STEROID DOSAGE

The considerable variation among clinicians with regards to the dose, type and duration of steroid treatment for COVID-19 is not surprising. Personal discretion and anecdotal escapades have found preference over the evidence based practice with detrimental consequences. It seems prudent that if a higher steroid dose is utilized initially, it should be tapered to 6 mg/day Dexamethasone as soon as the patient has improved. Corticosteroid pulses are known to downregulate immune cell activation and proinflammatory cytokine production, leading to reduced expression of adhesion molecules and neutrophil migration. The supra-pharmacological dosages offer benefit of an attenuated cumulative toxicity as compared to prolonged treatment at lower dosages. Arguments against higher steroid dosing have surfaced from the fact that 6 mg of Dexamethasone performed well to improve outcome in mechanically ventilated patients.[4]

TIMING OF STEROIDS

The timing of steroid administration should be the onset of clinical hypoxemia coinciding with the exaggerated inflammatory response following the initial phase of viral replication.[4] The conundrum to initiate steroids early, prior to oxygen requirement, on the basis of worsening clinical symptoms has not been studied well. Early during the course of infection, activation of the immune system may be helpful in controlling viral replication. At a later time, when hypoxemia develops, however, an excess inflammation is detrimental. It is for this reason that steroid initiation is best done when the patient requires oxygen which is an indicator of worsening hypoxemia. This is supported by the RECOVERY trial which raises the possibility of harm when steroids are administered to patients not receiving oxygen.[12]

CHOICE OF STEROID MOLECULE

Preference of a particular steroid molecule does not seem of importance if they are given in adequate dosages since the benefits are due to a class effect.[11] The RECOVERY trial advocates the use of 6 mg of Dexamethasone per day or its equivalent which equates to Prednisone 40 mg, Methylprednisolone 32 mg and Hydrocortisone 160 mg.[4] Hydrocortisone is commonly used in the management of septic shock in patients with COVID-19. Dexamethasone is peculiar in that it lacks mineralocorticoid activity as compared to the other molecules, leading to minimal sodium and water retention.[13]

DOSE OF STEROIDS

Higher doses of steroids may be used by clinicians when they assume an ongoing cytokine storm, and during unavailability of agents like Tocilizumab. This should be discouraged in light of paucity of data demonstrating any such benefit and the escalated risk of adverse effects. The cytokine storm is a natural event in COVID-19 and is much less robust than in non-COVID-19 ARDS, sepsis, trauma and cardiac arrest.[1] For patients who do not improve as expected despite completion of 10 days of steroids, there is no clear verdict on the benefits of a protracted duration of treatment. While it may be beneficial to prevent post-disease fibrosis, it can lead to inadvertent adverse effects. The procoagulant effects of steroids and their propensity to exacerbate the long COVID syndrome by causing myopathy, neuromuscular weakness and psychiatric symptoms cannot be discounted.[14]

IMMUNOMODULATION, NOT IMMUNOSUPPRESSION

A complex array of maladaptive immune-inflammatory mechanisms underlie endothelial and epithelial perturbations manifesting as multiorgan dysfunction and thromboembolic events in COVID-19.[1] The use of steroids is for immunomodulation rather than for immunosuppression. Although unsubstantiated, the latter may be the result of a higher steroid dose culminating into an increased risk of secondary infection, reactivation of a latent infection and metabolic disturbances.

ADVERSE EFFECTS

Hyperglycemia is ubiquitous among the majority receiving steroids while new onset diabetes mellitus has been attributed to COVID-19.[15] Secondary infections, elevated blood pressure, myopathy, peripheral edema, adrenal insufficiency, psychiatric effects and avascular necrosis are well-known complications. COVID-19 associated mucormycosis is closely associated with uncontrolled hyperglycemia secondary to the inappropriate use of corticosteroids. An epidemiological study from India studying COVID-19 associated mucormycosis found inappropriate steroid dosing (dexamethasone-equivalent doses >6 mg/day for >10 days) in 97/146 (66.4%) patients who received steroid as a part of the treatment regimen.[16]

QUESTIONS UNANSWERED

Future studies need to address the optimal duration of corticosteroids. The possibility of the use of biomarkers to help decide on the initiation or discontinuation of steroids needs to be explored. The nature and severity of the adverse effects posed by the use of steroids has yet to be evaluated systematically. Whether the combination of steroids with other agents such as antiviral agents or other immunomodulators is beneficial is still illusive.

STEROID STEWARDSHIP

With the publication of sufficiently powered studies that promulgate the use of steroids in COVID-19, their use in clinical practice has proved to be a cornerstone of current treatment guidelines. However undue use in patients not requiring oxygen, unjustified dosage regimens, household prescription and prolonged treatment without scientific benefit have led to unprecedented consequences.

A steroid stewardship program would be a step in the right direction to appropriately offer this invaluable treatment to those who require it while exploring explanations to unanswered questions through research.

This program should not be just limited to medical centers but to the broader community to prevent irrational use of steroids. Patients on steroids need to be educated on the importance of adherence to the prescribed regimen. The brunt of the responsibility lies on the prescribing physician who should be mindful of evidence-based practice while keeping a keen interest in avoiding harmful effects.

At an institutional level, a multidisciplinary interprofessional 'steroid committee' should formulate guidelines based on available scientific data. A physician should take the lead of the committee and the treating staff including both physicians and nurses should take responsibility of adhering to the guidelines. Any digression in terms of dosage, should require approval and if justified, the benefits should be documented while adverse effects monitored closely. Quarterly audits can ensure adherence to guidelines, address shortcomings, identify areas for research and continued improvement in clinical practices while appraising new evidence.

Antimicrobial and fluid stewardship programs have shown clinical benefits in a multitude of settings.[17,18] A similar set of co-ordinated interventions can be adopted to assess and improve rational use of steroids in COVID-19 by identifying proper indications, dosing and duration to confer a benefit similar to these other stewardships. The major objective of the steroid stewardship would be to achieve best clinical outcomes while minimizing adverse events.

To the best of our knowledge, steroid stewardship programs have been established as a part of management of asthma in the western world.[19] In our literature search, we did not come across a similar undertaking with relation to steroid use for other conditions.

WAY FORWARD

The concept of less is more has yet again come to the fore. With steroids recognized at the core of treatment in COVID-19, it seems appropriate that a steroid stewardship program is established at the community as well as the institutional level to exploit its benefits while limiting harm.

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