

CORTICOSTEROIDS

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Introduction

Corticosteroids are anti-inflammatory medications which have been used as an alternative therapy for cytokine storm syndrome (CSS).

Given a patient with a potentially lethal state of hyperinflammation, it may seem that immunosuppression with corticosteroids may be beneficial. Such was the rationale for the use of steroids in the SARS-CoV outbreak in 2003 as well as for MERS-CoV in 2018.^{1,2,3}

Mechanism of Action

Its mechanism of action is the inhibition of the transcription of many cytokine genes including IL-1, IL-6 and TNF. These inflammatory mediators are integral in the cascade of cytokine storm syndrome which has been observed in some fatal cases of COVID-19 infections. Corticosteroids suppress hyperinflammation and eliminate activated immune cells and infected antigen presenting cells (APCs), cytotoxic lymphocytes (CTLs) and histiocytes. Through its mechanism of action it is regarded as a standard therapy in addressing CSS as well as in the treatment of Macrophage Activation Syndrome (MAS) secondary to rheumatic diseases.^{4,5} However, its role in viral infections particularly, COVID-19 remains obscure.

Clinical Studies

According to the WHO Interim Guidance dated March 13, 2020, systemic glucocorticoids should not be given routinely to treat viral pneumonia outside of clinical trials. This is due to the lack of evidence of effectiveness and possible harm.⁶ The recommendation is based on previous a systematic review of observational studies on SARS where corticosteroids administered to patients with SARS provided no survival benefit and may pose possible harm. Early observational studies on COVID 19, however, showed a small improvement in mortality and faster resolution of shock with steroid use.⁷

The use of corticosteroids for COVID-19 patients as part of the clinical trials were first done in Wuhan, China where the first cases were observed.

One published retrospective observational study done in Wuhan Union Hospital looked at the effect of giving IV methylprednisolone 1-2 mg/kg per day to patients with severe COVID-19 pneumonia. Out of 46 patients, 26 received methylprednisolone in addition to standard of care. These patients had shorter duration of fever, faster improvement of SpO₂ and better resolution of chest CT scan findings.⁸

In another observational study in First Hospital in Changsha, 10 COVID-19 patients were given low dose methylprednisolone plus 10 grams/day of IVIG aside from standard of care. But it was only when both the methylprednisolone and IVIG were increased to 160 mg/day and 20 grams/day, respectively, did they observe clinical improvement, PaO₂/FiO₂ and lymphocyte counts increased and decreased infiltrates on chest CT scan.⁹

The sample size for both of the above studies, however, were too small to draw proper conclusions and support the use of steroids in severe COVID-19 patients.

Currently, there are two ongoing studies that have released preliminary data showing favorable outcome on the use of steroids. The Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial which provided evidence that treatment with dexamethasone at a dose of 6 mg once daily for up to 10 days decreased the incidence of death among patients receiving invasive mechanical ventilation (29.3% vs. 41.4%; rate ratio, 0.64; 95% CI, 0.51 to 0.81) and those receiving oxygen support without mechanical ventilation (23.3% vs. 26.2%; rate ratio, 0.82; 95% CI, 0.72 to 0.94) but not with those with no respiratory support at randomization (17.8% vs. 14.0%; rate ratio, 1.19; 95% CI, 0.91 to 1.55).¹⁰ The other ongoing study, GLUCOCOVID 63¹¹ is a multicentric, partially randomized, preference, open-label trial among adults with COVID-19 pneumonia. It involved administration of methylprednisolone (IV 40 mg q12 for 3 days the 20 mg q12 for 3 days). Preliminary reports showed reduction in the progression to severe respiratory insufficiency and ARDS among patients.

As of August 10, 2020 there have been nine additional studies on corticosteroids. Two randomized open label trials and one randomized triple blind study are investigating the use of inhaled corticosteroids either alone or in combination with an intranasal corticosteroid among patients with mild COVID-19.

Six studies (including the RECOVERY Trial and GLUCOCOVID 63) involve the use of systemic steroids as a short course treatment. One of these is an observational retrospective case control study on dexamethasone. It has been completed, but has not been published. Two randomized controlled trials are still in the recruitment phase. One involves the use of oral prednisone and the other methylprednisolone. Another randomized open label study looks into colchicine and prednisone versus standard of care in reducing mortality. (Appendix 9)

Recommended Dose

The use of methylprednisolone at 1-2 mg/kg/day for 5 to 7 days has been proposed.²

The RECOVERY Trial recommends the use of dexamethasone IV or oral at 6mg once per day for up to 10 days.⁴⁴¹⁰

Adverse Effects

Patients must be closely monitored and issues on hyperglycemia and electrolyte imbalances should be addressed. One must also watch out for recurrence of inflammation, secondary infections, adrenal insufficiency and possibly drug-drug interactions.

Conclusion

The use of corticosteroids (particularly dexamethasone) as adjunctive treatment for COVID-19 patients who are on supplemental oxygen or on mechanical ventilation is recommended by current treatment guidelines. It is NOT recommended for patients who do not require supplemental oxygen. The risk particularly on the delayed viral clearance and concomitant infection versus the benefit of its anti-inflammatory effect must always be weighed when carefully considering this for use in patients with severe COVID-19.

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