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Corticosteroid therapy for severe COVID-19 pneumonia: optimal dose and duration of administration

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Abstract: Severe COVID-19 is associated with a hyperinflammatory state, and corticosteroid therapy may be effective. We review the recent literature and discuss the appropriate dose and duration of corticosteroid therapy. Low-dose corticosteroid therapy is often used to treat COVID-19. However, several doses of methylprednisolone (or prednisolone) have been attempted, ranging from about 40 mg/day to 2 mg/kg/day. Doses may need to be adjusted depending on severity. Corticosteroid therapy is generally administered for a short period over several days. However, COVID-19-induced respiratory failure is often prolonged, so longer administration may be considered. Careful monitoring for complications due to corticosteroid therapy is vital.

***Keywords*:** COVID-19, SARS-CoV-2, corticosteroid therapy, acute respiratory distress syndrome, viral RNA clearance, complications

Introduction

The outcome for patients with COVID-19 who require mechanical ventilation is extremely poor. For example, 88% of such patients in New York City are reported to have died (*1*). Antiviral drugs and vaccines are awaited, but until those become available, the establishment of organ support therapies is also desirable. Considering that a hyperinflammatory state may be involved in severe COVID-19 (*2*), anti-inflammatory therapy may be effective.

The use of systemic corticosteroid therapy for COVID-19 is controversial. In Middle East respiratory syndrome, which like COVID-19 is caused by a coronavirus, corticosteroid therapy has been reported to be associated with decreased viral RNA clearance in respiratory secretions (*3*). Therefore, many clinicians are cautious about corticosteroid administration, even in patients with COVID-19. However, in a single-center observational study in Wuhan, the use of methylprednisolone was associated with decreased mortality (*4*). In a non-peer reviewed observational study (*5*), Wang *et al*. reported that the use of methylprednisolone was associated with early recovery of oxygen saturation. Citing that report, the Surviving Sepsis Campaign Guidelines suggested that corticosteroid therapy might be effective in patients with COVID-19 who require mechanical ventilation (*6*).

The optimal steroid therapy protocol for COVID-19 is not yet known, so here we review the recent literature and discuss the effectiveness, appropriate dosing, and duration of corticosteroid therapy for COVID-19 pneumonia.

Dose

Steroid therapy may reduce the mortality rate of severe pneumonia (*7,8*), with corticosteroids mainly administered as prednisolone 40-50 mg/day or hydrocortisone 240 mg/day. However, COVID-19 pneumonia with organ failure almost always meets the diagnostic criteria for acute respiratory distress syndrome (ARDS). The conventional corticosteroid dose for ARDS is methylprednisolone 1-2 mg/kg/day (*9,10*). In addition, dexamethasone 20 mg (corresponding to about 80 mg methylprednisolone) has recently been reported to reduce mortality in ARDS (*11*). Moreover, high-dose methylprednisolone (1-2 mg/kg) may be an option.

In a recently reported multicenter observational study, mortality was higher in patients with COVID-19 who received corticosteroids at ≥ 1 mg/kg/day in terms of prednisolone than in those who received no or low-dose corticosteroids (*12*). However, in an additional analysis, steroid dose was not associated with mortality during the first 15 days in critically ill patients only (*13*). This suggests that it may be ideal to adjust the initial dose according to severity. High-dose steroid therapy, at least for mild cases, is not supported.

A number of randomized controlled trials of corticosteroid therapy have been planned (Table 1). A

Table 1. Summary of randomized controlled trials of corticosteroid therapy for COVID-19

NCT number	Country	No.	Intervention	Control
Methylprednisolone < 1 mg/kg/day or equivalent				
NCT04244591	China	80	Methylprednisolone 40 mg, 5 days	Usual care
NCT04263402	China	100	Methylprednisolone < 40 mg, 7 days	Methylprednisolone 40-80 mg, 7 days
NCT04348305	Denmark	1,000	Hydrocortisone, 7 days	Placebo
Methylprednisolone ≥ 1 mg/kg/day or equivalent				
NCT04273321	China	400	Methylprednisolone 1 mg/kg, 7 days	Usual care
NCT04343729	Brazil	420	Methylprednisolone 1 mg/kg, 5 days	Placebo
NCT04325061	Spain	200	Dexamethasone 20 mg, days 1-5 and 10 mg, days 6-10	Usual care
NCT04327401	Brazil	290	Dexamethasone 20 mg, days 1-5 and 10 mg, days 6-10	Usual care

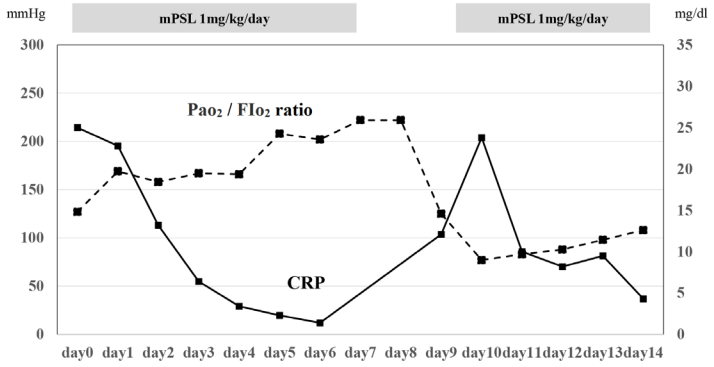

Figure 1. Clincial course of a COVID-19 patient requiring mechanical ventilation and corticosteroid therapy. The patient was admitted and intubated on day 0. She was given methylprednisolone 1 mg/kg/day until day 7. When corticosteroid therapy was stopped, respiratory status and inflammatory response worsened. CRP, C-reactive protein; FIo_2, fraction of inspiratory oxygen; mPSL, methylprednisolone; Pao_2, arterial partial pressure of oxygen.

randomized trial comparing different methylprednisolone doses (< 40 *vs*. 40-80 mg/day) is currently underway (NCT04263402). The results of these trials may soon determine the optimal dose of corticosteroids for COVID-19.

Discussion

Due to concerns about decreased viral RNA clearance, China and the European Society of Intensive Care Medicine (ESICM) have proposed a short treatment duration of 3-5 days. However, in a small retrospective study, short-term administration of corticosteroids was not associated with viral RNA clearance (*14*). It remains unclear whether corticosteroid use is associated with increased SARS-CoV-2 RNA.

COVID-19 pneumonia has a longer clinical course than non COVID-19 pneumonia (*2*). This suggests that a hyperinflammatory state may persist, even as the viral load begins to decline. China's National Health Commission suggests a short treatment period of 3-5 days when using corticosteroid therapy for COVID-19 (*15*). In real-world settings, however, various methods of administration have been attempted. For example, in a phase-3 trial of remdesivir in China, about two-thirds of participants received corticosteroid therapy for a median of 9 days (*16*). This indicates that in some patients with COVID-19, there is some difficulty in withdrawing corticosteroid therapy in a short treatment period.

In addition, an ESICM webinar also noted a biphasic course, with deterioration typically occurring after 5 to 7 days of improvement following the hyperacute phase (*17*). This suggests that longer dosing of corticosteroids may be more beneficial.

We present one of our patients with a characteristic clinical course (Figure 1). She was hospitalized with COVID-19 and immediately intubated for respiratory failure. Treatment was initiated with hydroxychloroquine, broad-spectrum antibiotics, and methylprednisolone 1 mg/kg/day. To improve oxygenation, we terminated methylprednisolone on day 7. However, soon thereafter, hypoxia was exacerbated and inflammatory markers increased, so we restarted methylprednisolone 1 mg/kg/day. Bacterial examination revealed no secondary infection. The long and complicated clinical course of COVID-19 pneumonia has consistently made it difficult to determine whether this should be attributed to corticosteroid discontinuation or the natural course. Such concerns may also arise with short-term administration. We considered that this patient would benefit from

the long-term corticosteroid therapy protocol used for conventional ARDS (10-14 days).

Complications

In addition to the discussion above, complications associated with long-term corticosteroid use cannot be ignored. First, corticosteroid use can cause hyperglycemia. Severe COVID-19 infection has been shown to be more common in diabetics (*1,2*), and corticosteroid use may make glycemic control difficult. Second, long-term corticosteroid therapy may delay improvement in pneumothorax. Gattinoni *et al*. demonstrated two different types of COVID-19 pneumonia according to lung elastance: low elastance or phenotype L and high elastance or phenotype H (*18*). Phenotype H requires high positive end-expiratory pressure and high driving pressure, which increases the risk of barotrauma. In our experience with COVID-19 intubation, pneumothorax or pneumomediastinum occurred in 4/6 (67%) of patients with phenotype H and 2/11 (18%) of patients with phenotype L. In the patients with pneumothorax or pneumomediastinum, long-term corticosteroid therapy may therefore not be appropriate. Third, gastrointestinal bleeding may also be a problem. Moreover, COVID-19 patients may be receiving heparin because venous thromboembolism is a known complication (*19,20*). In addition, it has recently been reported that heparin use is associated with better survival in COVID-19 patients with elevated D-dimer (*21*). Although data are limited, many clinicians are likely to consider anticoagulant therapy in these cases. Other patients may be given high doses of heparin for extracorporeal membrane oxygenation management. The combination of corticosteroids and heparin may increase the risk of gastrointestinal bleeding. Bleeding events have been reported in 7.5% of intubated patients with COVID-19 (*22*).

In summary, the corticosteroid dose is preferably low and adjusted for severity (methylprednisolone 1-2 mg/kg/day). Although short-term treatment is currently the mainstay, we believe that the long-term clinical course of COVID-19 pneumonia suggests that the option of a somewhat longer duration (10-14 days) should be considered.

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