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Therapeutic Application of Corticosteroids in COVID-19: A Focus on Optimum Dose and Duration of Therapy

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Sajad Khiali, PharmD[1] and Taher Entezari-Maleki, PharmD, PhD[1,2]

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The pandemic of coronavirus disease 2019 (COVID-19) has resulted in a global health crisis. Pathophysiologically, the disease has the initial phase of viral replication that could be followed by an immunologic phase, which is characterized by a systemic inflammatory response, cytokine release syndrome, acute respiratory distress syndrome (ARDS), and multisystem organ dysfunction, and associated with a considerable rate of mortality. The critical condition of the immunologic phase of the disease has raised many studies investigating the efficacy and safety of a series of anti-inflammatory agents, including proinflammatory cytokine inhibitors (anakinra, tocilizumab, sarilumab, adalimumab, infliximab), Janus kinase inhibitors (baricitinib, tofacitinib, ruxolitinib), convalescent plasma, and granulocyte-macrophage colony-stimulating factors (gimsilumab, lenzilumab, namilumab), as well as nonspecific immune modulators such as corticosteroids in patients with COVID-19.[1]

Corticosteroids could slow the viral clearance and increase the risk of infections. Accordingly, the application of corticosteroids in patients with pulmonary infection is still a controversial issue.[2] For example, in individuals with influenza-related severe pneumonia, the use of corticosteroids is associated with poor clinical outcomes, while it could decrease mortality risk in cases of *Pneumocystis jirovecii* pneumonia and hypoxia.[3,4] Furthermore, corticosteroids have been widely investigated in patients with classic ARDS with controversial results. A systematic review and meta-analysis of 7 randomized controlled trials (RCTs) including 851 patients showed a reduced rate of mortality (risk ratio [RR], 0.75; 95% confidence interval [CI], 0.59-0.95) and duration of mechanical ventilation (mean difference, −4.93 days; 95% CI, −7.81 to −2.06 days) in the corticosteroid group compared with the placebo group.[5,6]

Corticosteroids are classical anti-inflammatory and immunosuppressive medicines that reduce the production of proinflammatory cytokines, such as interleukin-6, interleukin-10, granulocyte-macrophage colony-stimulating factor, and tumor necrosis factor α, and suppress activation of both primary and secondary immune cells. The excessive activation and immune dysregulation of the innate and adaptive immune systems in the pathogenesis of COVID-19 were acknowledged at the beginning of the pandemic.[1,2] Since that time, numerous studies have been conducted to evaluate the safety and efficacy of corticosteroid therapy in patients with COVID-19. The largest trial to date is the Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial, in which a total of 6425 hospitalized patients with COVID-19 were randomly assigned to receive dexamethasone (n = 2104) or usual care (n = 4321). The impressive results of the open-label RECOVERY trial indicated that 6 mg of dexamethasone daily for 10 days could significantly decrease mortality in hospitalized patients with COVID-19 receiving oxygen with (29.3% vs 41.4%; rate ratio, 0.64; 95% CI, 0.51-0.81) or without (23.3%

[1] Department of Clinical Pharmacy, Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran
[2] Cardiovascular Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

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Corresponding Author:
Taher Entezari-Maleki, PharmD, PhD, Department of Clinical Pharmacy, Faculty of Pharmacy, Tabriz University of Medical, Sciences, Tabriz, Iran.
Email: entezarim@tbzmed.ac.ir

vs 26.2%; rate ratio, 0.82; 95% CI, 0.72-0.94) invasive mechanical ventilation.[7] A meta-analysis of 7 RCTs involving 6250 patients showed that administration of corticosteroids in patients with severe COVID-19 led to a decreased mortality rate (27.3 vs 31.1%; RR, 0.85; 95% CI, 0.73-0.99; $P = .04$).[8] Currently, a National Institutes of Health panel recommends the use of dexamethasone (6 mg/d for 10 days or until discharge) in hospitalized patients with COVID-19 who require supplemental oxygen, oxygen delivery through a high-flow device, and invasive mechanical ventilation or extracorporeal membrane oxygenation.[9]

Despite the mounting evidence supporting the benefits of corticosteroids in patients with COVID-19, owing to the substantial heterogeneity of the disease, the optimum dose and duration of corticosteroid therapy in different clinical situations are undetermined. Furthermore, the corticosteroid of choice is unknown in patients in different stages of COVID-19.[7,8] Some trials have been carried out to find out the corticosteroid of choice in the treatment of COVID-19. In some cases, clinical pharmacology properties of corticosteroids have been ignored, which could lead to misleading data.[10–12]

For example, Ranjbar et al[10] carried out a prospective triple-blinded RCT to compare the effectiveness of methylprednisolone (2 mg/kg/d and tapered to half dosage every 5 days [intervention group]) with the RECOVERY trial dose of dexamethasone (6 mg/d for 10 days [control group]) in 86 hospitalized adult patients with COVID-19. They concluded that methylprednisolone (2 mg/kg/d) is superior to dexamethasone (6 mg/d) in decreasing need for mechanical ventilation (18.2% vs 38.1%; $P = .040$), hospital length of stay (7.43 $\pm$ 3.64 vs 10.52 $\pm$ 5.47; $P = .015$), and improving clinical status at days 5 (4.02 vs 5.21; $P = .002$) and 10 (2.90 vs 4.71; $P = .001$). However, they did not report the mean weight of patients. According to the equivalent doses of corticosteroids, in fact, Ranjbar et al compared the effectiveness of 2 wide doses of methylprednisolone (32 mg/d vs 2 mg/kg/d).[13] Therefore, the significant findings of Ranjbar and colleagues' study could be derived by a misleading data interpretation and most likely tend to be due to the dissimilar doses of 2 medicines rather than the nature of the drugs (about 5- to 6-fold higher doses). The rational conclusion is that a high dose of methylprednisolone is associated with better clinical outcomes in the studied patients than the recommended moderate dose. Notably, in Ranjbar and colleagues' triple-blinded RCT, the blinding process was not described completely. Another limitation of the study is small sample size. In addition, a power calculation was not provided for the clinical end points. Therefore, the potential risk of bias should not be ignored.[10,13]

Another critical consideration of treatment with corticosteroids is the duration of therapy. It is important to note that while the long-lasting course of corticosteroids could prevent some of the post–COVID-19 complications such as lung fibrosis, it may increase the risk of thrombosis, psychiatric manifestations, neuromuscular weakness, and myopathy that are also observed in patients with COVID-19. Furthermore, the long-lasting course of corticosteroid therapy could increase the risk of hyperglycemia, avascular necrosis, secondary infections, and reactivation of latent infections such as tuberculosis, strongyloidiasis, hepatitis B virus, and herpes simplex virus.[1,2,9] Ko et al,[11] in a retrospective study of 262 COVID-19 patients requiring intensive care unit admission, showed that methylprednisolone $\geq$1 mg/kg/d (for $\geq$3 days) is associated with a 42% lower mortality rate compared with dexamethasone $\geq$6 mg (for $\geq$7 days) in patients with COVID-19 requiring mechanical ventilation (hazard ratio 0.48; 95% CI, 0.235-0.956, $P = .0385$). According to the treatment guidelines of classic ARDS and scientific evidence from previous literature, the duration of corticosteroid therapy does not seem to be logical in Ko and colleagues' study. Additionally, considering the longer half-life of dexamethasone compared with methylprednisolone, comparing a course of 3-day methylprednisolone with dexamethasone for 7 days does not seem to be rational. It is important to mention that the dose of corticosteroid in the methylprednisolone group was higher in Ko and colleagues' study than the National Institutes of Health panel recommendation; however, according to the previous evidence on the potential beneficial efficacy of high doses of corticosteroids in the treatment of classic ARDS, the evaluation effects of 1 mg/kg of methylprednisolone seems to be rational in patients with severe COVID-19.[9,11,14,15]

Pinzón et al,[12] in an ambispective cohort study in 216 patients with severe COVID-19 pneumonia showed that high-dose methylprednisolone (250-500 mg/d for 3 days) followed by oral prednisone (50 mg daily) for 14 days leads to statistically significant lower recovery time ($P < .0001$), C-reactive protein ($P < .0001$), d-dimer ($P = .04$), and lactate dehydrogenase ($P = .01$) compared with dexamethasone (6 mg/d for 10 days). Moreover, in Pinzón and colleagues' study, the rate of mortality and intensive care unit admission were lower in the methylprednisolone group compared with the dexamethasone group (4.8% vs 14.4%; 9.5% vs 17.1%). Considering the fact that in patients with classic moderate to severe ARDS (partial arterial pressure of oxygen/fraction ratio <200) the recommended dose of methylprednisolone is 1 mg/kg, it seems that the administration of 250 to 500 mg of methylprednisolone in Pinzón and colleagues' study is a high dose for the

included patients with COVID-19 with mild, moderate, or severe ARDS. Furthermore, the baseline severity of the disease was not homogenous between groups (severe ARDS; methylprednisolone group, 17.1%; dexamethasone group, 26.1%). It is important to mention that changing the treatment guideline during the study period and the effects of other therapies alongside corticosteroids in each group are other limitations of Pinzón and colleagues' study. Finally, the studies of Ko et al and Pinzón et al have low quality and level of evidence because of the high risk of bias resulting from the particularly small sample size and the retrospective and ambispective designs of the studies (Table 1).[9,12,14,15]

These limited data supported the superiority of high doses of methylprednisolone compared with moderate doses of dexamethasone in the late stages of the disease that could be similar to the treatment approach of the classic ARDS, in which a typical regimen is dexamethasone 20 mg/d intravenous for 5 days followed by 10 mg/d for an additional five days or methylprednisolone 1 mg/kg/d for 21 to 28 days followed by a dose tapering. Notably, the regimens of the medicines are approximate according to the equivalent doses and duration of action corticosteroids: dexamethasone 0.75 mg (half-life, 36-72 hours), prednisolone 5 mg (half-life, 8-12 hours), methylprednisolone 4 mg (half-life, 12-36 hours), and hydrocortisone 20 mg (half-life, 12-36 hours).[10–15]

Several clinical trials are ongoing to answer the important clinical questions about exact dose, treatment duration, time of administration, and using additional medicines with immunomodulatory properties in different clinical situations of patients with COVID-19. In critical conditions like the present pandemic, the concerning issues around the study design of the trials and subsequent misleading results could lead to inappropriate treatment strategies and harm to patients.

It seems that, due to the substantial heterogeneity of the disease, ongoing RCTs should incorporate plans for understanding heterogeneity and identifying patients who are responsive to corticosteroids and appropriate dose of the medicines considering the burden of lung injury, inflammatory markers such as neutrophil-to-lymphocyte ratio, sedimentation rate, levels of interleukins, presence of poor prognosis risk factors, and other clinical and paraclinical data. Finally, the pharmacokinetics, glucocorticoids/mineralocorticoids ratios, and equivalent doses of corticosteroids, as well as dose and duration of the drugs in similar situations like the classic ARDS, should be considered in the clinical trials and treatment centers.[1,8,13–15]

Table 1. Published Studies Comparing Different Corticosteroids Effects in Patients With COVID-19

Study, Year, Country	Design	Population (n = Sample Size)	Dose and Duration (Control Group)	Dose and Duration (Intervention Group)	Equivalent Doses of Corticosteroids Comparison	Outcomes
Ranjbar et al, 2021, Iran	Prospective triple-blinded RCT	Hospitalized patients with COVID-19 (n = 86)	Dexamethasone, 6 mg/d, 10 d	Methylprednisolone, 2 mg/kg/d, 10 d	Methylprednisolone: 32 mg vs 2 mg/kg	Clinical status at d 5 and 10 ($P = .002$ and $P = .001$) of admission, mean length of hospital stay ($P = .015$), and need for a ventilator ($P = .040$) were significantly better in intervention group than control group
Ko et al, 2021, United States	Retrospective study	ICU-admitted patients with COVID-19 (n = 262)	Dexamethasone, ≥6 mg/d, ≥7 d	Methylprednisolone, ≥ 1 mg/kg/d, ≥3 d	Methylprednisolone: 32 mg vs 1 mg/kg	50-d mortality was lower in patients receiving corticosteroids; in patients requiring mechanical ventilation, mortality was 42% lower in intervention group than control group ($P = .0385$)
Pinzón et al, 2021, Colombia	Ambispective cohort study	Hospitalized patients with COVID-19 (n = 216)	Dexamethasone, 6 mg/d, 10 d	Methylprednisolone, 250-500 mg/d, 3 d; with subsequent prednisolone, 50 mg, for 14 d	Methylprednisolone: 32 mg vs 250-500 mg, followed by 40 mg for 14 d	Rate of mortality, ICU admission, recovery time ($P < .0001$), C-reactive protein ($P < .0001$), d-dimer ($P = .04$), and lactate dehydrogenase ($P = .01$) improved significantly in intervention group compared with control group

COVID-19, coronavirus disease 2019; ICU, intensive care unit; RCT, randomized controlled trial.

Conflicts of Interest

The authors declare no conflicts of interest.

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