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LETTER

A Letter to the Editor Regarding 'Identifying Gaps in the Corticosteroid Treatment of COVID-19: We Need More Studies'

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Dear Editor,

We have read with great interest the study "Impact of Early Corticosteroids on Preventing Clinical Deterioration in Non-critically Ill Patients Hospitalized with COVID-19: A Multihospital Cohort Study" by Swaminathan et al. [1] which was published in the *Infectious Diseases and Therapy* in March. In this study, non-ICU patients with COVID-19 receiving corticosteroid treatment within the first 2 days of hospitalization were compared with the patient group who did not receive early corticosteroid treatment. Ninety-seven percent of the treatment group received methylprednisolone, while 6.1% received dexamethasone. In this study, where the median prednisolone equivalent dose was 75 mg/day and the median treatment duration was 4 days, 16.7% of the control group received steroid treatment after the 2nd day of hospitalization. According to the multivariable analysis, early corticosteroid use did not reduce in-hospital mortality, the need for intensive care and mechanical ventilation, and the duration of the hospitalization. In this multicenter study, it was reported that early steroid use did not prevent clinical worsening [1]. As stated by the authors, compared to the RECOVERY study [2], which showed a decrease in mortality in non-critically ill hospitalized patients with COVID-19 requiring oxygen therapy, the duration of steroid use was shorter (10 days vs median of 4 days), and almost one-fifth of the patients in the control group received steroid therapy. In addition, patients in this study were less severe than those in the RECOVERY study. On the basis of the results of this study, we felt the need to write this letter to highlight the gaps in corticosteroid therapy in COVID-19 and the areas that need further studies.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel coronavirus belonging to the family *Coronaviridae* and is now known to be responsible for the coronavirus disease 19 (COVID-19) pandemic. The pathogenesis of SARS-CoV-2 infection mainly consists of three stages. After the person encounters the virus and post inoculation period, the virus binds to the angiotensin-converting enzyme 2 (ACE-2) receptors in the upper respiratory tract, enter the cells, and replicates rapidly. ACE-2 receptors are abundant in

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pulmonary alveolar epithelial cells, especially in nasal epithelial cells. Thus, the lungs are the main target organ in COVID-19. In 80% of patients who encounter the SARS-CoV-2 virus, the infection stays limited to the nasal mucosa and the upper respiratory tract. In 20% of the patients, the virus reaches the lower respiratory tract through the conducting airways and invades the alveolar cells. Viral replication results in the apoptosis of alveolar cells, loss of type 1 and 2 pneumocytes, and pneumonia. In some of the patients, cytokine storm is caused by the excess host inflammatory reaction in response to viral replication and invasion, resulting in acute respiratory distress syndrome (ARDS) [3]. The main problem here is that one cannot clinically predict which patient the infection will be limited to, which patient will recover from the pneumonia stage, and which patient will develop ARDS with cytokine storm.

Although patients with advanced age (> 65 years old), cardiovascular disease, hypertension, and diabetes mellitus are defined as the population at risk for the progression of COVID-19, critical illness can also develop in young people who do not have any comorbidities. Studies have shown that patients with ACE-2 receptor polymorphism and a high number of ACE-2 receptors in the upper respiratory tract had a severe clinical course of COVID-19 [4, 5]. Therefore, corticosteroids have been one of the most investigated treatments in COVID-19 for limiting inflammation alongside antiviral agents. It is argued that very early use of corticosteroids will increase viral replication in COVID-19, while their late use will not reduce the alveolar damage. Short-term high-dose systemic corticosteroids used in the early stages of the inflammatory phase of COVID-19 have been shown to reduce mortality.

Systemic corticosteroids were widely used during previous coronavirus outbreaks owing to their anti-inflammatory properties [SARS and Middle East respiratory syndrome (MERS)] [5–8]. Current randomized controlled trials in COVID-19 recommended the short-term (3–5 days) use of methylprednisolone treatment (0.5–1 mg/kg/day for moderate cases and 1–2 mg/kg/day for severe cases) in patients with hypoxemia ($SpO_2 < 92\%$ in room air) and progressive hypoxemia, high inflammatory markers, and patients who had worsening chest X-rays during follow-up. The RECOVERY study demonstrated that once-daily 6 mg dexamethasone treatment reduced mortality compared to standard care in hospitalized hypoxemic patients with COVID-19 pneumonia [2]. In addition, dexamethasone treatment reduces mortality in severe and critical patients with COVID-19 [9].

One of the questions about corticosteroid treatment is whether their use will have an effect on the short-term symptoms and long-term course of COVID-19 before pneumonia or concomitant hypoxemia occurs. Investigating the presence of ACE-2 gene polymorphism may guide us in answering this question. However, genetic analysis is a time-consuming and expensive method and cannot be used in routine outpatient follow-ups. It is reported that patients with advanced age (> 65 years old), male gender, comorbidities, especially coronary artery disease, hypertension, diabetes mellitus, and cancer are at risk for critical COVID-19 due to increased risk of the systematic inflammatory response [10]. Can systemic corticosteroids, which are started within the first 3 days of SARS-CoV-2 positivity, be beneficial? Further randomized clinical trials and research are needed to answer this question.

Initiation of corticosteroid therapy this patient group before the disease progresses to the lower respiratory tract and before pneumonia and hypoxemia occur may limit the progression of COVID-19 and improve symptoms in a shorter time. In addition, long-term symptoms persist in a quarter of the COVID-19 cases with a WHO clinical progression scale of 1–3. Symptoms may persist even months later in patients who were not hospitalized and had milder COVID-19 course. In this condition, which is defined as the post-COVID syndrome, symptoms such as loss of smell, loss of taste, fatigue, and shortness of breath can last up to 7 months in a quarter of the patients [11]. Can short-term corticosteroid therapy reduce the frequency of long-term symptoms? This is another point that needs to be further investigated.

In the current COVID-19 pandemic, studies mainly have focused on hospitalized, hypoxic,

and critically ill patients. Randomized controlled studies are needed to determine whether corticosteroid treatments can prevent disease progression and prevent post-COVID symptoms besides reducing short-term symptoms in outpatients.

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