Impact of corticosteroid use in COVID-19 infection: A rapid clinical review

Zeinab Mohseni Afshar[1], Mohammad Barary[2], Soheil Ebrahimpour[2], Amirhossein Hasanpour[2], Alireza Janbakhsh[1], Babak Sayad[1], and Arefeh Babazadeh[2]

[1]Kermanshah University of Medical Sciences
[2]Babol University of Medical Science

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Abstract

Coronavirus disease 2019 (COVID-19) is caused by infecting with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that was recognized in late December 2019 in Wuhan, China. As the infection spread and rapidly becomes a global pandemic, effective therapy is urgently needed against the new coronavirus due to the increased morbidity and mortality rates. Based on this aspect, several therapeutic options have been explored, one of which is corticosteroids. Though the application of corticosteroids in treating COVID-19 remains controversial, this review aimed to evaluate and describe the effectiveness and safety of corticosteroids in the management of COVID-19.

Introduction

The coronavirus disease 2019 (COVID-19) pandemic made an excruciating situation over the past year as no practical therapeutic approach has been identified yet (1). Similar to those infected with severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV), and influenza virus, patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are believed to experience these phases: virus invasion, immune activation, exaggerated inflammatory response, acute respiratory distress syndrome (ARDS), and ultimately, recovery or death (2).

The severity of COVID-19 varies from mild or asymptomatic cases to severe and life-threatening ones. Only 5% of COVID-19 patients reach the critical phase of ARDS (3). Patients with the severe form of the disease have particular clinical or paraclinical characteristics, including decreased PaO_2/FiO_2 (P/F) ratio and the number of peripheral lymphocytes, high C-reactive protein (CRP), lactate dehydrogenase (LDH), D-dimer, or IL-6 (4). This condition typically occurs in the second week of illness or later, following a catastrophic, self-destructive immune response and cytokine storm. The cytokine storm eventually may result in multi-organ failure, shock, or death. Consequently, any strategy to prevent or modulate this crisis can contribute to a reduction in mortality and morbidity rates (5). Although different antivirals, hydroxychloroquine, azithromycin, intravenous immunoglobulin (IVIG), and immunomodulatory agents, such as tocilizumab, have been explored in the treatment of COVID-19, no significant positive outcomes have been achieved yet (6). Under these conditions, the only life-saving strategy could be to suppress inflammation, which is best achieved by corticosteroids (7).

The mechanism by which corticosteroids act to prevent or treat ARDS might be the down-regulation of the systemic and pulmonary inflammatory responses and preventing exudative fluid accumulation in the lung tissue, resulting in better respiratory indices and pulmonary repair, and decreases of respiratory failure (8). As soon as the patient develops any symptoms or signs of disease progression, corticosteroid therapy must be switched on (9). Low to moderate doses of corticosteroids are generally used to prevent their

potential adverse effects. Nevertheless, high doses are recommended for specific situations (10). As well as controlling or preventing ARDS in the context of COVID-19, corticosteroids offer many other benefits (11). Management of sepsis and the potential adrenal insufficiency induced by septic shock is another reason to administer corticosteroids (12). Patients with COVID-19 who began corticosteroid treatment would promptly experience shorter-term symptoms and more clinical improvement during the first seven days (13).

Different studies conducted on patients admitted to the intensive care unit (ICU) due to COVID-19 have shown the association between corticosteroid therapy and reduced hospitalization in the ICU, mechanical ventilation, and mortality if received early. Besides, more rapid defervescence, improved oxygenation, and reduced need for intubation and mechanical ventilation are other benefits of corticosteroid therapy in patients with COVID-19 (14). However, corticosteroids have been associated with a more extended hospitalization, which may advise against their use since corticosteroids are generally administered for more ill patients, and these patients are reasonably more likely to have longer hospitalization duration (15). Not only are corticosteroids used for ARDS, multi-organ failure, and shock in the setting of COVID-19, but also they have been applied for other purposes, such as SARS-CoV-2-related severe cutaneous manifestations. For instance, erythema multiforme (EM)-like exanthem and other dermatoses, which have been extensively reported in patients with COVID-19, respond well to corticosteroid treatment (16). Furthermore, oral corticosteroids, such as prednisolone, have also been used to relieve post-COVID-19 anosmia (17). There have also been cases of exacerbated immune thrombocytopenia (ITP) controlled by corticosteroids (18).

At the onset of the pandemic, hydrocortisone was applied for severe COVID-19, possibly due to its proven benefits in septic shock (19). Today, nearly all studies have emphasized dexamethasone as a drug of choice for COVID-19 treatment, while in the previous SARS-CoV, MERS-CoV, and influenza A (H1N1) epidemics, methylprednisolone was more tended to be applied (20,21). Methylprednisolone and dexamethasone have increased pulmonary bioavailability compared to other corticosteroids. Methylprednisolone has higher mineralcorticoid activity, whereas dexamethasone has higher glucocorticoid activity. Long-term adverse effects, such as volume overload, electrolyte imbalance, dysglycemia, and hypercortisolism, are less common with methylprednisolone due to its faster onset and shorter duration of action (22). The results of the RECOVERY trial illuminated the maximum benefit of low-dose dexamethasone (23). The mechanism by which dexamethasone exerts its immunosuppressive effects is reducing antibody synthesis by plasma cells, inhibition of T cells, and blockage of macrophages and NK cells (figure 1) (24). Some centers have tried nebulized triamcinolone preceded by a pulse of intravenous dexamethasone to maximize corticosteroids' concentration in the lungs (25). Interestingly, an inhaled corticosteroid named ciclesonide would have effectively inhibited the replication of SARS-CoV-2 (26).

In contrast to some therapeutic options for which we can consider a specific change in laboratory biomarkers to define their necessity, there is currently no such definition for corticosteroids in COVID-19 patients (27). For example, tocilizumab is typically indicated in situations where IL-6 levels are increased, or antimicrobials can be considered for patients with higher procalcitonin levels (28, 29). Timely administration of corticosteroids is vital for preventing and treating ARDS, disseminated intravascular coagulation, hypotension, shock, and death, all of which occur more prevalently in the first 5 to 7 days of disease. This matter corresponds to when a patient with COVID-19 develops shortness of breath. Patients whose oxygenation or radiological outcomes are progressively deteriorating are the best candidates for receiving glucocorticoids (30). The timing of a corticosteroid regimen for a COVID-19 patient should be decided cautiously since it should be administered neither too early to suppress the body's immune defense nor too late to be unable to overcome the advanced stages of ARDS (2). The reason why many critically ill, ICU-admitted COVID-19 patients do not respond to delayed corticosteroid therapy may be the excessive inflammatory responses that have caused irreversible damage to the lungs (31).

Almost all studies agree on the most beneficial effect of low-dose corticosteroids on severe forms of COVID-19, which are ventilated and have developed ARDS (32). Many centers have reached the point where a low-to-moderate dose of methylprednisolone (0.5 to 1 mg/kg/day) appears reasonable for approximately one week (33). However, at the beginning of the pandemic, when anti-retroviral drugs, such as ritonavir, were

studied for COVID-19 treatment, a lower dose of methylprednisolone or prednisolone was chosen because of ritonavir's interactions with those drugs, resulting in increased levels of the corticosteroids in serum (34). Furthermore, the RECOVERY trial revealed a lower mortality rate with 6 mg/day of dexamethasone than the control group (23). In critically decompensated patients, recovery therapy with a 3-day glucocorticoid pulse therapy (intravenous methylprednisolone: 200–400 mg/day) followed by low-to-moderate dose corticosteroids for 21 days is also indicated (35).

Any medical treatment may be otherwise harmful in certain respects if misused, used longer than necessary, or in inappropriate doses. Corticosteroids are a double-edged sword used to treat viral pneumonia (36). Despite their beneficial effects on controlling critically ill COVID-19 patients, corticosteroids should be administrated with caution due to their immunosuppressive effect. Their arbitrary administration can even trigger more viral replication, which is potentially harmful to the patient. Nonetheless, despite the controversy in their use in viral pneumonia, they had been abundantly used in influenza virus, SARS-CoV, and MERS-CoV epidemics (33,37). Studies have shown that patients taking chronic low-dose corticosteroid therapy for any disorder, such as neurologic or rheumatologic diseases, are not prone to severe forms of COVID-19 infection than those not on such regimen (38). Adrenal insufficiency due to removal of the hypothalamic-pituitary-adrenal (HPA) axis is another formidable consequence of the long-term use of corticosteroid (39). Other unwanted events include dysglycemia and unmasking of diabetes, avascular necrosis or osteonecrosis of the femoral head (ONFH), hypertension, bacterial super-infections and subsequent antibiotic overuse, opportunistic infections, such as pulmonary aspergillosis or rhino-orbital or rhino-cerebral mucormycosis, and electrolytes imbalances, such as hypernatremia and hypokalemia (10,32,40-45). Additionally, some patients with COVID-19 are prone to pneumothorax, the improvement of which may be delayed by corticosteroid therapy (46). Another critical issue that should be considered is the co-administration of corticosteroids and anticoagulants, such as heparin, in the context of COVID-19 is a predisposition to gastrointestinal (GI) bleeding (47).

Corticosteroid therapy has also been reported to prolong viral shedding. However, some studies suggest combining immunoglobulin and corticosteroids to enhance the immune response to overcome prolonged viral shedding, besides its synergistic effects in improving oxygen saturations (9,35).

Corticosteroids should be administered cautiously under certain conditions. For example, during pregnancy, the corticosteroid administration's benefits to the mother to manage her COVID-19 should be weighed carefully against the potential fetal harm (48). Measures must be taken to differentiate between chorioamnionitis and COVID-19 in pregnant patients with fever (48).

It is well-described that COVID-19 is less common or less severe in patients with chronic obstructive pulmonary disease (COPD) than in the general population. One reason may be the vital role of corticosteroids, whether inhaled or systemic, in the maintenance treatment of these patients, intended to protect them from severe COVID-19 infection (49). It is unknown whether patients afflicted with disorders like COPD who should take corticosteroids routinely for their condition must continue their corticosteroid regimen if they are infected with SARS-CoV-2 or not, since corticosteroids may be harmful in the early stages of COVID-19 infection (50).

Therefore, strategies should be undertaken to avoid corticosteroids associated adverse events, such as the most short-acting ones like methylprednisolone, should be used because as soon as it is tapered or discontinued, its adverse events are more likely to disappear (51). A further protective measure can be administering bisphosphonates and vitamin E to prevent osteoporosis or osteonecrosis (52). Close monitoring of blood sugar is required after the discharge of the patient (53). Choosing and administering the appropriate class of glucose-lowering agents, such as metformin or various types of short or long-acting insulin, depending on blood sugar levels, the exact corticosteroid type being utilized, and the hyperglycemic peak time is also warranted (54).

Various institutions or guidelines have provided advice on how to administer corticosteroids in the context of COVID-19. Both the world health organization (WHO) and the center for disease control and prevention (CDC) had prohibited corticosteroid use for this application at the beginning of the outbreak. Nonetheless,

currently, a low dose of dexamethasone is the drug of choice in many COVID-19 patients (10, 55). Also, the national health commission of the People's Republic of China recommended hydrocortisone as the appropriate corticosteroid in COVID-19 (56). Moreover, the surviving sepsis guideline of the COVID-19 has always recommended steroids for severe forms of COVID-19, particularly ARDS, to suppress the exaggerated inflammatory response (57).

Conclusion

In general, regarding different recommendations for corticosteroids use by various guidelines and authorities, the ultimate decision for corticosteroid therapy in a COVID-19 patient is primarily based on physicians' judgments and the patient's condition. The application of corticosteroids requires special attention to the benefit-risk relationships and the adjustment of doses if necessary. It is mandatory to monitor signs of hyperglycemia, adrenal insufficiency, and secondary bacterial and fungal infections in the context of glucocorticoid therapy.

Declarations

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Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Competing interests

All authors declare no conflict of interest.

Authors' contributions:

Zeinab Mohseni Afshar: Conceptualization, Methodology, Writing-original draft Mohammad Barary: Investigation, Writing-original draft, Writing-review & editing Soheil Ebrahimpour: Conceptualization, Methodology, Writing-original draft Amirhossein Hasanpour: Software, Visualization Alireza Janbakhsh: Investigation, Writing-original draft Babak Sayad: Investigation, Writing-original draft Arefeh Babazadeh: Project administration, Supervision, Writing-review & editing.

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Figure legends

Figure 1. A summary of the corticosteroid's immunomodulatory mechanisms. Abbreviations: IL, Interleukin; IFN γ, Interferon-gamma; TNF α, Tumor Necrosis Factor-alpha; DC, Dendritic cell; NK cell, Natural Killer cell; Th1, T helper cell type 1; Th2, T helper cell type 2; Th17, T helper cell type 17; TCR, T-cell receptor