Use of Corticosteroids in COVID-19

Should It Be Considered as a Standard-of-Care Therapy?

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By the end of 2019, a novel coronavirus was identified as the cause of several cases of pneumonia in Wuhan, China. Its appearance was rapidly evident throughout the world. In February 2020, the World Health Organization (WHO) designated the disease as coronavirus disease 2019 (COVID-19). The virus that causes COVID-19 is named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and it has been responsible of more than 1,200,000 deaths in the world to date.[1,2]

Until a vaccine or other effective treatment is available, the pandemic has created the urgent need to repurpose different therapeutic tools to stop the disease. In this context, corticosteroids (CSs) emerge as a highly available and known therapeutic alternative worldwide.

Corticosteroids had been used in the setting of previous severe coronavirus infection, including severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) with controversial results. SARS-CoV-2, SARS-CoV, and MERS-CoV share many genetic features, and SARS-CoV-2 is highly homologous to SARS-CoV.[3]

We will discuss the mechanism of action of CSs, and we will critically review the current literature to analyze the arguments against and in favor of using this therapy in COVID-19.

PHASES OF THE DISEASE

The immune system plays an important role in the pathogenesis of the disease, but its activation only occurs after the virus has entered into the cells, so the first pathological event responsible for the symptoms is the presence of the virus and, afterward, the immune response. Thus, we can divide the disease in different phases. The first one is characterized by viral replication, when antivirals seem to be the most useful therapy. The second phase is the characteristic pneumonia, where the viral clearance increases and, at the same time, the immune response is evident. The third phase is characterized by hyperactivation of the immune system. In this phase, the virus usually has been cleared and the hyperactivation of the immune system could harm the patient. In the second and third phase, antivirals probably do not have a role, but anti-inflammatory medication could. It has been described that there is a therapeutic window, especially between the second and third phase, where we can treat these patients with anti-inflammatory/immunomodulating drugs, to try to change the course of the disease.[4,5]

Given that CSs are the anti-inflammatory/immunomodulating drug per definition, they have been widely used in COVID-19. However, although CSs reduce the inflammation, they also decrease the capacity of the immune system to respond appropriately to infections and many authors have suggested that they could decrease viral clearance and be more harmful than useful.

CORTICOSTEROID MECHANISMS OF ACTION AND ADVERSE REACTIONS

Corticosteroids are known, widely available drugs that have important pleiotropic effects, with multiple anti-inflammatory and immunosuppressive effects. They antagonize macrophage differentiation and suppress their production of interleukin 1 (IL)-1, interleukin-6 (IL6), tumor necrosis factor, and the proinflammatory prostaglandins and leukotrienes. These agents also suppress neutrophil adhesion to endothelial cells and impair their lysosomal enzyme release, the respiratory burst, and chemotaxis to the inflamed site.

Regarding the adaptive immune system, CSs can cause marked lymphopenia involving all lymphocyte subpopulations; they inhibit T-cell activation by inhibiting IL-2, IL-3, IL-4, and IL-6. The maturity of double positive T lymphocytes (CD4+ CD8+), which are the majority of the thymocyte population, can be impaired by CSs as these cells are highly sensitive to CS-induced apoptosis. Corticosteroids also have immunosuppressive effects on dendritic cell (antigen presenting cells that can interact with naive T cells to instruct the adaptive immune response) maturation and function.[6]

Although these mechanisms are very useful in the treatment of autoimmune or inflammatory diseases, they provide an inevitable risk of infection, which is usually dose dependent. In addition, CSs are not exempt from adverse effects in the metabolic, electrolytic, bone metabolism, and psychiatric sphere, among others.[7]

Among the adverse effects of CSs, there are 2 that have been associated with greater complications in the context of COVID-19: hyperglycemia and bone metabolism disturbance. Corticosteroids can be responsible for fasting glucose levels rise and a greater increase in postprandial values in patients without preexisting diabetes mellitus. The mechanism whereby hyperglycemia could be explained is multifactorial, including heightened hepatic gluconeogenesis, inhibition of glucose uptake in adipose tissue, and alteration of receptor and postreceptor functions.[8]

This is important because hyperglycemia was found to be an independent risk factor for morbidity and mortality in SARS, and mortality of COVID-19 in patients with diabetes was found to be 7.6% versus 0.9% in patients with no comorbidities. This could be explained by the changes in glycosylation of the ACE2, as well as glycosylation of the viral spike protein, that may disturb the binding of the viral spike protein to ACE2 and the degree of the immune response to the virus. Eventually, glycosylated ACE2 in the lung, nasal airways, tongue, and oropharynx in uncontrolled hyperglycemia could enhance SARS-CoV-2 viral binding sites and lead to a higher propensity to COVID-19 infection and a higher disease severity.[9]

Improper use of systemic CSs can increase the risk of osteonecrosis of the femoral head. In a retrospective study of 539 patients with SARS who received CS therapy, the incidence of steroid-induced osteonecrosis of the femoral head was 24% and

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was associated with total CS dose and with the use of more than 1 type of CSs. The authors recommended cautious use of CSs as a routine treatment in COVID-19 patients and suggest limiting it to patients with septic shock or critical cases.[10] If we consider that COVID-19 affects more the elderly population, where there is usually more osteoporosis, this risk probably worsens, although this has not been confirmed.

Corticosteroid mechanism of action is summarized in Table 1.

CORTICOSTEROID UTILITY IN COVID-19

Evidence Against

A systematic review and meta-analysis on outcomes of patients with SARS-CoV or MERS infection showed that the CS use did not decrease deaths, hospital stay length, or invasive ventilation requirement. With this background, its effect on SARS-CoV-2 has been studied very carefully.[11]

On January 28, 2020, the WHO did not recommend the routine use of systemic CSs for treatment of viral pneumonia or acute respiratory distress syndrome (ARDS) outside of clinical trials, unless indicated for another reason. The WHO stated that CSs do not have benefit in terms of patient's survival and have possible risks such as avascular necrosis, psychosis, diabetes, and viral clearance delay.[12] However, China's National Health Commission recommended a systematic CS treatment (methylprednisolone, <1–2 mg/kg bodyweight, for 3–5 days) as an adjuvant therapy for severe COVID-19.[13] From then on, controversial evidence emerged.

On February 6, 2020, Russell et al[14] reported that clinical evidence did not support the CS treatment for COVID-19 based on extrapolation of the experience with other respiratory viruses. They described that CSs in MERS delayed clearance of viral RNA from respiratory tract, that in SARS-CoV there was a delay in viral clearance from blood as well, and that in patients with influenza CS use was associated with increased mortality.[14]

A systematic review and meta-analysis of the literature contemplated 15 studies that included 5270 patients with COVID-19 pneumonia from January to March 2020. Corticosteroid use was associated with higher mortality rate, longer hospital stay, higher risk of bacterial superinfection, and hypokalemia.[15] Wang et al[16] also showed that CSs increased the days of hospitalization in intensive care unit (ICU).

One of the great concerns of using CSs is the decrease in viral clearance and the consequent worsening of the disease. Ling et al[17] showed that patients with COVID-19 that received CSs had persistence of viral RNA in pharyngeal swabs and in fecal samples.

RECOVERY, a controlled, open-label trial that compared a range of possible treatments in patients who were hospitalized with COVID-19, showed that dexamethasone did not provide any benefit among nonventilated patients at randomization, even with potential harm in this subgroup. They also demonstrated that CSs did not improve mortality when used before 7 days after the onset of symptoms.[18]

Evidence in Favor

Considering that SARS-CoV-2 infection is a new entity, there is more information about CS use in other infections. In terms of bacterial infections, previous randomized clinical trials (RCTs) have shown that adjuvant CS therapy could modulate inflammatory responses, reducing treatment failure and shortening the time to clinical stability in community-acquired pneumonia without significant adverse events.[19] Corticosteroids in critical SARS patients in Guangzhou resulted in lower mortality and shorter hospitalization, and was not significantly associated with secondary lower respiratory infection or other complications.[20] In other studies, patients with SARS who received high doses or a pulse dosage of CSs had fewer requirements for oxygen and better radiographic outcome than those who did not.[21,22]

In COVID-19 patients, the less controversial indication has been in patients with ARDS. In this group, CS use has been associated with decreased risk of death.[23] A randomized controlled clinical trial showed that administration of dexamethasone reduced the duration of mechanical ventilation (MV) and overall

TABLE 1. Summary

CS mechanism of action
1. Antagonize macrophage differentiation and suppress their production of IL-1, IL-6, TNF
2. Suppress neutrophil adhesion to endothelial cells and impair their lysosomal enzyme release, the respiratory burst, and chemotaxis to the inflamed site
3. Impair dendritic cell maturation and function
4. Inhibit T-cell activation
5. Impair the maturity of double positive T lymphocytes
Evidence in favor for CS use in COVID-19 patients
1. Low-dose and short-term application of methylprednisolone in COVID-19 patients was associated with faster improvement of oxygen saturation and lower length of hospitalization and ICU stay.
2. Hospitalized COVID-19 patients that received dexamethasone showed a reduce death rate by one third in patients receiving invasive MV and by one fifth in patients receiving oxygen without invasive MV.
3. In patients with COVID-19 and ARDS, the treatment with CS has shown decreased risk of death.
4. Administration of dexamethasone in COVID-19 patients reduced the duration of MV and overall mortality in patients with moderate-to-severe ARDS.
Evidence against the use of CS in COVID-19 patients
1. CS has been associated with higher mortality rate, longer hospital stay, higher risk of bacterial superinfection, and increased the ICU hospitalization days in COVID-19 patients.
2. COVID-19 patients that received CSs have shown persistence of viral RNA in pharyngeal swabs and in fecal samples.
3. CS therapy was associated with increased odds of prolonged duration of viral shedding.
4. CS has not demonstrated improvement in mortality when used before 7 days after the onset of symptoms.

TNF, tumor necrosis factor; MV, mechanical ventilation.

mortality in patients with moderate-to-severe ARDS.[24] The recent multinational Surviving Sepsis Guideline in COVID-19 panel, formed by 36 experts from 12 countries, proposes giving CSs in patients with severe COVID-19 on MV with ARDS to reduce the destructive inflammatory immune response and to treat suspected adrenal insufficiency associated with sepsis, particularly in those with refractory shock.[25]

Some studies have shown benefits of the use of CSs in COVID-19 patients before the development of ARDS. A retrospective cohort study comparing the clinical outcomes of severe COVID-19 patients with or without methylprednisolone concluded that early (before the development of ARDS), low-dose, and short-term application of methylprednisolone was associated with faster improvement of oxygen saturation and lower length of hospitalization and ICU stay, so that CSs should be considered before the occurrence or ARDS.[26] In the same line, in a multicenter quasi-experimental study, a short course of methylprednisolone in moderate-to-severe COVID-19 patients reduced the escalation of care from ward to ICU, new requirement for MV, and mortality.[27]

The first published RCT study, RECOVERY, analyzed 2104 hospitalized COVID-19 patients who received dexamethasone. Deaths were reduced by one third in patients receiving invasive MV (29.0% vs 40.7%; relative risk [RR], 0.65; 95% confidence interval [CI], 0.51–0.82; $p < 0.001$), by one fifth in patients receiving oxygen without invasive MV (21.5% vs 25.0%; RR, 0.80; 95% CI, 0.70–0.92; $p = 0.002$), but did not reduce mortality in patients not receiving respiratory support at randomization (17.0% vs 13.2%; RR, 1.22; 95% CI, 0.93–1.61; $p = 0.14$).[18]

After the RECOVERY results were published, it was considered unethical to keep enrolling patients with COVID-19 in other placebo-controlled trials of CSs, and other RCTs were halted. Three large halted studies published their results soon after. The REMAP-CAP trial, a multicenter, multinational adaptive platform trial for pneumonia, suggested benefit for hydrocortisone in patients with severe COVID-19, but as it was stopped early and no treatment strategy met the prespecified criteria for statistical superiority, no definitive conclusions can be drawn.[28] The CoDEX trial in Brazil showed that intravenous dexamethasone plus standard care, compared with standard of care alone, resulted in a statistically significant increase in the number of days alive and free of MV over 28 days. Although 28-day mortality was not significantly different, stopping the study early resulted in a sample size underpowered to adequately evaluate this effect.[29] In the CAPE COVID, a blinded, placebo-controlled trial, of critically ill patients with COVID-19 and acute respiratory failure, low-dose hydrocortisone, compared with placebo, did not significantly reduce death or persistent respiratory support at day 21. This study was also stopped early and underpowered.[30]

Post mortem lung pathology of patients who died by COVID-19 have shown different patterns of fibrosis and organization (acute fibrinous and organizing pneumonia, lung fibrosis, and organizing pneumonia) correlated with lung image findings. Although CSs are not routinely recommended for these complications, this could be another scenario where CSs could have a role in COVID-19 patients.[31]

DISCUSSION

Corticosteroids are affordable and available medicines, well known by clinicians. However, they do have several undesirable adverse effects. Among them, the most worrying is the temporary immunodeficiency they produce, which clinically could translate into slower viral clearance and, therefore, complications from the virus itself.

Despite the adverse effects related to the treatment and the fact that some studies in SARS and MERS have demonstrated lack of usefulness of CSs in these infections,[11] it should be considered that these conclusions probably obscured the clinical benefits obtained with this drugs in some subgroups of patients, particularly those with severe symptoms, as the clinical effects might be related to the severity of illness, the timing of intervention, the dose, and duration of CS therapy.[32]

Many articles have been published in favor and against the use of CSs in COVID-19, but after RECOVERY published its results, the guidelines changed, including dexamethasone, and other CSs, as standard care in hypoxic patients.[33] We believe that, in the first days of infection, in which the main cause of symptoms and systemic damage is secondary to viral replication, the use of CSs could be harmful, by potentially delaying viral clearance. In healthy patients without immunocompromise, the viral phase is, usually, not long, and the reductions in viral load concur with the inflammatory phase secondary to activation of the immune system. The intersection of both phases, where hypoxia and hyperinflammation usually coincide, seems to be the better time, the "window of opportunity," to use CSs. This moment could be detected by clinical findings and laboratory tests (ferritin, C-reactive protein, NLR, IL-6, D-dimer, lactate dehydrogenase).[34] Critically ill patients with COVID-19 have an overwhelming inflammation and cytokine-related lung injury, which can physiopathologically end in fibrosis.[35,36] Corticosteroids could be an adjuvant therapy, and it could be useful to prevent or treat chronic lung complications derived from the disease.

It would be ideal to have biomarkers that could predict success with CS treatment. A single-center retrospective cohort study in a university hospital in Madrid that included 463 hospitalized patients with COVID-19 pneumonia treated with CSs showed that lactate dehydrogenase was a good marker that could be useful in the decision of starting CSs, because it can be considered a surrogate marker for the extent of lung involvement and patients with more extensive lung damage might benefit more from CS treatment. However, more evidence is needed to use it as a unique biomarker.[34]

Although there is evidence in favor of the use of CSs in COVID-19, it is important to consider that, as COVID-19 is a new disease, results should be interpreted cautiously, and in any case, it is necessary to be very meticulous when choosing the moment and the dose of CSs, because these medications can affect adaptive immunity by inhibiting lymphocyte activation and promoting lymphocyte apoptosis. At high concentrations, glucocorticoids also inhibit the production of B cells and T cells.[7] Whether or not this affects seroconversion in patients with COVID-19 is not clear at this time, but at least in terms of pathophysiology it is a possibility. Therefore, whenever we think about indicating CSs, we must weigh the risks and benefits and carefully consider the best time of use, especially in patients without hypoxia or those that are in the first week of symptoms.

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