Dexamethasone in Treatment of COVID-19

Subjects: Infectious Diseases

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Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has rapidly spread globally, becoming a huge public health challenge. Even though the vast majority of patients are asymptomatic, some patients present with pneumonia, acute respiratory distress syndrome (ARDS), septic shock, and death. It has been shown in several studies that the severity and clinical outcomes are related to dysregulated antiviral immunity and enhanced and persistent systemic inflammation. Corticosteroids have been used for the treatment of COVID-19 patients, as they are reported to elicit benefits by reducing lung inflammation and inflammation-induced lung injury. Dexamethasone has gained a major role in the therapeutic algorithm of patients with COVID-19 pneumonia requiring supplemental oxygen or on mechanical ventilation. Its wide anti-inflammatory action seems to form the basis for its beneficial action, taming the overwhelming “cytokine storm”. Amid a plethora of scientific research on therapeutic options for COVID-19, there are still unanswered questions about the right timing, right dosing, and right duration of the corticosteroid treatment.

Keywords: dexamethasone ; corticosteroids ; COVID-19

1. Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has rapidly spread around the world since its first appearance in China [1][2][3]. Although the vast majority of patients present with mild symptoms, about 15% of COVID-19 cases become severe [4], with approximately 31–41.8% of hospitalized patients rapidly developing acute respiratory distress syndrome (ARDS) [1][2] with a subsequent increased risk of death. The mortality rates referring to critically ill COVID-19 patients range between 26% and 61.5% around the world [1][2][3][4].

In the context of inflammation being a key role player in the evolvement of severe disease, corticosteroids have been used for the treatment of COVID-19 patients, as they are reported to elicit benefits by reducing lung inflammation and inflammation-induced lung injury. Early enough, in the first pandemic wave, corticosteroids were introduced in the treatment of critically ill COVID-19 patients with respiratory failure in low-to-moderate doses and for short courses [4][5][6][7]. Wu et al. showed that the corticosteroid treatment in patients with ARDS reduced the mortality risk (46% in patients receiving corticosteroids vs. 61.8% in patients not receiving corticosteroids [8]. Furthermore, the Surviving Sepsis Campaign suggests the use of low-dose corticosteroid therapy in COVID-19 patients with refractory shock to suppress the cytokine storm caused by SARS-CoV-2 and to improve peripheral vasodilation [9]. With the RECOVERY trial, a significant benefit of glucocorticoid dexamethasone was shown in patients with COVID-19 on mechanical ventilation or oxygen alone at the time of randomization [10]. Based on the positive results of the RECOVERY trial, the National Institutes of Health (NIH) COVID-19 Treatment Guidelines and the World Health Organization (WHO) approved the findings on the beneficial use of dexamethasone in treating critically ill patients with COVID-19 and recommended the dexamethasone treatment in hospitalized patients with respiratory failure requiring a noninvasive/high-flow oxygen device or invasive ventilation [11]. Nonetheless, several studies have reported deleterious effects caused by the corticosteroid treatment that was associated with the use of an increased dose of corticosteroids [12][13][14], the delay of SARS-CoV-2 viral clearance in patients receiving corticosteroids [12][15], and the increased risk of secondary infections and complications due to the corticosteroid treatment. Therefore, the clinical benefit of this treatment in COVID-19 patients still remains controversial.

2. Dexamethasone in COVID-19: Mode of Action

Corticosteroids are known to temper down the host inflammatory response in the lungs, which may lead to acute lung injury and ARDS [16]. They exert their anti-inflammatory effects by binding to their receptor, the glucocorticoid receptor-GR. GR is a ligand-activated transcription factor whose signaling plays a key role in the modulation of numerous biological functions of the immune cells. Upon ligand binding, GR translocates to the nucleus, where it can enhance transcription by binding to glucocorticoid response elements (GREs). On the other hand, GR, when tethering directly to negative

glucocorticoid response elements (nGREs) or GRE half-sites or by binding to transcription factors such as NF-κB, may repress the expression of several genes [17]. Thus, it is evident that the corticosteroid treatment is a double-edged sword, which may induce or inhibit inflammatory cell activity. Several studies have shown that corticosteroids may inhibit T-lymphocyte immunity, an important antiviral mechanism, resulting in persistent viral replication and a delay in viral clearance. At the same time, the suppression of proinflammatory cytokines such as TNF, interleukins, and other genes, such as cyclooxygenase-2 and inducible nitric oxide synthase (iNOS), and the inhibition of the neutrophils, macrophages, and lymphocytes inflammatory activity are documented as effects of corticosteroid use [18].

Dexamethasone has both anti-inflammatory and immunosuppressive effects. Specifically, when binding to GR, it initiates a cascade of immune cell responses that lead to the suppression of proinflammatory cytokines, such as IL-1, IL-6, IL-8, TNF, and IFN-γ, by inhibiting gene transcription [18]. In the case of SARS-CoV-2 infection, those are the produced proinflammatory cytokines that result in local tissue inflammation and in the so-called “cytokine storm” [19]. Furthermore, dexamethasone exerts anti-inflammatory effects by inhibiting macrophage activation [20], neutrophil’s adhesion to endothelial cells, and the release of lysosomal enzymes, preventing chemotaxis at the site of inflammation. Finally, it increases IL-10 gene expression, thus exhibiting further anti-inflammatory effects [21].

3. Dexamethasone in COVID-19: Clinical Considerations

3.1. When to Start Corticosteroids?

The time of corticosteroid treatment initiation is of great importance in order to have favorable outcomes. Siddiqi and Mehra [22] suggested three escalating phases of COVID-19 disease progression, with associated signs, symptoms, and potential phase-specific treatments: the early infection phase, the pulmonary phase, and the hyperinflammation phase, in which anti-inflammatory treatments (such as corticosteroids) are recommended as beneficial. Indeed, in the RECOVERY trial [10], a clear benefit was shown in the patients who were treated with dexamethasone for more than 7 days after symptom onset, when inflammatory lung damage was likely to be more common, and not among those with more recent symptom onsets. It is evident that randomized controlled trials are needed in order to clarify the right timing for the initiation of a corticosteroid treatment course.

3.2. At What Dose and for How Long?

Another consideration is whether “one size fits all” and how effective dexamethasone is in the dose of 6 mg/day for ten days in all COVID-19 patients with respiratory failure, irrespectively of them developing ARDS or not. This daily dose is considered low, with few adverse events [23], as opposed to the 20–40 mg needed daily for hematologic malignancies, autoimmune diseases, or shock.

In an early single-center observational study in Wuhan [24], there was a lower risk of death in the patients who received low-dose corticosteroids (<1 mg/kg/day) or no corticosteroids at all compared to high-dose regimens, but the difference was not statistically significant.

In the CoDEX randomized trial in patients with COVID-19 with moderate-to-severe ARDS, the dose of dexamethasone administered (20 mg of dexamethasone intravenously daily for 5 days and 10 mg of dexamethasone daily for 5 days or until ICU discharge) [25] was higher than that used in the RECOVERY trial. The selection of this higher dose was based on the design of a previous study [26] in patients with non-COVID-19 ARDS who were treated with dexamethasone (or equivalent) in the dose of 30 mg/day. Eventually, a statistically significant increase in the number of ventilator-free days (days alive and free of mechanical ventilation) was shown over 28 days, with a good safety profile [25].

Furthermore, Papamanoli et al. [27] showed that, in nonintubated patients with severe COVID-19 pneumonia, higher doses of methylprednisolone (160 mg for a median duration of approximately 10 days) were associated with a lower risk for mechanical ventilation or death (37%) and without consequent adverse effects. Interestingly, among the intubated patients, those that were treated with corticosteroids had more ventilator-free days and shorter length of ICU stays compared to the patients not receiving corticosteroids.

Fernandez-Cruz et al. [28] showed lower in-hospital mortalities in patients with SARS-CoV-2 pneumonia treated with corticosteroids, no matter if they received an initial regimen of 1 mg/kg/day of methylprednisolone or with corticosteroid pulses.

A more recent review and meta-analysis of 35 studies by Cano et al. [29] depicted the high heterogeneity of the practices in dosing steroids; in 74.2% of the studies, steroids were given in low doses, in 11.4%, in high or pulse doses, and in 5.6%, a mixed regimen was used. The meta-analysis failed to prove a beneficial or harmful effect of either dosing scheme.

To complicate the dosing dilemmas further, the published data showed that serum albumin plasma levels, competing drugs, and albumin glycation are important clinical variables influencing the effectiveness of dexamethasone in treating COVID-19 patients [30]. Each one of these factors decreases the binding capacity of albumin, complicating the transport capacity of dexamethasone and resulting in a shorter half-life of the drug and potential toxicity at its peak concentration. It might be appropriate to modify the dose of dexamethasone according to the albumin levels, patient's weight, and/or plasma levels in order to achieve the therapeutic levels and to avoid toxicity [31].

From a pathophysiology point of view, as Chrousos and Meduri concluded, corticosteroid administration in severe COVID-19 should start early, before the irreversible exhaustion of homeostatic reserves, with large doses to saturate the ubiquitous glucocorticoid receptors, so that the maximum effect is attained [32][33]. Following precision medicine, the dosing of corticosteroids should be tailored to each patients' unique manifestations, as Gogali et al. explained [34]. From the evidence-based medicine side, though, it is evident that the optimal corticosteroid dosing and duration of treatment still need clarification, especially in critically ill COVID-19 patients with ARDS. Towards this direction, the results of currently undergoing trials like "HIGHLOWDEXA" [14], assessing the efficacy of high doses of dexamethasone (20 mg/day for 5 days and then 10 mg/day for 5 days) vs. low doses of dexamethasone (6 mg/day for 10 days) in patients with respiratory failure might shed more light on the therapeutic algorithms of severe COVID-19.

3.3. Do Corticosteroids Prolong Viral Shedding?

An analysis of the retrospective observational studies from the first pandemic wave showed results associating corticosteroids with immune suppression, an increased viral load, delayed clearance from the body, and increased mortality [15][35]. The early administration of corticosteroids in non-severely ill patients may be deleterious due to an increase of viral shedding or a delay in viral clearance [36]. Prolonged viral shedding has been supported by several retrospective studies [8][37]. Notably, nonsevere COVID-19 pneumonia patients who received early corticosteroid treatment had a more prolonged viral shedding compared to patients of similar severity who did not receive corticosteroids, as was shown in two cohorts [38][39] and one randomized study [40]. A recent review and meta-analysis of 15 studies examining, among others, the SARS-CoV-2 clearance concluded a delay in viral clearance in patients receiving corticosteroids compared with patients who did not receive corticosteroids but failed to prove a statistical significance [14]. Importantly, there are implications that viral shedding prolongation follows a dose-dependent scheme of corticosteroids [41]. However, this theory was not confirmed in the study of Fang et al. [42], who used a low dose of corticosteroids in patients with COVID-19; there was no significant difference in the duration of viral shedding between patients receiving and patients not receiving corticosteroids, irrespective of the severity of the disease. Accordingly, no significant difference in the viral clearance was shown in other studies [35][43][44][45][46]. Two retrospective studies by Xu, K. and Shi, D. [47][48] concluded that corticosteroids were not independent predictors of prolonged viral shedding as opposed to the male sex, lymphocytopenia, APACHE score, and IVIG treatment.

To sum up, there is no clear conclusion as to whether corticosteroids delay the SARS-CoV-2 clearance, and more importantly, there is no certainty about the clinical significance of this.

3.4. How Safe Are Corticosteroids in the Treatment of Severely Affected COVID-19 Patients?

The long-term use of corticosteroids has well-established adverse effects. The short-term use of steroids, although frequent in the pre-pandemic era, was only recently examined for its potential adverse effects. Two large population-based studies in adults, an American [49] and a Chinese [50] one, underline the increased risk of complications in the outpatient setting. Waljee et al. [49] concluded that, within 30 days of steroid initiation, there was a two to five-fold increase in the incidence rates of fractures, venous thromboembolism, and admission for sepsis, in that order of frequency, in steroid users 18–64 years of age compared to non-users. Yao et al. [50] found a significant increase in gastrointestinal bleeding, sepsis, and heart failure in the respective Chinese population.

Currently the recommendations on corticosteroid use in COVID-19 concern severely ill inpatients requiring O_2 or mechanical ventilation and definitely not outpatients. Is this sicker population threatened by the same harms of short-term corticosteroids use as the general population? The existing literature on COVID-19, although abundant, is not centered on adverse events.

Certain studies concluded that there were no significant differences in serious adverse events between corticosteroid and the standard-of-care groups [51][25][44][40][46][36], while others pointed to a greater probability of myocardial or liver injury, shock [15], and agitation [52] in corticosteroid-treated COVID-19 patients.

Supporting the safety of corticosteroids, the RECOVERY trial [10] reported a similar incidence of new cardiac arrhythmia in the dexamethasone group and the usual care group. In a total of 2104 patients, there were four reports of serious adverse

reactions that were deemed by the investigators to be related to dexamethasone: two of hyperglycemia, one of gastrointestinal hemorrhage, and one of psychosis (all recognized adverse effects of corticosteroids).

In the CAPE COVID trial [53], which was stopped early after the publication of the results from the RECOVERY trial, the administration of a low dose hydrocortisone in 148 patients was followed by three serious events: one was cerebral vasculitis, attributed to the SARS-CoV-2 itself, the second was an episode of pulmonary embolism with cardiac arrest, which was considered single and unrelated to steroids, and the third event was an intrabdominal hemorrhage related to anticoagulation for pulmonary embolism.

In REMAP-CAP [54], the only adverse events that were considered relevant to the corticosteroid treatment were one event of neuromyopathy and one event of fungemia.

The recently published results of the OUTCOMEREA network [55] showed that COVID-19 critically ill patients have a higher risk for bloodstream infections (BSI) than their non-COVID-19 counterparts after 7 days of ICU stay, but this negative event was associated with the use of anti-IL-1 and anti-IL-6 and not to corticosteroids. Similarly, no difference in BSI incidence was detected in the MetCOVID randomized trial [43] or the retrospective study by Papamanoli et al. [27].

On the contrary, Giacobbe et al. [56] in their retrospective single-center study, found a higher BSI risk for corticosteroid-treated patients (csHR 3.95, 95% CI 1.2–13.03) than those receiving only tocilizumab (csHR 1.07, 95% CI 0.38–3.04), the risk being even higher with their combination (csHR 10.69, 95% CI 2.71–42.17).

The clinical research points towards an association between corticosteroid use and secondary infections. More secondary infections with sepsis have been recorded [29][37], but the difference was not always significant [7]. The indirect evidence on increased secondary infections may come from the increased antibiotic use in corticosteroid-treated patients, as two retrospective studies [38][39] and one systematic review and meta-analyses [29] have shown.

The literature is more extensive on fungal infections in COVID-19 patients. Corticosteroid treatment is a well-known risk factor for invasive mycoses [57]. An excellent review of retrospective studies from China and Europe reported a 20–35% incidence of COVID-19-associated pulmonary aspergillosis (CAPA) [58] A case report of mucormycosis following the treatment with dexamethasone was reported in a 44-year-old diabetic woman [59] raising concerns about the duration and dosing of the corticosteroid treatment in diabetic COVID-19 patients. Hyperglycemia, which led to increased doses of insulin, was mentioned in most studies [7][52][43][40] as an adverse event of the corticosteroid treatment as expected, but it was not severe [25].

Reviewing the literature concerning the adverse events of corticosteroid treatment in COVID-19 patients, we underline a significant deficit, as safety is not among the primary outcomes of most studies. This is not a surprise, because corticosteroids are used extensively, and physicians are very familiar with their use. Additionally, some of the main adverse effects of corticosteroids (i.e., VTE, secondary infections and GI hemorrhage) are the main COVID-19 complications or harms from other necessary treatments (i.e., anticoagulation), and perhaps, it is difficult to discriminate the proportional contribution of the virus or the steroids.

Targeting a safe treatment alternative to systemic corticosteroids, inhaled corticosteroids (ICS) have been proposed. There is a cumulative experience of ICS in chronic airways diseases like asthma and COPD, linking their use to changes in the microbiome and, finally, to the increased frequency of upper and lower respiratory tract infections [60][61]. However, an association of ICS with the susceptibility to viral infections is lacking. Instead, a paradoxical protection against viral infections has risen [62][63]. Ciclesonide seems to block SARS-CoV-2 replication in vitro, and in addition, it impedes its cytopathogenicity [64][65]. Early-stage COVID-19 treatment with inhaled corticosteroids might inhibit the progression of SARS-CoV-2 infection to COVID-19. This was shown in a small study of COVID-19 patients on oxygen (not mechanically ventilated) who improved after the treatment with inhaled ciclesonide [66] Similarly, there was in vitro evidence of budesonide's direct antiviral and anti-inflammatory properties [67]. In the recent open-label, in parallel groups, phase 2 randomized control trial in mild outpatient COVID-19 patients that received inhaled budesonide vs. the usual care, a 91% reduction in the relative risk for COVID-19-related urgent care or hospitalization was shown in the budesonide-treated patients [68].

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