The use of corticosteroids in COVID-19

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In its most severe form, hyperinflammation driven by a dysregulated immune/inflammatory response to SARS-CoV-2 causes acute respiratory distress syndrome, contributing to disease severity and even death. Several therapeutic interventions are currently being investigated to determine treatment strategies based on the stage of disease progression. Corticosteroid therapy targets hyperinflammation, also known as a "cytokine storm". There are disparities in research findings that probe the benefit of corticosteroids in improving the life expectancy in patients with severe or critical COVID-19. As a result, corticosteroids should be used with caution taking into account the risk-benefit ratio.

Keywords: corticosteroids, COVID-19, SARS-CoV-2

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Introduction

Corticosteroids are a class of drugs commonly used to treat numerous inflammatory and autoimmune diseases.[1,2] Corticosteroids are synthetic analogues of the natural steroid hormones produced by the adrenal cortex. They are indicated for various medical conditions and are among the most widely prescribed drug classes worldwide.[3] There is a growing interest in using corticosteroids to treat the novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).[4] SARS-CoV-2 is believed to have originated in a seafood market in Wuhan, China, in 2019, giving rise to the coronavirus disease (COVID-19).[4] As COVID-19 progresses, patients tend to get more ill, and present with acute respiratory distress syndrome (ARDS), which is associated with a phenomenon known as a "cytokine storm".[5] This occurs when the immune system goes into overdrive, producing large quantities of pro-inflammatory cytokines.[5] The use of corticosteroids by COVID-19 patients has been widely debated and has become a topic of great interest to scientists and healthcare providers. Despite the relatively low cost of corticosteroids,[6] researchers urged caution and the need for further studies to confirm the drug's use in treating COVID-19. Corticosteroids have been registered in the World Health Organization (WHO) list of essential medicines[6] and has now been recommended as a potentially effective treatment against COVID-19.[7] A recent trial evaluating COVID-19 therapy, showed that treatment with dexamethasone, at a dose of 6 mg once daily for up to 10 days significantly decreased 28-day mortality in patients with severe or critical COVID-19.[7] The trial also highlighted the potential harm to patients who did not need supplemental oxygen when given corticosteroids, however, these findings were not statistically significant.[7] In light of this, a second recommendation by the WHO suggests that corticosteroids should not be used when treating patients with non-severe COVID-19.[6] Based on these findings, corticosteroids, therefore, seem to be a double-edged sword in the fight against COVID-19 and need to be used judiciously, taking into consideration the risk-benefit ratio.

Mechanism of action of corticosteroids

Corticosteroids are a class of steroid hormones that are produced and released by the adrenal glands, which include glucocorticoids and mineralocorticoids.[8] Glucocorticoids are produced in the mid-zone of the adrenal cortex, i.e. the zona fasciculata, in response to adrenocorticotrophic hormone (ACTH) released from the anterior pituitary gland.[9] The secretion of ACTH is stimulated by a number of physical or psychological stressors.[10] These steroids act by binding to intracellular receptors, which then modulate gene transcription in target tissues.[8] Steroids are carried by the transporter glucocorticoid binding protein to the target site,[11] where they diffuse across the cell membrane and bind to the glucocorticoid receptor complex coupled to two heat shock proteins located within the cytoplasm.[12] This induces a conformational change in the receptor,[13] resulting in its activation and dissociation of two proteins from the complex, which in turn allows the activated glucocorticoid receptor complex to translocate into the nucleus, where it dimerises and binds to the glucocorticoid response element.[14] This activates the complex and alters gene transcription,[13,14] while inhibiting the transcription factors responsible for

controlling the production of pro-inflammatory mediators in lymphocytes, eosinophils, macrophages, mast cells, and dendritic cells.[13] Firstly, it upregulates the gene for lipocortin. Lipocortin, in turn, inhibits the phospholipase A2 enzyme, responsible for the production of numerous inflammatory mediators by preventing the liberation of arachidonic acid from membrane phospholipids reducing the production of prostaglandins, prostacyclin and thromboxane A2.[15] Secondly, the activated complex decreases gene transcription for other proteins leading to down-regulation of the cyclooxygenase II enzyme while reducing neutrophil migration to inflammatory sites.[13]

Efficacy of corticosteroids in COVID-19 patients

Since corticosteroids have been shown to be effective in a number of medical conditions, including inflammatory diseases, it is imperative to investigate their efficacy in COVID-19 patients. In a controlled, open-label trial, a number of treatments in hospitalised patients with COVID-19 were assessed.[7] Patients were administered either oral or intravenous (IV) dexamethasone at a dosage of 6 mg once daily for up to 10 days, or were given standard care alone (Table I).[7] The study aimed to measure 28-day mortality in hospitalised patients with COVID-19. Results from the study suggested that 6 mg of dexamethasone once daily for up to 10 days as compared to patients who received usual care (receiving invasive mechanical ventilation at randomisation or oxygen alone), resulted in a reduction in 28-day mortality among patients; however, not among those that did not receive respiratory support.[7]

A study conducted by the WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group aimed to establish if there was a link between corticosteroid therapy and 28-day all-cause mortality when compared to usual care or placebo.[16] Data from seven randomised clinical studies evaluating the efficacy of corticosteroids in 1 703 critically ill patients with COVID-19 were collected in this study.[16] The trials were conducted in 12 countries between February and June 2020, with the final follow-up in July 2020. Six hundred and seventy-eight patients were randomly assigned to receive systemic methylprednisolone, dexamethasone, hydrocortisone, or to receive usual treatment or placebo (1 025 patients) (Table I).[16] In this prospective meta-analysis of clinical trials, the administration of systemic corticosteroids, compared to usual care or placebo, was associated with decreased 28-day all-cause mortality in critically ill patients with COVID-19.[16] The studies, however, had limited population sizes (adult recruitment only) and carried a minimal risk of bias. In addition, there were limited missing outcome data and several trials censored follow-ups following patient discharge from the hospital (Table I).[16]

Tomazini et al. investigated the effect of IV dexamethasone and standard care compared with standard care alone on days alive and ventilator-free in patients with moderate or severe ARDS and COVID-19.[17] In this CoDEX randomised clinical trial (RCT), when comparing patients treated with dexamethasone together with standard care, to patients treated with standard care alone, the number of days alive and free from mechanical ventilation during the first 28 days was considerably higher in the dexamethasone plus standard care group, i.e. 6.6 days vs 4.0 days (Table I).[17] These results were found to be statistically significant.[17] However, published data on adverse events and infections may have led to bias with regards to how these events were described. The design of this trial was open labelled due to time constraints in producing placebo during the COVID-19 pandemic.[17] In addition, sample sizes were limited (Table I).[17]

A study conducted by Wang et al. investigated the efficacy and safety of corticosteroids in patients with severe COVID-19 pneumonia.[18] The study included 46 patients that were divided into two groups, group one (26 patients) received methylprednisolone (1–2 mg/kg/d for 5–7 days), while group two received standard therapy without methylprednisolone (Table I).[18] Findings revealed that the early administration of a low dose, short-term corticosteroids in patients with severe COVID-19 pneumonia demonstrated faster improvement in clinical symptoms, namely, fever and peripheral oxygen saturation as well as lung lesions as detected by imaging.[18] In addition, patients who did not receive methylprednisolone required longer periods of supplemental oxygen.[18] The study had the following limitations: small sample sizes and failure to include mid- and long-term outcomes following patient discharge, as well as follow-up observations (Table I).[18]

A study by Sarkar et al. aimed to analyse evidence on the efficacy and safety of systemic steroid therapy in treating patients with COVID-19.[19] The paper analysed 12 studies, comprising ten cohort studies and two RCTs (total participants, n = 15 754 patients).[19] Administration of systemic glucocorticoids in patients with COVID-19 was not found to have an effect in reducing mortality (odds ratio [OR] = 1.94, 95% confidence interval [CI] 1.11–3.4, I^2 = 96%), nor did it shorten the duration of hospital stay (mean difference [MD] = 1.18 days, 95% CI -1.28–3.64, I^2 = 93%) and period of viral shedding (MD = 1.42 days, 95% CI -0.52–3.37, I^2 = 0%) (Table I).[19] The study concluded that systemic steroid therapy may be ineffective in reducing the mortality rate, duration of hospital stay, and period of viral shedding in patients with COVID-19.[19] It was recommended that further RCTs be carried out due to the heterogenicity and low quality of evidence of many of the current studies.[19] The study did not provide evidence of benefit to patients infected with COVID-19. Many of the studies included were not peer-reviewed (Table I).[19]

The effect of hydrocortisone on treatment failure on day 21 in critically ill patients infected with SARS-CoV-2 and acute respiratory failure was investigated in a study by Dequin et al.[20] The administration of low-dose hydrocortisone, compared with placebo, was not found to significantly reduce treatment failure (defined as death or persistent respiratory

support) on day 21 (Table I).[20] However, it is important to note that the study was terminated quite early, and as a result, it was likely to demonstrate a statistical and clinically important difference in the primary outcome.[20] In addition, data related to COVID-19, e.g. prevalence of hypertension, was not included. To date, the COVID-19 pandemic has not made it possible to collect and analyse data (Table I).

In a prospective, multicenter, single-blind RCT by Tang et al., the efficacy and safety of a corticosteroid administered to hospitalised patients with COVID-19 pneumonia were investigated.[21] Adult patients admitted to the general ward with COVID-19 pneumonia were assigned at random to either receive or not to receive methylprednisolone for 7 days. The incidence of clinical deterioration, 14 days following randomisation was measured as the primary endpoint.[21] The trial was terminated prematurely as the number of patients with COVID-19 pneumonia had

Table I: Summary of clinical data from trials conducted on corticosteroids in COVID-19

Authors	Treatment or Intervention	Treatment outcome	Limitation(s)
The randomised evaluation of COVID-19 therapy (RECOVERY) Collaborative Group[7]	A total of 2 104 patients received dexamethasone (dose of 6 mg once daily for up to 10 days) vs 4 321 patients receiving usual care	Dexamethasone resulted in a reduction in 28-day mortality in patients receiving invasive mechanical ventilation or oxygen alone; however, not among patients receiving no respiratory support	None reported
The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group[16]	Systemic dexamethasone, hydrocortisone, or methylprednisolone (678 patients) vs usual care or placebo (1 025 patients)	Systemic corticosteroids, compared to usual care or placebo, was associated with decreased 28-day all-cause mortality in critically ill patients with COVID-19	Limited population sizes (adult recruitment only) Risk of bias (minimal) Limited missing outcome data Several trials censored follow-ups following patient discharge from the hospital
Tomazini et al.[17]	Dosage: 20 mg of dexamethasone IV daily for 5 days, 10 mg of dexamethasone daily for 5 days or until ICU discharge, plus standard care (n=151) or standard care alone (n=148)	IV dexamethasone plus standard care compared with standard care alone resulted in an increase in the number of ventilator-free days over a period of 28 days	Data on adverse events and infections may have led to bias Time constraints in producing placebo Limited sample size
Wang et al.[18]	Methylprednisolone (1–2 mg/kg/d for 5–7 days) vs standard therapy without methylprednisolone	Faster improvement of clinical symptoms Patients that did not receive methylprednisolone required longer periods of using supplemental oxygen	Small sample size Failure to include mid- and long-term outcomes following patient discharge, as well as follow-up observations
Sarkar et al.[19]	Systemic glucocorticoids	Administration of systemic glucocorticoids was not found to have an effect in reducing mortality, nor did it shorten the duration of hospital stay and period of viral shedding in patients with COVID-19	Study fails to provide any evidence of benefit in patients with COVID-19 Findings were heterogeneous and of low-quality evidence A large number of the studies included were not peer-reviewed
Dequin et al.[20]	Low-dose hydrocortisone (n=76) or placebo (n=73)	Administration of low-dose hydrocortisone, compared with placebo, was not found to significantly reduce treatment failure at day 21	Study was terminated early, and as a result, it was likely to demonstrate a statistical and clinically important difference in the primary outcome
Tang et al.[21]	Methylprednisolone for 7 days vs no methylprednisolone	No significant difference in the incidence of clinical deterioration between the group receiving methylprednisolone compared to the control group Short-term early use of corticosteroids could potentially suppress immune cells, which in turn could prolong SARS-CoV-2 shedding in patients with COVID-19 pneumonia	Study was terminated prior to reaching the goal size due to the decreased number of cases of COVID-19 in China Quantitative viral load measurement was undetected Presence or absence of SARS-CoV-2 RNA in throat swabs was detected but not in the blood or the other specimens Observation durations were short, making it difficult to follow up long-term complications

decreased.[21] Eighty-six patients with COVID-19 underwent randomisation.[21] Results from the study showed no difference in the incidence of clinical deterioration between the group receiving methylprednisolone and the control group (4.8% vs 4.8%, $p = 1.000$) (Table I).[21] The study concluded that the short-term early use of corticosteroids could potentially suppress immune cells, which could prolong SARS-CoV-2 shedding in patients with COVID-19 pneumonia.[21] The study was terminated prior to reaching the goal size due to a reduction in COVID-19 cases in China. Quantitative viral load measurement was undetected. Additionally, the presence or absence of SARS-CoV-2 ribonucleic acid in throat swabs was detected; however, it was not found in the blood or other specimens. Lastly, the duration of observations was short, thus making it difficult to follow up long-term complications (Table I).[21]

Discussion

A systemic inflammatory response in patients with severe COVID-19 can result in acute lung injury and multisystem organ dysfunction. It is believed that the anti-inflammatory effects of corticosteroids may play a role in preventing or mitigating these effects. Due to their anti-inflammatory activities, corticosteroids have been used as adjuvant therapy for acute respiratory distress syndrome associated with viral infections.[22] However, there have been controversial reports, with some discouraging their use while others promote them. The studies investigated confirm the beneficial use of corticosteroids in treating patients with COVID-19. Based on the evidence obtained from the various clinical trials, systemic corticosteroid therapy was recommended for severe and critically ill COVID-19 patients. Corticosteroid therapy has demonstrated promising efficacy in stabilising haemodynamics, shortening intensive care unit stay and the duration of mechanical ventilation needed.[23] The safety of corticosteroids has been concluded based on evidence that suggested that systemic corticosteroids reduced the 28-day mortality rate in patients with critical COVID-19.[7,16]

In addition, the ease of administration, relatively short duration of action, and the general safety profile of systemic corticosteroids led to the acceptability and approval of corticosteroid therapy in COVID-19 patients. Generally, corticosteroids are well tolerated; however, adverse effects have been linked to their prolonged usage. Side effects are less common in short-term treatment, even at high doses; however, long-term use has also been linked to glaucoma, myocardial infarction, stroke, osteoporosis, and gastrointestinal ulcers. However, one of the most serious side effects associated with the use of corticosteroids is the increased risk of infection. Opportunistic infections are also believed to occur when an individual's immune system is weakened by corticosteroids. In addition, there may be an increased risk of potential drug-drug interactions as corticosteroids may induce cytochrome P450 enzymes.[24] Furthermore, the reported studies have noted several limitations, confounding factors, and potential bias. In summary, the WHO has concluded that routine corticosteroid use, i.e. systemic (IV or oral) corticosteroid therapy at a dosage of 6 mg of dexamethasone or 50 mg of hydrocortisone IV every 8 hours for a period of 7 to 10 days is recommended in patients with severe and critical COVID-19. In addition, corticosteroid therapy is not to be used in patients with non-severe COVID-19.[25]

Conclusion

Results obtained from various RCTs confirm the beneficial use of corticosteroid therapy in reducing mortality rates in patients, as well as the need for mechanical ventilators. Due to the fact that corticosteroids are affordable and easily accessible to many healthcare systems, which have been terribly strained as a result of the effects of the global pandemic, corticosteroids should only be used where the benefits outweigh the risks. However, further studies will need to be conducted to validate its use in treating COVID-19 patients.

Conflict of interest
The authors declare no conflict of interest.

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