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The Role of Glucocorticoids in the Management of COVID-19

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ABSTRACT

Coronavirus disease 2019 (COVID-19), caused by an infection with the novel coronavirus SARS-CoV-2, has resulted in a global pandemic and poses an emergency to public health systems worldwide. COVID-19 is highly infectious and is characterized by an acute respiratory illness that varies from mild flu-like symptoms to the life-threatening acute respiratory distress syndrome (ARDS). As such, there is an urgent need for the development of new therapeutic strategies, which combat the high mortality in severely ill COVID-19 patients. Glucocorticoids are a frontline treatment for a diverse range of inflammatory diseases. Due to their immunosuppressive functions, the use of glucocorticoids in the treatment of COVID-19 patients was initially regarded with caution. However, recent studies concluded that the initiation of systemic glucocorticoids in patients suffering from severe and critical COVID-19 is associated with lower mortality. Herein we review the anti-inflammatory effects of glucocorticoids and discuss emerging issues in their clinical use in the context of COVID-19.

Introduction

Coronavirus disease 2019 (COVID-19), first reported at the end of 2019 in Wuhan, China, rapidly spread around the globe and was declared a pandemic by the WHO in March 2020 [1]. As of October 2020, more than 30 000 000 cases and 950 000 deaths were reported worldwide. COVID-19 is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). SARS-CoV-2 shows close relation to SARS-CoV, the underlying viral cause of the 2002

SARS epidemic, as well as to MERS-CoV, which causes sporadic outbreaks centered in the Middle East [2]. COVID-19 patients develop an acute respiratory illness, which may cause mild fevers and coughs but may also lead to acute respiratory distress syndrome (ARDS), hypoxic respiratory failure, and ultimately death [3]. Immunologically, critical cases of COVID-19 are signified by an excessive inflammatory response, manifested by strong leukocyte influx into the lungs and increased plasma levels of inflammatory markers [4]. Additionally, coagulopathies and increased risk of blood clot formation have been reported as significant contributors of COVID-19 related mortality [5]. The excessive inflammatory response observed in severe and critical COVID-19 patients raised the possibility of the use of anti-inflammatory drugs to combat the excessive and damaging immune response. While medical professionals were apprehensive about the use of immunosuppressants to treat an infectious disease in the early stages of the pandemic, over time, evidence accrued that glucocorticoids lead to improved patient outcomes [6].

Glucocorticoids and the glucocorticoid receptor (GR)

Glucocorticoids are stress hormones synthesized in the adrenal cortex under the control of the hypothalamic-pituitary-adrenal (HPA) axis [7, 8]. Under normal conditions glucocorticoids are released in a circadian and ultradian rhythm [7, 8]. Stress stimuli activate the HPA axis: in particular pro-inflammatory cytokines, such as IL-6, TNF, and IL-1β, act on the hypothalamus triggering HPA axis activation and leading to adrenal glucocorticoid production [7–9]. In turn, circulating glucocorticoids exert strong immunomodulatory effects and constrain inflammation, while also limiting their own production through a negative feedback on the HPA axis [7, 8, 10]. Following their release into the bloodstream glucocorticoid tissue availability and function are determined by several regulatory mechanisms. Corticosteroid-binding globulin (CBG) binds and keeps approximately 90 % of cortisol in an inactive state. Neutrophil elastase cleaves CBG, thereby releasing bioactive glucocorticoids at sites of inflammation [7, 8]. Moreover, 11β-hydroxysteroid dehydrogenases 1 and 2 (11β-HSD1, 11β-HSD2) regulate the interconversion of bioactive cortisol to inactive cortisone in target tissues [7]. Inflammatory signals can regulate the expression of 11β-HSD1 and 2, which determines local glucocorticoid activity [8].

Glucocorticoids are lipophilic molecules diffusing through the cell membrane and binding to the cytosolic glucocorticoid receptor (GR), which is abundantly expressed in most cell types [7]. The GR contains an N-terminal domain, which interacts with co-factors and transcription factors, a zinc-finger motif-containing DNA-binding domain and a ligand-binding domain [7, 11]. The GR is subjected to post-translational modifications, including phosphorylation, acetylation, ubiquitylation, and sumoylation at multiple sites, which regulate its compartmentalization, function and degradation [11]. While GRα is the ligand-binding GR isoform, its splice isoform GRβ does not bind glucocorticoids and exerts dominant-negative effects on GRα. In its inactive state GR forms complexes with heat-shock proteins, chaperones, and immunophilins. Upon ligation the receptor undergoes conformational changes, partially disassembles from its interactors, translocates to the nucleus, and controls gene transcription as a monomer or dimer [7]. Upon its translocation to the nucleus, GR can directly bind to glucocorticoid response elements (GRE) to induce or inhibit gene expression [7]. High glucocorticoid doses favor binding of GR homodimers rather than monomers on palindromic GRE [12]. In addition, GR can tether transcription factors through protein-protein interactions without the requirement of DNA binding [13]. Through the latter mechanism GR can block the function of transcription factors mediating inflammatory responses, such as nuclear factor-κB (NF-κB) and activator protein 1 (AP-1) [8]. However, transrepression can also be mediated by competition for binding to the DNA or for co-factors [7]. Moreover, GR directly interacts with NF-κB, hindering its translocation to the nucleus and induces the expression of the NF-κB inhibitor glucocorticoid-induced leucine zipper protein (GILZ) [14, 15].

Additionally to the GR-mediated genomic effects, glucocorticoids may also exert non-genomic effects, leading to rapid biological events [7, 16]. This mechanism of action has been shown to contribute to the effects of glucocorticoids on T-cell receptor (TCR) signaling, neutrophil degranulation, macrophage inflammatory activation, mast cell-mediated histamine release and ion channel function in bronchial epithelial cells [16–18].

Anti-inflammatory effects of glucocorticoids

Glucocorticoids regulate inflammation through pleiotropic mechanisms [8, 19]. Their effects on immune responses depend on the cell type, disease, dose and timing of application, that is, whether application precedes or follows exposure to the inflammatory stimulus [20–22]. While exposure to low doses of glucocorticoids prior to a noxious stimulus can promote the inflammatory response, glucocorticoids in high doses applied after the inflammatory stimulus act in an anti-inflammatory fashion [8, 19–22]. In the absence of inflammation, glucocorticoids promote the expression of pattern recognition receptors (PRR), such as Toll-like receptor (TLR), thereby maintaining the cells sensitivity to noxious stimuli, such as pathogen- and damage-associated molecular patterns (PAMP, DAMP) [8, 19]. In the context of an acute inflammatory response glucocorticoids taper inflammation through several mechanisms. Glucocorticoids inhibit PRR signaling by tethering NF-κB and AP-1 and induce the expression of negative regulators of TLR signaling, such as dual-specificity protein phosphatase 1 (DUSP1) and IL-1 Receptor-Associated Kinase M (IRAK-M) [8, 23]. In macrophages glucocorticoids down-regulate the expression of pro-inflammatory cytokines, such as IL-1β, IL-6, IL-12, IL-17, TNF, and granulocyte–macrophage colony-stimulating factor (GMCSF), and inducible nitric oxide synthase (iNOS) and inhibit cyclooxygenase 2 in a GILZ-dependent manner, thereby attenuating release of prostaglandins [8, 22, 24–27]. Moreover, in endothelial cells they inhibit the expression of adhesion molecules, like E-selectin, intercellular adhesion molecule 1 (ICAM1) and vascular cell adhesion molecule 1 (VCAM1). In immune cells they down-regulate the expression of integrins, such as lymphocyte function-associated antigen 1 (LFA1) and very late antigen 4 (VLA4), thereby attenuating leukocyte recruitment [8, 28, 29]. Glucocorticoids also shift macrophages towards an anti-inflammatory state, which secretes more IL-10 and transforming growth factor-β (TGFβ), and promote efferocytosis and cell debris clearance due to increased expression of scavenger molecules (CD163, CD206 and tyrosine-protein kinase MER (MERTK)), thereby favoring resolution of inflammation [8, 19, 22, 30–35]. The

reaction to antigens is regulated by glucocorticoids at both, the level of antigen presentation and T cell activation. Glucocorticoids inhibit maturation, promote apoptosis and attenuate antigen presentation in dendritic cells [8, 36, 37]. Glucocorticoids also regulate thymopoiesis through induction of lymphocyte apoptosis and attenuate T cell receptor signaling [38, 39]. Moreover, glucocorticoids increase regulatory T cell (Tregs) frequency through GILZ and TGFβ-dependent induction of Forkhead box P3 (FoxP3), a transcription factor determining Treg differentiation [40].

Overall, therapeutic glucocorticoids exert potent anti-inflammatory effects across both the innate and adaptive immune system. Due to these wide-ranging anti-inflammatory effects glucocorticoids are a mainstay of immunosuppressive therapies. Synthetic glucocorticoid compounds, such as dexamethasone and prednisolone, show increased potency compared to cortisol owing to longer half-life in plasma, improved parenteral absorption and reduced binding to CBG. However, due to their wide-ranging receptor expression and the large-scale GR-mediated transcriptional changes – overall approximately 20 % of the genome is responsive to GR – glucocorticoids are not only potent immunosuppressants, but also exert broad off-target effects [7, 41, 42].

Adverse effects of glucocorticoids

Adverse effects related to glucocorticoid treatment are common and numerous, and depend on the dose and duration of therapy [7, 42, 43]. A number of glucocorticoid side effects are a result of glucocorticoid-mediated inhibition of glucose uptake and other metabolic alterations of basic cellular metabolism, which typically occur in most cells and tissues [42, 43]. Common side effects include weight gain and the development of diabetes mellitus, sarcopenia, and osteoporosis. Also, an increase in the incidence of hypertension, atherosclerosis, cardiovascular disease, and thromboembolism may be observed. Additionally, therapeutic doses of glucocorticoids raise susceptibility to infections and can cause impaired wound healing, psychiatric disturbances, and suppression of the HPA axis with the risk of secondary adrenal insufficiency [42, 44].

COVID-19 immunopathogenesis and glucocorticoids

Following priming of the viral spike (S) protein through the serine protease TMPRSS2 [45], SARS-CoV-2 gains access to respiratory epithelial cells through the hosts angiotensin-converting enzyme 2 (ACE2) protein [4]. Upon cellular entry, the viral RNA genome is released into the host cell and new virions are produced [46]. The viral capture of the host cell is followed by the initiation of an innate immune response, which features inflammatory cytokine and chemokine production, coupled to neutrophil and monocyte infiltration of the respiratory tract and lungs. This inflammatory response is typically associated with increased capillary leakage and alveolar cell destruction, damaging respiratory function. Systemic inflammation is reflected by increased plasma concentrations of inflammatory cytokines, such as IL-1β, IL-6, IL-8, IL-10, IL-17, IP10, and TNF, in COVID-19 patients, whereas levels of type I and III interferons remain low [47–49]. Increased circulating neutrophil numbers correlate with poor prognosis in COVID-19 and strong neutrophil infiltration of pulmonary capillaries was reported in postmortem lung tissues [47, 50]. The complement system is activated during ARDS and activation of C3 exacerbates disease in SARS-CoV-associated ARDS [51, 52]. Thus, the complement system may drive part of the inflammatory response and thrombosis to COVID-19 [51, 53–55]. Observational studies suggest that, elevated levels of C-reactive protein (CRP) and lactate dehydrogenase are predictors of COVID-19 severity [4, 47]; similar correlations have been established for elevated neutrophil/lymphocyte ratio, low platelet count and increased numbers of $CD14^+CD16^+$ monocytes and Th17 cells [4, 56, 57].

Due to the rapidly developing nature of the COVID-19 pandemic studies examining the molecular effects of glucocorticoids in patients suffering from severe disease are few and far between. Based on the known and extensive immunosuppressive effects of glucocorticoids outlined above, corticosteroid treatment likely attenuates the COVID-19 induced inflammatory response – particularly in severely affected patients. Indeed, administration of glucocorticoids was reported to reduce CRP and IL-6 plasma levels in COVID-19 patients, without affecting virus clearance [58, 59]. Future studies identifying glucocorticoid target cells and anti-inflammatory mechanisms in the context of COVID-19 are critical in order enable the development of targeted therapies in the future.

The clinical use of glucocorticoids in acute respiratory distress syndrome (ARDS) and COVID-19

ARDS is primarily signified by hypoxic respiratory failure. In general, ARDS is associated with increased vascular permeability and pulmonary edema as well as increased systemic inflammation, frequently leading to multi-organ failure and death. Thus, ARDS-related mortality is as high as 50 % [60].

Treatment of ARDS is primarily focused on a combination of low tidal volume mechanical ventilation and prone positioning [61, 62]. Even though inflammation likely plays a key role in the pathogenesis of ARDS, anti-inflammatory therapeutic strategies using glucocorticoids have yielded mixed results. For example, two meta-analysis examining the subject of glucocorticoid use in ARDS a decade ago reached opposite conclusions ranging from advising against their use to recommending steroid treatment in ARDS [63, 64]. These inconsistent conclusions arose from original research studies, which included small numbers of patients, and varied in their definition of ARDS, type of steroid used, as well as timing and dosing strategies. In order to address this issue efforts have been made to clarify the effectiveness of glucocorticoids in ARDS through large-scale multi-centered randomized controlled trials. The recent Dexa-ARDS trial found that patients receiving high-dose dexamethasone had a lower all-cause mortality than patients receiving standard care (21 % vs. 36 % respectively) [64]. A meta-analysis, which included the Dexa-ARDS trial, as well as others, also favored the use of glucocorticoids in ARDS, although some reservations remained regarding the reliability of the findings [65]. Additionally, a recent meta-analysis attempted to dissect the issues of timing and dosing of glucocorticoid use in ARDS and came to the conclusion that early initiation of glucocorticoid therapy and use of a low to medium dose were associated with lower mortality [66]. Overall, the issue of glucocorticoid use in ARDS is still not entirely resolved, however, recent evidence has tipped the balance in favor of glucocorticoid treatment with a recommendation for early commencement of steroids at a low to medium dose. Of note, the

large-scale LUNG SAFE study of 2377 patients with ARDS found an overall rate of glucocorticoid use of < 20 % [60].

With the beginning of the COVID-19 pandemic, medical professionals were at a loss as to whether glucocorticoids could have a role in treating severely affected patients, particularly in those suffering from hypoxic respiratory failure and ARDS. In the absence of studies examining the effects of glucocorticoids in COVID-19 patients specifically, doctors were apprehensive to utilize a potent immunosuppressive agent to treat an infectious disease. Evidence originating from the SARS und MERS outbreaks showed a delayed virus clearance in patients receiving glucocorticoids potentially indicating an impaired host response to the viral infection [67]. Moreover, the use of steroids in the treatment of influenza has been studied to some degree, and while the evidence is far from conclusive, the general consensus does not recommend the use of glucocorticoids in patients suffering from influenza infections [68]. Adding to the concern was an increased risk of bacterial superinfection, which typically is associated with the use of medium to high dose glucocorticoids [69, 70].

Following encouraging case reports and small observational studies using glucocorticoids in severely affected COVID-19 patients, multiple large-scale RCTs were initiated, most notably the RECOVERY trial in the United Kingdom [71]. As part of this study 2104 intrahospital COVID-19 patients received 6 mg of dexamethasone for 10 days (or until discharge from hospital, if sooner), while 4321 patients received standard care [72]. Overall the mortality rate after 28 days was significantly lower in the Dexamethasone group (22.9 vs. 25.7 %). Interestingly, subgroup analysis revealed that patients requiring mechanical ventilation benefited the most from the pharmacological intervention with glucocorticoids. In this group of patients, the mortality after 28 days was reduced by more than 12.1 percentage points in the dexamethasone group (29.3 vs. 41.4 %). Dexamethasone also conferred a survival benefit in patients requiring oxygen – without the need for invasive mechanical ventilation – however, the effect remained small (28-day mortality: 23.3 % vs. 26.2 %). In patients who did not require ventilation support or oxygen Dexamethasone showed no significant effect. Following the publication of the RECOVERY data as a preliminary report, treatment guidelines were updated to recommend the use of glucocorticoids in severely affected COVID-19 patients. This also led to an arrest of patient recruitment for other ongoing trials examining the effects of glucocorticoids for the treatment of (severe) COVID-19.

The Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group of the WHO performed a meta-analysis of all available data regarding the use of glucocorticoids in COVID-19 [6]. The analysis included the RECOVERY trial as well as 6 other trials – some of which had to be abrogated before reaching their recruitment goal due to the publication of the RECOVERY data. The meta-analysis concluded that initiation of systemic glucocorticoids was associated with lower 28-day all-cause mortality in critically ill patients with COVID-19. Consequently, based on these and other studies, the WHO issued two recommendations regarding the treatment of COVID-19: First, systemic glucocorticoid therapy should be initiated in patients with severe and critical COVID-19, whereby therapy is defined as 6 mg daily of dexamethasone orally or intravenously or 50 mg of hydrocortisone intravenously every 8 hours for 7 to 10 days. Secondly, the use of glucocorticoids in non-severe COVID-19 is not advised (for definition of critical, severe and non-critical COVID-19, see ▶ **Table 1**).

▶ **Table 1** Mutually exclusive categories of illness severity.

Critical COVID-19	Defined by the criteria for acute respiratory distress syndrome (ARDS), sepsis, septic shock or other conditions that would normally require the provision of life-sustaining therapies, such as mechanical ventilation (invasive or non-invasive) or vasopressor therapy.
Severe COVID-19	Defined by any of: oxygen saturation < 90 % on room air. Respiratory rate > 30 breaths per minute in adults and children > 5 years old; ≥ 60 in children less than 2 months; ≥ 50 in children 2–11 months; and ≥ 40 in children 1–5 years old. Signs of severe respiratory distress (i. e., accessory muscle use, inability to complete full sentences; and in children, very severe chest wall indrawing, grunting, central cyanosis, or presence of any other general danger signs).
Non-severe COVID-19	Defined as absence of any signs of severe or critical COVID-19.

Reference: Corticosteroids for COVID-19, WHO, 2. September 2020.

Glucocorticoids, COVID-19 and metabolic comorbidities

Diabetes mellitus is associated with an increased risk of infection and infection-related death [73, 74]. Accordingly, diabetic patients were at an increased risk of severe or lethal infection for both SARS as well as MERS during the respective outbreaks [75, 76]. When the Sars-Cov-2 spread around the world it quickly emerged that in the country of origin, China, diabetes was associated with increased mortality due to COVID-19 [77] – a finding later confirmed elsewhere [78]. Amongst patients suffering from diabetes mellitus, COVID-19 related mortality was not only associated with the presence of cardiovascular complications but also with glycemic control and BMI [79, 80]. An elevated BMI as well as obesity are also associated with severe outcomes of COVID-19 such ICU admission and mechanical ventilation in non-diabetic patients, thus indicating their role as an independent risk factors for COVID-19 related mortality [81, 82]. The association between good glycemic control and survival of COVID-19 amongst diabetics highlights the importance of adequate control of blood sugar levels during Sars-CoV-2 infection. As a modifiable risk factor, this association has already led to expert recommendations for the management of diabetes in patients with COVID-19 [83]. The reasons for increased mortality from COVID-19 in diabetic patients and the potential contribution of blood sugar levels to infection outcomes remain largely obscure. Multiple potential molecular mechanisms have been described and include a diabetes associated (i) increase in Coronavirus

load, (ii) dysregulated immune response, (iii) alveolar dysfunction, (iv) epithelial dysfunction and (v) coagulopathy [84]. However, the relative importance of these molecular phenomena needs to be investigated further and clinically validated. Interestingly, to our current knowledge, no study investigated the efficiency of glucocorticoid treatment in diabetic COVID-19 patients specifically. While the overall benefit of glucocorticoid therapy in severe and critical COVID-19 infections has been established, the efficiency of glucocorticoids in diabetics is currently less clear. Thus far – to the best of our knowledge – no subgroup analysis has examined the effect of glucocorticoids in diabetic patients suffering from COVID-19. This question is of particular relevance as exposure to supraphysiological levels of glucocorticoids frequently leads to worse glycemic control [85, 86]. Additionally, it is well established that medium to high doses of therapeutic glucocorticoids cause hypertension [87, 88], weight gain [89] as well as an increase in cardiovascular events [90, 91], all of which are associated with worse outcomes in COVID-19. Whether the adverse effects of therapeutic glucocorticoids are of concern during short exposure of 7–10 days (as recommended for COVID-19 treatment) remains to be evaluated.

Conclusion

Recent large-scale clinical trials support the use of glucocorticoids in the treatment of both ARDS as well as severe and critical COVID-19 infections. The use of glucocorticoids in high-risk COVID-19 patients suffering from diabetes mellitus and additional co-morbidities such as obesity, hypertension, and cardiovascular disease should be evaluated in further clinical trials. Furthermore, COVID-19 patients treated with glucocorticoids should undergo close immunological characterization in order to enable identification of molecular pathways for the development of targeted therapies.

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Conflict of Interest

V.I.A. declares no conflict of interest. H.H. has received speaking fees from Amgen and has served on scientific advisory boards for Novo Nordisk and Takeda.

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