Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Endocrine Practice 28 (2022) 1100–1106

Contents lists available at ScienceDirect

Endocrine Practice

journal homepage: www.endocrinepractice.org

Review Article

New Insights on Effects of Glucocorticoids in Patients With SARS-CoV-2 Infection

Elena Chertok Shacham, MD [1, *], Avraham Ishay, MD [1, 2]

[1] Endocrinology Unit, HaEmek Medical Center, Afula, Israel
[2] Faculty of Medicine, Technion – Israel Institute of Technology, Haifa, Israel

ARTICLE INFO

Article history:
Received 2 May 2022
Received in revised form
20 June 2022
Accepted 14 July 2022
Available online 21 July 2022

Key words:
glucocorticoids
anti-inflammatory effects
COVID-19
hyperinflammatory syndrome

ABSTRACT

Objective: Since January 2020, the highly contagious novel coronavirus SARS-CoV-2 has caused a global pandemic. Severe COVID-19 leads to a massive release of proinflammatory mediators, leading to diffuse damage to the lung parenchyma, and the development of acute respiratory distress syndrome. Treatment with the highly potent glucocorticoid (GC) dexamethasone was found to be effective in reducing mortality in severely affected patients.

Methods: To review the effects of glucocorticoids in the context of COVID-19 we performed a literature search in the PubMed database using the terms COVID-19 and glucocorticoid treatment. We identified 1429 article publications related to COVID-19 and glucocorticoid published from 1.1.2020 to the present including 238 review articles and 36 Randomized Controlled Trials. From these studies, we retrieved 13 Randomized Controlled Trials and 86 review articles that were relevant to our review topics. We focused on the recent literature dealing with glucocorticoid metabolism in critically ill patients and investigating the effects of glucocorticoid therapy on the immune system in COVID-19 patients with severe lung injury.

Results: In our review, we have discussed the regulation of the hypothalamic-pituitary-adrenal axis in patients with critical illness, selection of a specific GC for critical illness-related GC insufficiency, and recent studies that investigated hypothalamic-pituitary-adrenal dysfunction in patients with COVID-19. We have also addressed the specific activation of the immune system with chronic endogenous glucocorticoid excess, as seen in patients with Cushing syndrome, and, finally, we have discussed immune activation due to coronavirus infection and the possible mechanisms leading to improved outcomes in patients with COVID-19 treated with GCs.

Conclusion: For clinical endocrinologists prescribing GCs for their patients, a precise understanding of both the molecular- and cellular-level mechanisms of endogenous and exogenous GCs is imperative, including timing of administration, dosage, duration of treatment, and specific formulations of GCs.

Introduction

Synthetic glucocorticoids (GCs) are a highly effective and non-expensive class of drugs that have been extensively used for >70 years to treat a large range of immune-related disorders and diseases. Although the common practice was to avoid prescribing GCs during acute infections because of their immunosuppressive effects, in recent decades, adjunctive treatment with GCs has been shown.[1,2] The outbreak of the novel coronavirus disease has led to the revival of GC treatment in the context of viral infections.

Recent studies have raised the concept that severe inflammatory response (hyperinflammatory syndrome), responsible for rapidly deteriorating COVID-19 infection, closely resembles macrophage activation syndrome and other cytokine release syndromes associated with autoimmune disorders.[3] The treatment of macrophage activation syndrome is based on a high dose of intravenous GCs to prevent the vicious cycle of a perpetuating self-injuring inflammatory state.[4]

Indeed, recent studies have demonstrated beneficial effects of GCs in the treatment of COVID-19 disease, suggesting that SARS-CoV-2 infections exhibit unique features that enable the therapeutic efficacy of GCs.[5-7] SARS-CoV-2 infections induce significant changes in infected cells, many of which influence intracellular GC actions.[8-10] These changes are generated mainly to promote virus replication but inadvertently modulate glucocorticoid receptor

Abbreviations: ACTH, adrenocorticotropic hormone; ARDS, acute respiratory distress syndrome; CS, Cushing syndrome; GC, glucocorticoid; GR, glucocorticoid receptor; HPA, hypothalamic-pituitary-adrenal; ICU, intensive care unit; IL, interleukin; JAK, Janus-activated kinase; NK, natural killer; TH, T-helper.

* Address correspondence to Dr Elena Chertok Shacham, Endocrinology Unit, HaEmek Medical Center, Yitzhak Rabin Av. 21, Afula 18101, Israel.
E-mail address: elenachertok12@gmail.com (E.C. Shacham).

https://doi.org/10.1016/j.eprac.2022.07.006
1530-891X/

(GR) activity and contribute to the therapeutic effects of GCs in patients with severe COVID-19.[10]

More than 50% of patients with COVID-19 pneumonia admitted to the intensive care unit (ICU) develop acute respiratory distress syndrome (ARDS).[11] Remarkably, the hyperinflammatory phenotype of ARDS, characterized among others by elevated interleukin (IL)-8 and C-reactive protein levels, is associated with an elevated mortality rate.[12] According to recent studies, alveolar macrophages play an important role in the pathogenesis of ARDS.[13]

The accumulation of macrophages with an acquired profibrotic phenotype was found in the lung tissue of patients with COVID-19 complicated by ARDS.[13] A recent study on patients with symptomatic post-COVID-19 diffuse parenchymal lung abnormalities showed that treatment with a high dose of prednisolone was not superior to a low-dose regimen.[14]

In this review, we focus on the current literature that relates to the effects of GCs in the context of a novel coronavirus infection.

Highlights

- The novel coronavirus SARS-CoV-2 damages the lung parenchyma, leading to the development of acute respiratory distress syndrome (ARDS)
- Severe SARS-CoV-2 infection leads to an excessive inflammatory reaction called hyperinflammatory syndrome
- Glucocorticoids reduce excessive inflammation caused by infectious diseases
- Dexamethasone reduces mortality in patients with severe COVID-19
- Glucocorticoid treatment appears to be of value in the early phases of ARDS but ineffective or harmful in later phases

Clinical Relevance

Tailoring an optimal treatment regimen is of prime importance for improving outcomes in patients with COVID-19. We believe that our review focusing on the anti-inflammatory actions of glucocorticoids would provide clinicians with valuable information to treat such patients.

Hypothalamic-Pituitary-Adrenal (HPA) Axis in Patients With Critical Illness

Under stressful conditions, the HPA axis is activated, leading to increased cortisol production.[15] The levels of cortisol are found to be significantly higher in patients with sepsis and patients undergoing a major surgery to combat stress and major trauma.[16] Patients receiving critical care have higher cortisol and lower adrenocorticotropic hormone (ACTH) levels. Reduced cortisol clearance in these patients is associated with reduced expression and activity of cortisol-metabolizing enzymes in the liver and kidneys.[17] Enhanced levels of corticosteroid-binding globulin and expression of multidrug resistance P-glycoprotein transporter as well as changes in 11β-hydroxysteroid dehydrogenase enzyme activity (decrease in 11β-hydroxysteroid dehydrogenase 1 and increase in 11β-hydroxysteroid dehydrogenase 2) decrease the levels of bioactive GCs, leading to a state of GC resistance.[18] Critical illness-related corticosteroid insufficiency is a term indicating an inadequate HPA axis response during critical illness.[19,20] Critically ill patients, with reduced delta cortisol levels, ie, a change in the baseline cortisol level of <9 μg/dL at 60 minutes after 250-μg ACTH stimulation, presumably have relative adrenal dysfunction and have been found to have poor outcomes.[19] According to updated guidelines, adult patients with septic shock should be treated with intravenous hydrocortisone at <400 mg/d (or methylprednisolone equivalent in persistent ARDS for ≥3 days).[19] Methylprednisolone is the preferred GC for the treatment of ARDS because of its greater affinity to GRs, high penetration in lung tissue, and high potency for both genomic and nongenomic activities.[20] Moreover, high-certainty evidence has indicated that GCs result in significant reductions in the length of ICU and hospital stays.[20,21] In a systematic review presented by Annane et al[21] that included 33 eligible studies, treatment with a long course of low-dose corticosteroids significantly reduced the 28-day mortality rates and the mortality rates in the ICU. A recent small study showed that 40% of patients admitted for COVID-19 disease had low basal levels of cortisol (<300 nmol/L), whereas the corresponding ACTH levels, measured in the same samples, were also in the lower end of the normal range, thus pointing toward COVID-19–related HPA dysregulation.[22] On the other hand, Tan et al[23] found that patients with COVID-19 whose baseline cortisol concentration was ≤744 nmol/L had a median survival of 36 days, whereas patients whose cortisol concentration was >744 nmol/L had a median survival of 15 days ($P = .0001$). Unfortunately, studies aiming to assess HPA function by performing the low-dose ACTH test in moderately-to-severely ill patients with COVID-19 are lacking, although primary and secondary adrenal insufficiency have been occasionally reported.[24,25]

Mechanisms of Anti-inflammatory and Immunosuppressive Effects of GCs

The anti-inflammatory effect of GCs includes the repression of genes related to inflammation via the activation of monomeric GRs, which negatively regulate transcription factors, such as nuclear factor kappa B and activator protein 1, or through crosstalk with other transcription factors.[26]

Annexin 1 is a ubiquitous phospholipid-binding protein, activated by GRs, implicated in signal transduction processes and plays an important role in the regulation of inflammatory responses. Annexin 1 mediates the adhesion and migration of leukocytes; upregulates anti-inflammatory cytokines, such as IL-10; modulates the response to apoptosis, thereby preventing tissue necrosis.[27,28] A high expression of annexin 1 was found in the lung tissue of patients with inflammatory lung disease treated with GCs.[27]

In the context of acute inflammation, GCs influence several steps that downregulate the activation of the innate and adaptive immune systems.

Components of the Innate Immune System Influenced by GCs

Granulocytes

Endogenous and exogenous GCs promote neutrophil maturation and mobilization from the bone marrow to the blood while reducing neutrophil apoptosis. GCs inhibit the expression of adhesion molecules and, thus, inhibit the adhesion and extravasation of neutrophils to the site of inflammation.[29] In patients with asthma and those with rheumatoid arthritis, exogenous GCs have been shown to significantly accelerate basophil and eosinophil apoptosis and/or reversal of cytokine-induced eosinophil survival.[30,31]

Monocytes or Macrophages

GCs inhibit the activation of monocytes by microbial products such as lipopolysaccharides and, thus, cause resistance to lipopolysaccharide-induced apoptosis. Additionally, GCs induce the differentiation of an anti-inflammatory monocyte phenotype.[32,33] In activated macrophages, high doses of GCs inhibit the expression of inflammatory cytokines, including IL-1β, IL-6, and IL-12 (tumor necrosis factor-α), and the production of nitric oxide.[34]

Dendritic Cells

Exogenous GCs enhance the endocytic activity of dendritic cells, causing impairment of differentiation, maturation, and T-cell activation.[35]

Natural Killer (NK) Cells

GCs dampen the expression of several genes that influence the capacity of NK cells to bind to targets cells and reduce the production of granule constituents (perforin and granzyme B), thereby decreasing the cytotoxic activity of NK cells.[36,37] Additionally, GCs inhibit the production of interferon gamma, a key NK cell cytokine.[38]

Components of Adaptive Immune System Influenced by GCs

T-Cell Activity

GCs modulate T-cell activity directly by interfering with T-cell receptor signaling and indirectly by attenuating dendritic cell functions: antigen presentation, costimulation, and cytokine production.[35] Additionally, GCs exert potent regulatory effects on T-cell activity; they influence the polarization of T-helper (TH) cells, thereby favoring the differentiation of TH2 cells and regulatory T cells over that of TH1 and TH17 cells.[38]

B-Cell Activity

GCs impair B-cell receptor and Toll-like receptor signaling, thus preventing the activation of B cells by endogenous immune complexes. GCs also promote significant upregulation of genes associated with the expression of the anti-inflammatory cytokine IL-10.[39]

GCs also have an important role in the resolution phase of inflammation. They mediate survival of an anti-inflammatory monocytic phenotype and programming of alternatively activated macrophage (M2c-like) macrophages that are characterized by a high expression of scavenger receptors, which clear apoptotic cells and secrete anti-inflammatory cytokines.[33]

Genomic and Nongenomic Mechanisms of GC Activity

GCs act through binding to cytosolic GRs, predominantly to GR alpha, which is the most active isoform of GRs.[40,41] This classic genomic mechanism includes conformation changes in cytoplasmic GRs, phosphorylation at serine 211, dissociation from a hetero complex, and translocation into the nucleus, where it regulates gene expression.[41]

Exogenous and endogenous GCs bind unequally to GRs, leading to uneven effects on genomic and nongenomic immune responses as well as on HPA axis suppression,[42] as illustrated in Table 1.

Among synthetic GCs, dexamethasone has been shown to have a higher affinity for GRs, minor mineralocorticoid activity, greater bioavailability, and a much longer half-life than endogenous GCs.[43] Remarkably, the anti-inflammatory effects (potency) of GCs are positively correlated with effects on glucose metabolism, hepatic deposition of glycogen and glycogenesis.[44] The degree of cytosolic GR saturation and the plasma concentration of GCs is correlated with the extent of their therapeutic effects.[43] Dose equivalents of ≥100 mg of prednisone cause virtually full cytosolic receptor saturation; therefore, a higher dosage could change drug pharmacodynamics and lead to the appearance of nonclassical, nongenomic effects.[43]

The nongenomic effects of GCs manifest within minutes of GC exposure and do not involve the activation of classical genomic pathways.[45] These effects can be classified as involving physicochemical interactions with cellular membranes (nonspecific effects), interference with cytoplasmic signaling complexes that are mediated by cytosolic GRs, or specific interactions with membrane-bound GRs.[40,45] The nongenomic mechanisms of GC activity may provide an explanation for the beneficial therapeutic effects of pulse GC therapy for many inflammatory or immune-mediated diseases, including severe forms of rheumatoid arthritis, immune thrombocytopenia, juvenile dermatomyositis, juvenile chronic arthritis, optic neuritis, rapidly progressive glomerulonephritis, and pemphigus vulgaris.[43] The genomic and nongenomic effects of commonly used GCs are summarized in Table 1.

Table 1
Schematic Comparison Between Genomic and Non-genomic Potencies of Various Glucocorticoids

Glucocorticoids	Immunosuppression	Genomic versus nongenomic effects	HPA suppression
Prednisone	↑	↑ ↑	↑
Methylprednisolone	↑	↑ ↑	↑
Hydrocortisone	↑	↑ ↑	↑
Dexamethasone	↑	↑ ↑	↑

The data on relative nongenomic effects were taken from references 47 and 49.
The data on relative genomics effects were taken from reference 47.

Cushing Syndrome (CS) and COVID-19 Infection

Patients with CS are immunosuppressed and are at the risk of bacterial, viral, and opportunistic infections because of immune system dysregulation.[46] Chronic endogenous glucocorticoid excess alters the innate immune system response because of suppressed NK cytotoxic activity and an adaptive immune system reaction resulting from the reduction of TH1 and B lymphocyte counts as well as increased apoptosis in the early phase of lymphocyte development.[46,47]

It was hypothesized that patients with CS with severe COVID-19 infection complicated by ARDS might have more severe outcomes because of a pre-existing inflammatory state and deepening lymphopenia, due to T- and B-cell maturation impairment resulting from CS and concomitant lymphopenia caused by COVID infection along with reduced CD4 T lymphocytes. At the same time, impairment of the cytokine response in patients with CS may also lead to a more stable clinical course, avoiding ARDS development.[47] The main features of case reports on patients with COVID-19 and CS are summarized in Table 2.[48-51] Notably, the most severe course of COVID-19 infection occurred in a patient with severe florid, uncontrolled CS. These findings are in concordance with previous data that showed that predisposition to severe bacterial and opportunistic infections seems to be directly and positively correlated with cortisol levels and is more frequent in patients with ectopic CS.[48]

Role of GCs and Other Immunomodulatory Drugs in the Treatment of Severe COVID-19 Infection and the Connection to ARDS and Systemic Hyperinflammatory Syndrome

Macrophages play an important role in the development and progression of inflammatory responses associated with COVID-19 infection complicated by ARDS as well as other acute and chronic inflammatory pulmonary diseases such as chronic obstructive pulmonary disease and idiopathic pulmonary fibrosis.[52] A significant similarity between COVID-19–associated macrophages and profibrotic macrophage populations ($CD163^{+}$) identified in the lung tissue of patients with idiopathic pulmonary fibrosis was demonstrated.[13] Noticeably, acute exacerbations of interstitial pulmonary fibrosis closely resemble the symptoms of ARDS.[53] Beneficial effects of GCs in patients with ARDS have been found in a few large clinical trials,[19-21] although patients treated with a high dose of corticosteroids (>500 mg/d of methylprednisolone) had a higher mortality rate.[54,55]

The role of GCs in the management of interstitial pulmonary fibrosis is highly controversial, either for maintenance or for acute exacerbations. Moreover, harmful effects probably outweigh the benefits of the anti-inflammatory action of GCs. A possible explanation for this effect is related to the pathogenesis of interstitial pulmonary fibrosis, in which alveolar tissue damage and poor wound healing predominate over chronic inflammation.[53]

Elevated IL-6 level is a sensitive biomarker of hyperinflammatory syndrome in patients with COVID-19 as well as of other hyperinflammatory syndromes, and it has been found to be an early predictor of severe COVID-19 disease, the requirement for mechanical ventilation, and worse prognoses in patients with ARDS.[56-58] Recently, additional treatment with an anti-IL-6 receptor monoclonal antibody tocilizumab, in addition to the standard treatment including antiviral drugs, systemic GCs at a dose of $\leq$1 mg/kg/d of methylprednisolone or its equivalent, and the nucleotide analog remdesivir, was found to reduce progression to mechanical ventilation and death in patients with moderate-to-severe COVID-19 pneumonia.[59]

Recently, tofacitinib, a small-molecule Janus-activated kinase (JAK (inhibitor (preferentially inhibits JAK1 and JAK3) that dampens Janus kinase or signal transducers and activators of transcription)JAK-STAT(pathways related to the synthesis of inflammatory mediators, was found to be effective in reducing respiratory failure and death in patients with COVID-19 pneumonia.[60]

Several prospective controlled studies have been conducted to evaluate the role of GCs in patients hospitalized for COVID-19 (Table 3).[61,62-64] Among them, a large prospective randomized controlled trial that included >6000 patients clearly demonstrated the beneficial effects of dexamethasone treatment on 28-day mortality, when the patients needed invasive mechanical ventilation.[63] The results of this study are in accordance with a recent meta-analysis review that reported a significant reduction in hospital mortality (risk ratio, 0.79; 95% CI, 0.64-0.98) and ICU mortality (RR, 0.64; 95% CI, 0.42-0.97; $P = .04$), especially with early (<7 days) rather than late administration of GCs.[5]

Tocilizumab, tofacitinib, and dexamethasone were found to reduce mortality, due to respiratory failure, in patients with COVID-19 pneumonia.[59,60,63] It is worth noting that these drugs alter multiple signaling transduction pathways, downregulate a variety of inflammatory mediators, and inhibit the synthesis of inflammatory cytokines.

According to National Institutes of Health COVID-19 treatment guidelines, dexamethasone treatment, alone or in combination

Table 2
Patients With COVID-19 and Cushing Syndrome

Patients data	Patient 1 (49)	Patient 2 (49)	Patient 3 (49)	Patient 4 (50)	Patient 5 (51)	Patient 6 (52)
Age, y	71	38	66	67	27	71
Sex	F	F	F	M	F	M
Comorbidities						
BMI > 30 kg/m^2	Yes	Yes	Yes	N/A	No	Yes
Hypertension	Yes	No	Yes		Yes	Yes
Diabetes mellitus	Yes	No	Yes		No	Not reported
Cardiovascular disease	Yes	No	Yes		No	Not reported
Duration of CS	<3 mo	5 y	4 y	7 y	New diagnosis	N/A
Treatment of CS before COVID-19	No	No	No	Pasireotide Cabergoline Metyrapone	Metyrapone	Metyrapone
Max. morning ACTH level, pg/mL	445.8	74.4	25.6	425	37.8	N/A
Reference range	7.2-63.3	7.2-63.3	7.2-63.3	10-50	N/A	
Max. urine cortisol	N/A	959.7	286.2	315	1300	N/A
Reference range, nmol/24 h	100-379	100-379	100-379	16-168	27-137	
Severity of COVID-19	Critical	Moderate	Mild	Moderate	Severe	Mild
Oxygen supplementation or mechanical ventilation	Yes	Yes	No	Yes	Yes	No

Abbreviations: ACTH = adrenocorticotropic hormone; BMI = body mass index; CS = Cushing syndrome; Max. = maximum; N/A = not available.

Table 3
Randomized Controlled Trials Evaluating the Role of Glucocorticoids in Patients Hospitalized for COVID-19

Name	Allocation of patients	Dose and duration	Cumulative dose dexamethasone equivalent	Main outcome
Glucocovid study, Corral-Gudino et al[61]	N = 61(35 GT, 29 SOC)	Methylprednisolone 80 mg for 3 d 40 mg for 3 d	72 mg	Primary outcome in 48%[a]: SOC versus 40% in GT group ($P = .04$)
Effect of hydrocortisone on 21-d mortality. Dequin et al[62]	N = 149 (76 GT, 73 SOC) ICU 100%	Hydrocortisone (2 regimens) 200 mg for 4 d 100 mg for 2 d 50 mg for 2 d Or 200 mg for 7 d 100 mg for 4 d 50 mg for 3 d	44 mg 78 mg	Primary outcome[b]: SOC 50.7% versus 42.1% in GT group ($P = .29$)
The RECOVERY trial[63]	N = 6425 (2104 GT, 4321 SOC)	Dexamethasone 6 mg for 10 d	60 mg	Primary outcome[c]: 22.9% in SOC versus 25.7% in GT group ($P < .001$) 40.9% in SOC versus 29% in GT group (mechanically ventilated) (RR, 0.64; CI, 0.5-0.8). 26.2% in SOC versus 23.3% in GT group (RR, 0.82; CI, 0.72-0.94)
The efficacy of corticosteroid therapy in patients with moderate-to-severe SARS-CoV-2 infection. Ghanei et al[64]	N = 336 120 GT 116 azithromycin 116 lopinavir or ritonavir	Prednisolone 25 mg for 5 d	20 mg	Primary outcome: Number of deaths Percentage of ICU admissions Mechanical ventilation (NS) Shortened LOS ($P = .028$, $P = .0007$)

Abbreviations: GT = glucocorticoid treatment; ICU = intensive care unit; NS = not specified; RR = risk ratio; SOC = standard of care.
[a] The primary outcome was a composite of death, admission to the intensive care unit, or requirement for noninvasive ventilation.
[b] The primary outcome was death or persistent dependency on mechanical ventilation or high-flow oxygen therapy.
[c] The primary outcome was 28-day mortality.

with other immunomodulators, such as tocilizumab, baricitinib, and tofacitinib, has demonstrated clinical benefits in patients with early severe disease and/or systemic hyperinflammation.[65]

The roles of dexamethasone in the treatment of severe COVID-19 disease may be summarized as follows:

1. Inhibits the activation of the transcription factor nuclear factor kappa B in various cells, such as lung macrophages, and prevents inflammatory cell infiltration and diffuse pulmonary alveolar injury.[66,67]
2. Decreases IL-6 activity, thus reducing the activation of multiple cytokines.[66]
3. Represses the activator protein 1 signal transduction pathway, thereby increasing the gene transcription of anti-inflammatory cytokines.[68]
4. Increases the expression of annexin 1 and modulates anti-inflammatory responses.[28]
5. Inhibits the endothelial expression of adhesion molecules, such as endothelial-leukocyte adhesion molecule 1 and intercellular adhesion molecule 1, and consequently probably prevents thrombotic complications.[69-71]
6. Promotes macrophage differentiation toward an anti-inflammatory phenotype, improving, in this way, macrophage survival and healing of damaged tissue.[72]
7. Influences TH anti-inflammatory activity through the inhibition of interferon gamma response and IL-12 synthesis.[73]
8. Replaces relative cortisol deficiency, due to an inappropriate HPA axis response related to severe illness.[19]
9. Synergistically acts with other immunomodulatory treatments.[74,75]

Although the World Health Organization recommend GCs for patients with severe or critical COVID-19,[76] several aspects of this treatment (ie, dosage, adequate timing, duration, proper weaning, and choice of the right patient) are still a matter of debate and need more clinical trials to be clarified.

In the Figure, we have summarized the anti-inflammatory versus profibrotic effects of GCs related to late stages of ARDS.

Conclusion

Recent studies have shown the dramatic effects of dexamethasone in patients with COVID-19 in reducing mortality, particularly in the subset of critically ill, mechanically ventilated patients, whereas there was no benefit and potential harm in hospitalized patients not receiving oxygen support. In our review, we focused on the current understanding of the unique anti-inflammatory and immunomodulating effects of GCs on pathophysiologic processes induced by SARS-CoV-2 infection, which underlie the present recommendations on the use of GCs in COVID-19 management. We reviewed the effects of exogenous GCs on different immune cells and mediators of the innate and adaptive immune systems and discussed the alterations of HPA axis activity during severe COVID-19. We also evaluated the relevance of the administration of GCs in patients with relative adrenal insufficiency, which has been described recently in severely ill patients with COVID-19. The efficacy of highly potent GCs in treating ARDS was proven in large randomized controlled trials. Moreover, recently acquired data showed that patients with persistent severe ARDS related to SARS-CoV-2 infection experienced pulmonary fibrotic changes such as those seen in patients with idiopathic pulmonary fibrosis. In such patients, GC treatment is not effective, at least, and is probably harmful. Although the right time to administer GCs after the onset of symptoms is a subject of debate, it seems that in well-assessed patients with data on inflammatory marker results, respiratory parameters, and chest imaging, GCs alone or in combination with other immunomodulatory treatments could shorten the length of hospital stay and reduce mortality.

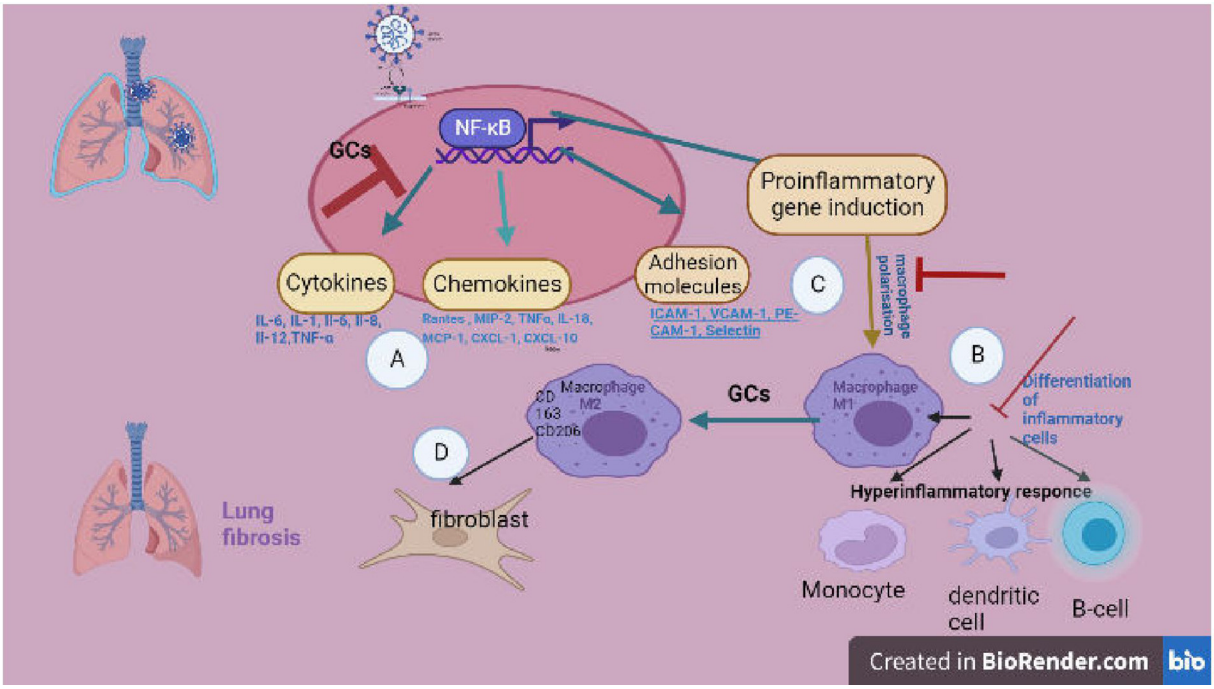

Fig. Hypothetical dual anti-inflammatory and profibrotic action of glucocorticoids (GCs) in severe COVID-19 infection. *A*, GCs inhibit nuclear factor kappa B expression and downregulate the expression of proinflammatory cytokines, chemokines, and adhesion molecules.[69] *B*, GCs prevent hyperinflammatory response by dampening the activation of monocytes, macrophages, and dendritic cells.[34,35,37] *C*, GCs restrain macrophage differentiation in M1 type inflammatory macrophages and mediates alternatively polarization into M2 type anti-inflammatory macrophages.[35] *D*, GCs are not effective and are probably harmful in the fibrotic phase of acute respiratory distress syndrome related to severe lung involvement, related to COVID-19.[54] *CXCL* = chemokine (C-X-C motif) ligand; *PECAM1* = platelet endothelial cell adhesion molecule-1; *GC* = glucocorticoid; *ICAM* = intercellular adhesion molecule; *IL* = interleukin; *MCP* = monocyte chemoattractant protein; *NFκB* = nuclear factor kappa B; *TNFα* = tumor necrosis factor-α; *VCAM* = vascular cell adhesion protein.

Acknowledgment

We sincerely thank Ms Dalia Dawn Orkin for her English language contributions and editing services.

Author Contributions

E.C.S. and A.I. contributed equally to the manuscript and both should be considered as first co-authors.

Disclosure

The authors have no multiplicity of interest to disclose.

References

1. Stern A, Skalsky K, Avni T, Carrara E, Leibovici L, Paul M. Corticosteroids for pneumonia. *Cochrane Database Syst Rev*. 2017;12(12):CD007720.
2. De Gans J, Van de Beek D. Dexamethasone in adults with bacterial meningitis. *N Engl J Med*. 2002;347(20):1549–1556.
3. Kim JS, Lee JY, Yang JW, et al. Immunopathogenesis and treatment of cytokine storm in COVID-19. *Theranostics*. 2021;11(1):316–329.
4. Carter SJ, Tattersall RS, Ramanan AV. Macrophage activation syndrome in adults: recent advances in pathophysiology, diagnosis and treatment. *Rheumatology (Oxford)*. 2019;58(1):5–17.
5. Zayed Y, Barbarawi M, Ismail E, et al. Use of glucocorticoids in patients with acute respiratory distress syndrome: a meta-analysis and trial sequential analysis. *J Intensive Care*. 2020;8(1):1–10.
6. Van Paassen J, Vos JS, Hoekstra EM, Neumann KM, Boot PC, Arbous SM. Corticosteroid use in COVID-19 patients: a systematic review and meta-analysis on clinical outcomes. *Crit Care*. 2020;24(1):1–22.
7. Sterne JA, Murthy S, Diaz JV, Slutsky AS, Villar J. Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: a meta-analysis. *JAMA*. 2020;324(13):1330–1341.
8. V'kovski P, Kratzel A, Steiner S, Stalder H, Thiel V. Coronavirus biology and replication: implications for SARS-CoV-2. *Nat Rev Microbiol*. 2020;19(3):155–170.
9. Suryawanshi RK, Koganti R, Agelidis A, Patil CD, Shukla D. Dysregulation of cell signaling by SARS-CoV-2. *Trends Microbiol*. 2021;29(3):224–237.
10. Kino T, Burd I, Segars JH. Dexamethasone for severe COVID-19: how does it work at cellular and molecular levels? *Int J Mol Sci*. 2021;22(13):6764.
11. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med*. 2020;8(5):475–481.
12. Sinha P, Delucchi KL, McAuley DF, O'Kane CM, Matthay MA, Calfee CS. Development and validation of parsimonious algorithms to classify acute respiratory distress syndrome phenotypes: a secondary analysis of randomised controlled trials. *Lancet Respir Med*. 2020;8(3):247–257.
13. Wendisch D, Dietrich O, Mari T, et al. SARS-CoV-2 infection triggers profibrotic macrophage responses and lung fibrosis. *Cell*. 2021;184(26):6243–6261.
14. Dhooria S, Chaudhary S, Sehgal IS, et al. High-dose versus low-dose prednisolone in symptomatic patients with post-COVID-19 diffuse parenchymal lung abnormalities: an open-label, randomised trial (the COLDSTER trial). *Eur Respir J*. 2022;59(2), 2102930.
15. Widmer IE, Puder JJ, Konig C, et al. Cortisol response in relation to the severity of stress and illness. *J Clin Endocrinol Metab*. 2005;90(8):4579–4586.
16. Prete A, Taylor AE, Bancos I, et al. Prevention of adrenal crisis: cortisol responses to major stress compared to stress dose hydrocortisone delivery. *J Clin Endocrinol Metab*. 2020;105(7):2262–2274.
17. Boonen E, Vervenne H, Meersseman P, et al. Reduced cortisol metabolism during critical illness. *N Engl J Med*. 2013;368(16):1477–1488.
18. Silverman MN, Sternberg EM. Glucocorticoid regulation of inflammation and its functional correlates: from HPA axis to glucocorticoid receptor dysfunction. *Ann N Y Acad Sci*. 2012;1261(1):55–63.
19. Pastores SM, Annane D, Rochwerg B. Guidelines for the diagnosis and management of critical illness-related corticosteroid insufficiency (CIRCI) in critically ill patients (part II): Society of Critical Care Medicine (SCCM) and European Society of Intensive Care Medicine (ESICM) 2017. *Crit Care Med*. 2018;46(1):146–148.
20. Meduri GU, Siemieniuk RA, Ness RA, Seyler SJ. Prolonged low-dose methylprednisolone treatment is highly effective in reducing duration of mechanical ventilation and mortality in patients with ARDS. *J Intensive Care*. 2018;6(1):1–7.
21. Annane D, Bellissant E, Bollaert PE, et al. Corticosteroids for treating sepsis in children and adults. *Emergencias*. 2021;33(2):137–138.

22. Alzahrani AS, Mukhtar N, Aljomaiah A, et al. The impact of COVID-19 viral infection on the hypothalamic-pituitary-adrenal axis. *Endocr Pract*. 2021;27(2):83–89.
23. Tan T, Khoo B, Mills EG, et al. Association between high serum total cortisol concentrations and mortality from COVID-19. *Lancet Diabetes Endocrinol*. 2020;8(8):659–660.
24. Sanchez J, Cohen M, Zapater JL, Eisenberg Y. Primary adrenal insufficiency after COVID-19 infection. *AACE Clin Case Rep*. 2022;8(2):51–53.
25. Hashim M, Athar S, Gaba WH. New onset adrenal insufficiency in a patient with COVID-19. *BMJ Case Rep*. 2021;14(1), e237690.
26. Vandevyver S, Dejager L, Tuckermann J, Libert C. New insights into the anti-inflammatory mechanisms of glucocorticoids: an emerging role for glucocorticoid-receptor-mediated transactivation. *Endocrinology*. 2013;154(3):993–1007.
27. Purvis GS, Solito E, Thiemermann C. Annexin-A1: therapeutic potential in microvascular disease. *Front Immunol*. 2019;10(4):938.
28. Mui L, Martin CM, Tschirhart BJ, Feng Q. Therapeutic potential of annexins in sepsis and COVID-19. *Front Pharmacol*. 2021;12(9):2377.
29. Cavalcanti DM, Lotufo CM, Borelli P, Ferreira ZS, Markus RP, Farsky SH. Endogenous glucocorticoids control neutrophil mobilization from bone marrow to blood and tissues in non-inflammatory conditions. *Br J Pharmacol*. 2007;152(8):1291–1300.
30. Yoshimura C, Miyamasu M, Nagase H, et al. Glucocorticoids induce basophil apoptosis. *J Allergy Clin Immunol*. 2001;108(2):215–220.
31. Wallen N, Kita H, Weiler D, Gleich GJ. Glucocorticoids inhibit cytokine-mediated eosinophil survival. *J Immunol*. 1991;147(10):3490–3495.
32. Ehrchen JM, Roth J, Barczyk-Kahlert K. More than suppression: glucocorticoid action on monocytes and macrophages. *Front Immunol*. 2019;10(8):2028.
33. Ehrchen J, Steinmuller L, Barczyk K, et al. Glucocorticoids induce differentiation of a specifically activated, anti-inflammatory subtype of human monocytes. *Blood*. 2007;109(3):1265–1274.
34. Lim HY, Muller N, Herold MJ, Van Den Brandt J, Reichardt HM. Glucocorticoids exert opposing effects on macrophage function dependent on their concentration. *Immunology*. 2007;122(1):47–53.
35. Szatmari I, Nagy L. Nuclear receptor signalling in dendritic cells connects lipids, the genome and immune function. *EMBO J*. 2008;27(18):2353–2362.
36. Eddy JL, Krukowski K, Janusek L, Mathews HL. Glucocorticoids regulate natural killer cell function epigenetically. *Cell Immunol*. 2014;290(1):120–130.
37. Capellino S, Claus M, Watzl C. Regulation of natural killer cell activity by glucocorticoids, serotonin, dopamine, and epinephrine. *Cell Mol Immunol*. 2020;17(7):705–711.
38. Cari L, De Rosa F, Nocentini G, Riccardi C. Context-dependent effect of glucocorticoids on the proliferation, differentiation, and apoptosis of regulatory T cells: a review of the empirical evidence and clinical applications. *Int J Mol Sci*. 2019;20(5):1142.
39. Franco LM, Gadkari M, Howe KN, et al. Immune regulation by glucocorticoids can be linked to cell type-dependent transcriptional responses. *J Exp Med*. 2019;216(2):384–406.
40. Mitre-Aguilar IB, Cabrera-Quintero AJ, Zentella-Dehesa A. Genomic and non-genomic effects of glucocorticoids: implications for breast cancer. *Int J Clin Exp Pathol*. 2015;8(1):1–10.
41. Ramamoorthy S, Cidlowski JA. Exploring the molecular mechanisms of glucocorticoid receptor action from sensitivity to resistance. *Endocr Dev*. 2013;24(2):41–56.
42. Coutinho AE, Chapman KE. The anti-inflammatory and immunosuppressive effects of glucocorticoids, recent developments and mechanistic insights. *Mol Cell Endocrinol*. 2011;335(1):2–13.
43. Buttgereit F, da Silva JAP, Boers M, et al. Standardised nomenclature for glucocorticoid dosages and glucocorticoid treatment regimens: current questions and tentative answers in rheumatology. *Ann Rheum Dis*. 2002;61(8):718–722.
44. Henzen C, Suter A, Lerch E, Urbinelli R, Schorno XH, Briner VA. Suppression and recovery of adrenal response after short-term, high-dose glucocorticoid treatment. *Lancet*. 2000;355(9203):542–545.
45. Urbach V, Walsh DE, Mainprice B, Bousquet J, Harvey BJ. Rapid non-genomic inhibition of ATP-induced Cl- secretion by dexamethasone in human bronchial epithelium. *J Physiol (Lond)*. 2002;545(3):869–878.
46. Hasenmajer V, Sbardella E, Sciarra F, Minnetti M, Isidori AM, Venneri MA. The immune system in Cushing's syndrome. *Trends Endocrinol Metab*. 2020;31(9):655–669.
47. Guarnotta V, Ferrigno R, Martino M, et al. Glucocorticoid excess and COVID-19 disease. *Rev Endocr Metab Disord*. 2021;22(4):703–714.
48. Belaya Z, Golounina O, Melnichenko G, et al. Clinical course and outcome of patients with ACTH-dependent Cushing's syndrome infected with novel coronavirus disease-19 (COVID-19): case presentations. *Endocrine*. 2021;72(1):12–19.
49. Beretta F, Dassie F, Parolin M, et al. Practical considerations for the management of Cushing's disease and COVID-19: a case report. *Front Endocrinol (Lausanne)*. 2020;11(9):554.
50. Yuno A, Kenmotsu Y, Takahashi Y, et al. Successful management of a patient with active Cushing's disease complicated with coronavirus disease 2019 (COVID-19) pneumonia. *Endocr J*. 2021;68(4):477–484.
51. Serban AL, Ferrante E, Carosi G, Indirli R, Arosio M, Mantovani G. COVID-19 in Cushing disease: experience of a single tertiary centre in Lombardy. *J Endocrinol Invest*. 2021;44(6):1335–1336.
52. Lee JW, Chun W, Lee HJ, et al. The role of macrophages in the development of acute and chronic inflammatory lung diseases. *Cells*. 2021;10(4):897.
53. Brereton CJ, Jo HE. Acute exacerbations of idiopathic pulmonary fibrosis and the role of corticosteroids. *Breathe (Sheff)*. 2020;16(3), 200086.
54. Takaki M, Ichikado K, Kawamura K, Gushima Y, Suga M. The negative effect of initial high-dose methylprednisolone and tapering regimen for acute respiratory distress syndrome: a retrospective propensity matched cohort study. *Crit Care*. 2017;21(1):1–7.
55. Kido T, Muramatsu K, Asakawa T, et al. The relationship between high-dose corticosteroid treatment and mortality in acute respiratory distress syndrome: a retrospective and observational study using a nationwide administrative database in Japan. *BMC Pulm Med*. 2018;18(1):1–7.
56. Aziz M, Fatima R, Assaly R. Elevated interleukin-6 and severe COVID-19: a meta-analysis. *J Med Virol*. 2020;92(11):2283–2285.
57. Zhu J, Pang J, Ji P, et al. Elevated interleukin-6 is associated with severity of COVID-19: a meta-analysis. *J Med Virol*. 2021;93(1):35–37.
58. Herold T, Jurinovic V, Arnreich C, et al. Elevated levels of IL-6 and CRP predict the need for mechanical ventilation in COVID-19. *J Allergy Clin Immunol*. 2020;146(1):128–136.
59. Salama C, Han J, Yau L, et al. Tocilizumab in patients hospitalized with Covid-19 pneumonia. *N Engl J Med*. 2021;384(1):20–30.
60. Guimaraes PO, Quirk D, Furtado RH, et al. Tofacitinib in patients hospitalized with Covid-19 pneumonia. *N Engl J Med*. 2021;385(5):406–415.
61. Corral-Gudino L, Bahamonde A, Arnaiz-Revillas F, et al. Methylprednisolone in adults hospitalized with COVID-19 pneumonia: an open-label randomized trial (GLUCOCOVID). *Wien Klin Wochenschr*. 2021;133(7):303–311.
62. Dequin PF, Heming N, Meziani F, et al. Effect of hydrocortisone on 21-day mortality or respiratory support among critically ill patients with COVID-19: a randomized clinical trial. *JAMA*. 2020;324(13):1298–1306.
63. RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with Covid-19. *N Engl J Med*. 2021;384(8):693–704.
64. Ghanei M, Solaymani-Dodaran M, Qazvini A, et al. The efficacy of corticosteroids therapy in patients with moderate to severe SARS-CoV-2 infection: a multicenter, randomized, open-label trial. *Respir Res*. 2021;22(1):1–14.
65. Coronavirus disease 2019 (COVID-19) treatment guidelines. National Institutes of Health (US). Accessed September 1, 2022. https://www.covid19treatmentguidelines.nih.gov/.
66. Kircheis R, Haasbach E, Lueftenegger D, Heyken WT, Ocker M, Planz O. NF-κB pathway as a potential target for treatment of critical stage COVID-19 patients. *Front Immunol*. 2020;11(12), 598444.
67. Hariharan A, Hakeem AR, Radhakrishnan S, Reddy MS, Rela M. The role and therapeutic potential of NF-kappa-B pathway in severe COVID-19 patients. *Inflammopharmacology*. 2021;29(1):91–100.
68. Cruz-Topete D, Cidlowski JA. One hormone, two actions: anti- and pro-inflammatory effects of glucocorticoids. *Neuroimmunomodulation*. 2015;22(1-2):20–32.
69. Zielinska KA, Van Moortel L, Opdenakker G, De Bosscher K, Van den Steen PE. Endothelial response to glucocorticoids in inflammatory diseases. *Front Immunol*. 2016;7(12):592.
70. Yao S, Luo N, Liu J, et al. Elevated serum levels of progranulin and soluble vascular cell adhesion molecule-1 in patients with COVID-19. *J Inflamm Res*. 2021;14(9):4785–4794.
71. Bauer W, Ulke J, Galtung N, et al. Role of cell adhesion molecules for prognosis of disease development of patients with and without COVID-19 in the emergency department. *J Infect Dis*. 2021;223(8):1497–1499.
72. Desgeorges T, Caratti G, Mounier R, Tuckermann J, Chazaud B. Glucocorticoids shape macrophage phenotype for tissue repair. *Front Immunol*. 2019;10(7):1591.
73. Banuelos J, Lu NZ. A gradient of glucocorticoid sensitivity among helper T cell cytokines. *Cytokine Growth Factor Rev*. 2016;31(10):27–35.
74. Lu Y, Liu F, Tong G, et al. Clinical evidence of an interferon-glucocorticoid therapeutic synergy in COVID-19. *Signal Transduct Target Ther*. 2021;6(1):1–11.
75. Rubin EJ, Longo DL, Baden LR. Interleukin-6 receptor inhibition in Covid-19—cooling the inflammatory soup. *N Engl J Med*. 2021;384(16):1564–1565.
76. Keyt H. WHO recommends corticosteroids for patients with severe or critical COVID-19. *Ann Intern Med*. 2021;174(1):JC2.