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Review Article

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

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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.

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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. 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. 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.

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. SARS-CoV-2 infections induce significant changes in infected cells, many of which influence intracellular GC actions. 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.

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ACTH test in moderately-to-severely ill patients with COVID-19 studies aiming to assess HPA function by performing the low-dose methylprednisolone equivalent in persistent ARDS for had a median survival of 15 days (whereas patients whose cortisol concentration was < 744 nmol/L had a median survival of 36 days, a signifi- cantly superior to a low-dose regimen). 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. Critical illness-related corticosteroid insufficiency is a term indicating an inadequate HPA axis response during critical illness. 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. 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). 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. Moreover, high-certainty evidence has indicated that GCs result in significant reductions in the length of ICU and hospital stays. In a systematic review presented by Annane et al 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 corres- ponding 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. On the other hand, Tan et al 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.

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

Under stressful conditions, the HPA axis is activated, leading to increased cortisol production. The levels of cortisol are found to be significantly higher in patients with sepsis and patients un- dergoing a major surgery to combat stress and major trauma. 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. 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. Critical illness-related corticosteroid insufficiency is a term indicating an inadequate HPA axis response during critical illness. 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. 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). 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. Moreover, high-certainty evidence has indicated that GCs result in significant reductions in the length of ICU and hospital stays. In a systematic review presented by Annane et al 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 corres- ponding 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. On the other hand, Tan et al 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.

**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. 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. A high expression of annexin 1 was found in the lung tissue of patients with inflammatory lung disease treated with GCs. 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 extravasa- tion of neutrophils to the site of inflammation. 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.
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.32 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.39

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-10.40

GCs also have an important role in the resolution phase of inflammation. They mediate survival of an anti-inflammatory monocytophenotype 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.13

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.30,41 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.42 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      |                   | ![Diagram]                        |                |
| Methylprednisolone |               | ![Diagram]                       |                |
| Hydrocortisone  |                   | ![Diagram]                        |                |
| Dexamethasone   |                   | ![Diagram]                        |                |

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

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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. 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. 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. The main features of case reports on patients with COVID-19 and CS are summarized in Table 2. 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.

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. 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. Noticeably, acute exacerbations of interstitial pulmonary fibrosis closely resemble the symptoms of ARDS. Beneficial effects of GCs in patients with ARDS have been found in a few large clinical trials, although patients treated with a high dose of corticosteroids (>500 mg/d of methylprednisolone) had a higher mortality rate.

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.

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. 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 ≤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.

Several prospective controlled studies have been conducted to evaluate the role of GCs in patients hospitalized for COVID-19 (Table 3). 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. 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.

Tocilizumab, tofacitinib, and dexamethasone were found to reduce mortality, due to respiratory failure, in patients with COVID-19 pneumonia. 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 with Tocilizumab, tofacitinib, and dexamethasone were found to reduce mortality, due to respiratory failure, in patients with COVID-19 pneumonia.

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                                          |
| Comorbidities                              |
| BMI > 30 kg/m²                             |
| Yes                                        |
| Yes                                        |
| Yes                                        |
| No                                         |
| No                                         |
| Hypertension                               |
| No                                         |
| Yes                                        |
| No                                         |
| Yes                                        |
| No                                         |
| Cardiovascular disease                     |
| Yes                                        |
| No                                         |
| Yes                                        |
| Yes                                        |
| No                                         |
| 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                                |
| 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                                      |
| 1300                                       |
| Max. urine cortisol                        |
| N/A                                        |
| 959.7                                      |
| 286.2                                      |
| 315                                        |
| N/A                                        |
| Reference range, mmol/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                                        |
| No                                         |

Abbreviations: ACTH — adrenocorticotrophic hormone; BMI — body mass index; CS — Cushing syndrome; Max. — maximum; N/A — not available.
with other immunomodulators, such as tocilizumab, baricitinib, and tofacitinib, has demonstrated clinical benefits in patients with early severe disease and/or systemic hyperinflammation.55

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.56,67
2. Decreases IL-6 activity, thus reducing the activation of multiple cytokines.56
3. Represses the activator protein 1 signal transduction pathway, thereby increasing the gene transcription of anti-inflammatory cytokines.58
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.70
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.

### 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 al61 | N = 61 (35 GT, 29 SOC) | Methylprednisolone 80 mg for 3 d 40 mg for 3 d | 72 mg | Primary outcome in 48%: SOC versus 40% in GT group (P = .04) |
| Effect of hydrocortisone on 21-day mortality. Dequin et al62 | 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 | Primary outcome: SOC 50.7% versus 42.1% in GT group (P = .29) |
| The RECOVERY trial63 | N = 6425 (2104 GT, 4321 SOC) | Dexamethasone 6 mg for 10 d | 60 mg | Primary outcome: 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 al64 | 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.

* The primary outcome was a composite of death, admission to the intensive care unit, or requirement for noninvasive ventilation.

* The primary outcome was death or persistent dependency on mechanical ventilation or high-flow oxygen therapy.

* The primary outcome was 28-day mortality.
monocytes, macrophages, and dendritic cells.34,35,37

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involvement, related to COVID-19.54

IL

adhesion molecule; MCP

 interleukin; GCs

PECAM1

NF

k

B

¼

fibrotic 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.36,37 B, GCs prevent hyperinflammatory response by dampening the activation of monocytes, macrophages, and dendritic cells.41,42,43 C, GCs restrain macrophage differentiation in M1 type inflammatory macrophages and mediates alternatively polarization into M2 type anti-inflammatory macrophages.35,36 D, GCs are not effective and are probably harmful in the fibroblastic phase of acute respiratory distress syndrome related to severe lung involvement, related to COVID-19.36 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; NFkB – nuclear factor kappa B; TNFa – tumor necrosis factor-a; VCAM – vascular cell adhesion protein.

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; B, GCs prevent hyperinflammatory response by dampening the activation of monocytes, macrophages, and dendritic cells; C, GCs restrain macrophage differentiation in M1 type inflammatory macrophages and mediates alternatively polarization into M2 type anti-inflammatory macrophages. D, GCs are not effective and are probably harmful in the fibroblastic phase of acute respiratory distress syndrome related to severe lung involvement, related to COVID-19. 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; NFkB – nuclear factor kappa B; TNFa – tumor necrosis factor-a; VCAM – vascular cell adhesion protein.

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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.

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