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EDITORIAL

The ten reasons why corticosteroid therapy reduces mortality in severe COVID-19

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The recent finding of the effectiveness of corticosteroid therapy in reducing mortality in patients with severe coronavirus disease-19 (COVID-19) is a welcome breakthrough [1–6]. In this article, we highlight the current understanding of the effect of corticosteroid therapy in severe COVID-19.

1. *Evidence of effectiveness from randomized controlled trials in hospitalized patients with COVID-19.*
   The RECOVERY randomized controlled trial (RCT) demonstrated that dexamethasone (6 mg daily for 10 days) in hospitalized patients with COVID-19 reduced (i) 28-day mortality (rate ratio 0.83; 95% confidence interval [CI], 0.75–0.93), (ii) duration of hospitalization and (iii) progression to invasive mechanical ventilation [1]. The greatest mortality reduction was observed in those receiving oxygen supplementation or invasive mechanical ventilation; no improvement was observed in those without respiratory support [1]. A prospective meta-analysis of 7 RCTs further confirmed the benefit of corticosteroid therapy in reducing mortality critically ill patients with COVID-19 (summary odds ratio [OR] 0.66, 95% CI, 0.53-0.82) [2]. This is the best direct evidence supporting corticosteroid therapy in severe COVID-19.
2. *Evidence of effectiveness in non-viral acute respiratory distress syndrome (ARDS).*
   A recent Spanish RCT ($n=277$) of patients with moderate-to-severe ARDS, found that dexamethasone (20 mg and 10 mg for 5 days each), in comparison to placebo, was associated with more mechanical ventilation-free days and lower mortality. An updated meta-analysis of ten RCTs shows that corticosteroid therapy initiated before day 14 of ARDS was associated with a significant reduction in duration of mechanical ventilation and hospital mortality (risk ratio [RR] 0.67; 95% CI 0.52–0.87) [7].
3. *Evidence of effectiveness in community-acquired pneumonia.*
   Several systematic reviews demonstrated that in patients hospitalized with community-acquired pneumonia (CAP), corticosteroid therapy was associated with reduction in mortality, length of stay and time to clinical stability [8].
4. *Dysregulated immune response in COVID-19.*
   Corticosteroid therapy aims to support the central regulatory function of the activated glucocorticoid receptor α (GC-GRα) throughout disease development and resolution. The dysregulated immune response observed in COVID-19 is qualitatively similar to that of multifactorial ARDS [9]. In patients with severe COVID-19, glucocorticoid receptor expression in bronchoalveolar lavage myeloid cells is negatively related to lung neutrophilic inflammation, NETosis, and severity of symptoms [10]. Translational research in ARDS patients randomized to methylprednisolone has demonstrated the ability of corticosteroid therapy to rescue the cellular concentrations and functions of activated GC-GRα leading to downregulation of systemic and pulmonary nuclear factor- κB-activated markers of inflammation, coagulation, and fibroproliferation [11, 12]. Biological improvement was associated with accelerated disease resolution [11]. Further work is needed

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to understand the effect of corticosteroid therapy on the immune response to COVID-19.

5. *Computed tomographic and pathology findings.* Computed tomographic findings of ground glass appearance and histopathologic features (post-mortem studies) of diffuse alveolar damage and acute fibrinous and organizing pneumonia [13] are consistent with corticosteroid-responsive inflammatory lung diseases.
6. *The role of hypothalamic–pituitary–adrenal axis.* Evidence from studies of severe acute respiratory syndrome (SARS) suggest that infection with SARS-CoV-2 is associated with impaired cortisol stress response (Fig. 1).
7. *Microthrombi and coagulopathy.* The pathogenesis of COVID-19 illness appears to be induced by dysregulated systemic and pulmonary inflammation, along with endothelial injury, hypercoagulability and thrombosis [14, 15]. Platelet–fibrin thrombi formation in small arterial vessels are com-

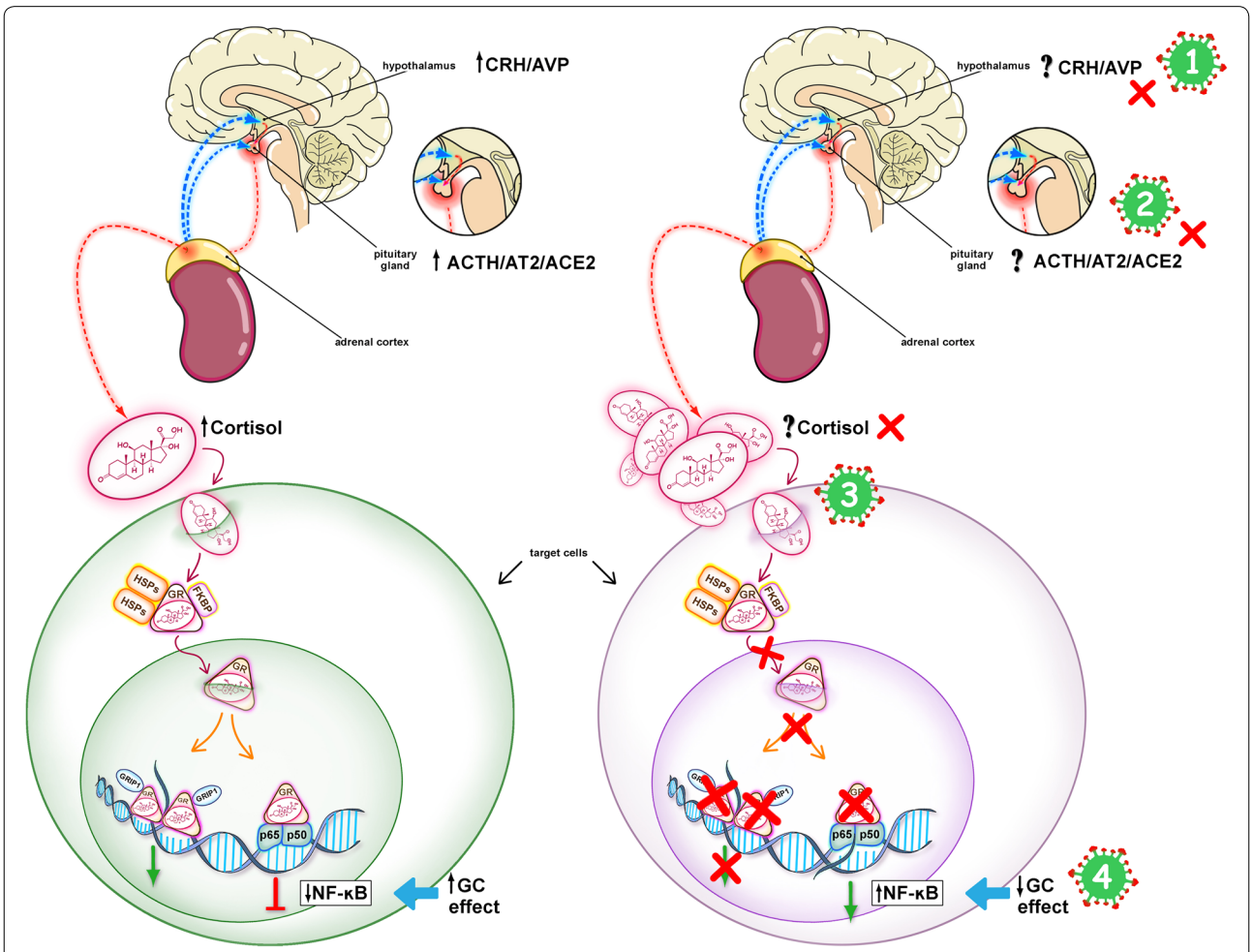

Fig. 1 Hypothalamic–pituitary–adrenal (HPA) response in COVID-19. The left panel shows an intact HPA axis response to stress leading to the downregulation of NF-kB. The right panel shows mechanisms potentially involved in an impaired HPA axis response to stress in COVID-19. COVID-19 may be associated with CIRCI, as a result of inhibition of the hypothalamic–pituitary–adrenal (HPA) axis at any or all of its levels, as shown by the red X's: (1) Hypothalamus (CRH/AVP), (2) pituitary gland (ACTH/AT2/ACE2), (3) adrenal cortex (cortisol), and (4), target tissues (Glucocorticoid receptor signaling system). In CIRCI, target tissue resistance to glucocorticoids may occur even in the presence of elevated levels of circulating cortisol. SARS -CoV-2 has an epitope that binds the ACE2 enzyme facilitating entry into host cells, which might influence the function of the HPA axis at level (2). SARS-CoV-2 may have an ACTH-mimic peptide that could act as an agonist or antagonist at the ACTH receptor at level (3). Prolonged glucocorticoid treatment is indicated when cortisol production and/or target tissue sensitivity to cortisol are compromised (Online Supplement for Supplementary References). *CIRCI* Critical illness-related corticosteroid insufficiency, *CRH* corticotropin-releasing hormone, *AVP* arginine-vasopressin, *ACE2* angiotensin-converting enzyme 2, *AT2* angiotensin 2, *ACTH* corticotropin, *GR* glucocorticoid receptor–alpha, *HSP* heat shock protein, *FKBP* immunophilin, *GRIP1* coactivator, *p65/p50* nuclear factor (NF)-kB

monly observed in post-mortem examination of the lungs from patients with COVID-19 [16]. Emerging data indicate that hypercoagulability in COVID-19 is induced by dysregulated release of neutrophil extracellular traps (NETs). In an equine experimental model, dexamethasone decreased NETs formation [17], which may contribute to the observed benefit from corticosteroid therapy in COVID-19.

8. *Acceptable safety profile*.
   Short-term (up to 4 weeks) corticosteroid therapy in patients with life-threatening systemic inflammation is well-tolerated. Data from systematic reviews in CAP and ARDS showed that corticosteroid therapy was associated with transient hyperglycemia but did not increase the frequency of gastrointestinal hemorrhage, neuromuscular weakness, or nosocomial infections [8, 12]. Hyperglycemia did not affect outcome. Recent data have provided evidence that the GRα is essential for activation and reinforcement of innate immunity and when applied correctly (i.e., appropriate duration of corticosteroid administration) is associated with restoration of anatomy and function of the affected tissues, along with a parallel support of adaptive immunity. Corticosteroid treatment-associated downregulation of systemic and pulmonary inflammation might lower the risk of developing nosocomial infections by (i) decreasing duration of mechanical ventilation, (ii) achieving an inflammatory milieu less favorable to intra- and extra- cellular growth of bacterial pathogens frequently encountered in ARDS (*Staphylococcus aureus*, *Pseudomonas aeruginosa*, and Acinetobacter sps.), and (iii) improving opsonization-dependent phagocytic neutrophil function and intracellular killing [18]. (Online Supplement for Supplementary References).
9. *Long-term outcome*.
   In RCTs of ARDS patients, corticosteroid therapy was associated with survival benefit that persisted after up to one year of hospital discharge (limit of measurement) [19]. Extensive literature suggests pro-inflammatory cytokines do influence the brain, and may be involved in the pathogenesis of depression and post-traumatic stress disorder (PTSD). Data from five small RCTs ($n=292$) suggest that longer duration of corticosteroid therapy may be associated with lower anxiety scores and improved PTSD symptomatology. Corticosteroid therapy-associated reduction in duration of mechanical ventilation and sedation may also have a positive impact on long-term PTSD symptoms and cognitive function. (Online Supplement for Supplementary References).
10. *Scalability*.
    The low cost and wide availability make corticosteroid therapy easily equitable and available globally across different income settings.

Recent data on corticosteroid therapy represent a milestone in the of management of COVID-19, while many questions remain. Efforts for worldwide implementation of corticosteroid therapy protocols should be supported by data regarding generalizability of the observed effect in randomized controlled trials across subgroups of patients, different populations, and resource settings. More data are needed to evaluate the impact of type of corticosteroid, timing of initiation, dose, mode of administration, duration, and dose tapering on outcome. And also to (i) identify modalities to adjust treatment dose and duration based on laboratory parameters of oxygenation and inflammation, and (ii) to evaluate the impact of co-interventions directed at improving response to corticosteroid therapy [20]. Limited data are presently available on the impact of corticosteroid therapy on SARS CoV-2 replication, and on the potential benefits of concomitant antiviral treatment. The interaction between corticosteroid therapy and other COVID-19 therapeutics, such as interferons (IFNs) [21] and anticoagulation should be explored.

In conclusion, corticosteroid therapy is a safe and effective intervention in downregulating the integrated pathways of inflammation-coagulation-fibroproliferation, in the lung and systemically, in COVID-19 patients. There is an ethical urgency to invest in this field of research.

Electronic supplementary material
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Compliance with ethical standards

Conflicts of interest
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