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Glucocorticoid-Glucocorticoid Receptor Response to Severe Acute Respiratory Syndrome Coronavirus 2*

KEY WORDS: coronavirus disease 2019; glucocorticoid-induced leucine zipper; immune response; sepsis

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In the beginning of the coronavirus disease 2019 (COVID-19) pandemic, a disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), corticosteroids were contraindicated in the management of these patients (1). Few months later, the demonstration that, like a sepsis, COVID-19 is mainly driven by a deregulated hyperinflammatory host response to the virus triggered a renewed interest in corticotherapy (2). Eventually, clinical trials convincingly reported clinical benefits from corticosteroids (3–7), which became the standard of care for patients with COVID-19 pneumonia and requirement of oxygen supplementation (8). The immunomodulatory effects of glucocorticoids are mediated mainly by the glucocorticoid-glucocorticoid receptor pathway, in which the glucocorticoid-induced leucine zipper (GILZ) protein plays a major role (9, 10). GILZ is strongly induced by glucocorticoids and contributes to the regulation of immune cell activation including the synthesis and

***See also p. 2131.**

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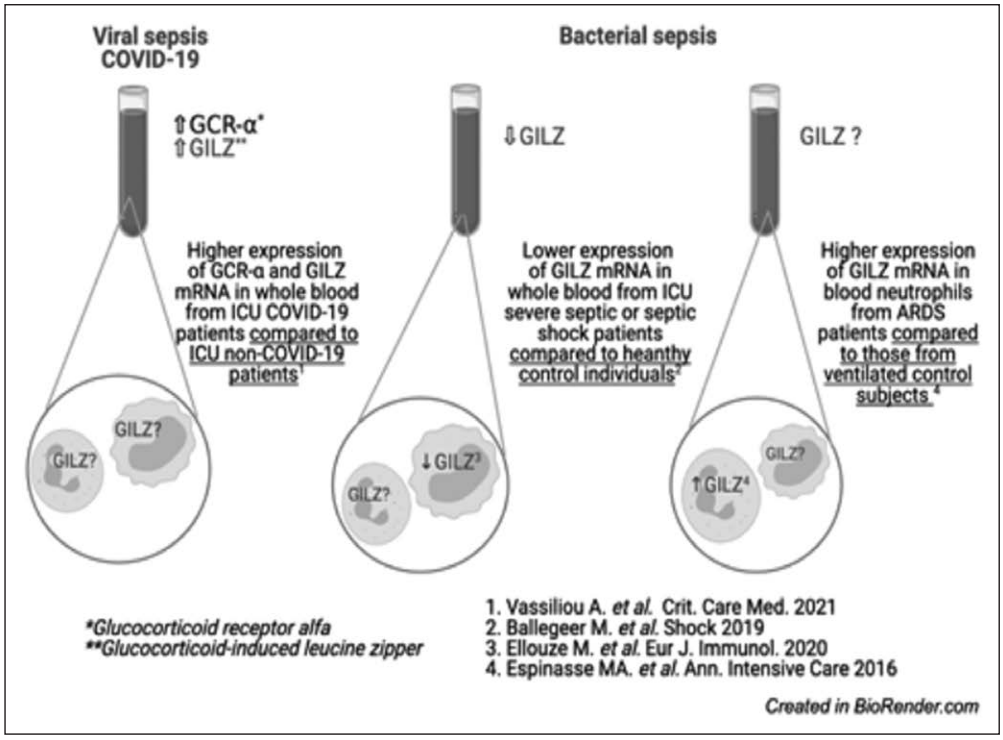

Figure 1. Schematic summary of current knowledge about glucocorticoid-induced leucine zipper (GILZ) protein in the setting of viral or bacterial sepsis. ARDS = acute respiratory distress syndrome, COVID-19 = coronavirus disease 2019, GCR-α = glucocorticoid receptor-α, mRNA = messenger RNA.

release of cytokines and chemokines mainly by inhibiting the nuclear factor kB (9–11). GILZ is expressed in almost all immune cells, and its expression by monocytes/macrophages is of the utmost importance to control inflammation (9).

In this issue of *Critical Care Medicine*, Vassiliou et al (12) have investigated on ICU admission, the expression of the glucocorticoid receptor alfa and of GILZ in whole blood of critically ill adults with and without COVID-19. Compared with patients without COVID-19 and comparable severity of illness core, patients with COVID-19 had increased expression of glucocorticoid receptor alfa and GILZ, and increased serum cortisol levels. Up-regulation of GILZ correlated with up-regulation of the glucocorticoid receptor alfa but not with serum levels of cortisol, interleukin (IL)-6, or IL-10. In the study by Vassiliou et al (12), there was no patient who met critical illness-related corticosteroid insufficiency (CIRCI) as defined by serum cortisol levels of less than 10 μg/dL. Although the degree of activation of the glucocorticoid-glucocorticoid receptor pathway was much higher in the patients with versus without COVID-19, the crude ICU mortality did not differ between the groups. Altogether these findings suggested COVID-19 is associated with strong activation of endogenous cortisol response to SARS-CoV-2 that might be insufficient to prevent death. A study published more than 10 years ago and performed in animal models of bacterial sepsis has shown that antisepsis resistance can be achieved through stress-induced immunosuppression and has highlighted GILZ as one of the molecules involved in this protective effect (13). The question is now to determine which level of GILZ expression must be reached to obtain this immunosuppression in patients with COVID-19. The study by Vassiliou et al (12) provided additional rationale for corticotherapy in patients with COVID-19. The strengths of the study by Vassiliou et al (12) included being the first prospective cohort investigating the glucocorticoid-glucocorticoid pathway in patients with COVID-19 and focusing on corticosteroid-free patients. The study has several limitations. First, the sample size was small resulting in a fairly large variability in the biological biomarkers and wide CIs for clinical outcomes. Second, the control group is rather heterogenous and should have been limited to patients with sepsis. Third, the authors did not use the recommended definition for CIRCI (14). Therefore, the true prevalence of CIRCI in the study by Vassiliou et al (12) remains unknown. Fourth, the authors have analyzed glucocorticoid receptor alfa and GILZ expression in whole blood. GILZ is ubiquitously expressed and particularly in hematopoietic cells (9). Thus, measuring GILZ expression in whole blood is more likely to reflect its expression by neutrophils that are the most abundant circulating white cells rather than by monocytes. Indeed, in patients with bacterial-induced

acute respiratory distress syndrome, blood neutrophils express higher levels of GILZ compared with those from ventilated control subjects (15), whereas monocytes have a defective GILZ expression (16) (**Fig. 1**). The expression of GILZ is not solely mediated by glucocorticoids but also by numerous circulating factors including hormones (aldosterone and vasopressin) and cytokines (9). And apart from glucocorticoids, the inducers of GILZ vary between cell types. The observed up-regulation of GILZ on whole blood in the study by Vassiliou et al (12) cannot rule out an inappropriate expression of GILZ by monocytes/macrophages. These cells are the more relevant circulating target cells for corticosteroids mediated immune host response in sepsis (16).

The study by Vassiliou et al (12) did not aim at providing data to impact on routine practice. The recommendation for the use of corticotherapy in COVID-19 remains targeting patients with severe pneumonia requiring oxygen supplementation. The study provided additional rationale supporting this recommendation. The study also may stimulate additional investigations on the role of GILZ expression in COVID-19, particularly in an attempt to fine-tune the phenotyping of patients who should or should not be treated by corticosteroids. Further investigations may focus on measuring GILZ expression on isolated monocytes before and after ex vivo stimulation by dexamethasone. They may target patients in whom corticosteroids have been initiated to assess treatment response and guide duration of corticotherapy.

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Severe COVID-19 and Stroke—Another Piece in the Puzzle*

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KEY WORDS: coronavirus disease 2019; extracorporeal membrane oxygenation; hemorrhagic stroke; intensive care; ischemic stroke; neurocritical care

Concomitant neurologic manifestations have been described since the early emergence of the coronavirus disease 2019 (COVID-19) pandemic (1). While the range of reported neurologic manifestations is wide (2), occurrence of acute cerebrovascular disease drew specific attention due to the high rate of coagulopathy and thrombotic complications that was observed early on in patients with severe COVID-19 (3–5). Early case series and cohort studies reported an occurrence rate of stroke between 2% and 6% (2), and a meta-analysis of studies published up to June 2020 found the frequency of stroke to be 1.1% among hospitalized COVID-19 patients (6). However, these reports used varying definitions for stroke and other data, limiting accurate estimates across populations. In a recent combined publication of two global consortia formed to specifically address incidence, type, and outcomes of neurologic manifestations among patients hospitalized with COVID-19, the observed overall stroke incidence was 3% (7–9).

How do these data compare to those in general critical illness? Stroke occurs in 1–4% of patients admitted to ICUs for non-neurologic conditions (10–12). As applies for COVID, stroke risk factors in ICU patients are different than for the general population, with systemic infections and coagulopathy (13, 14), other pro-inflammatory states (15), and invasive vascular and cardiac procedures, especially extracorporeal membrane oxygenation (ECMO), playing a major role (14, 16, 17). In ECMO patients, a subpopulation of the critically ill of specific interest in the COVID pandemic due to the common failure of respiratory support with regular mechanical ventilation (18), the overall occurrence of neurologic complications is estimated to be around 13% (19), but also ranges widely, dependent on study and methodology. With specific respect to venoarterial or venovenous ECMO, neurologic complication rates vary between 15% and 18% (venoarterial) and 4–13% (venovenous), respectively (19–22). In a recent single-center analysis of 416 ECMO patients between 2009 and 2017, 13.3% had an imaging-confirmed CNS complication, including 7% ischemic stroke and 3.4% hemorrhagic stroke (20). With respect to COVID-19 and ECMO utilization, the current study by Cho et al (23) sheds further light on these potential complications.

***See also p. e1223.**

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