One Size Does Not Fit All

Moving Towards a Personalized Approach for Steroids in COVID-19

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Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 infection, presents with heterogeneous and a wide range of clinical manifestations, from asymptomatic patients to those with severe ARDS, and with different pathophysiologic mechanisms that are determined by host-pathogen interaction.[1] Although a complete mechanistic description is lacking, the pathogenesis of severe COVID-19 illness appears to be induced by dysregulated systemic and pulmonary inflammation along with endothelial injury, hypercoagulability, and thrombosis.[2,3] Patients with severe COVID-19 show a reduced glucocorticoid receptor expression in BAL myeloid cells.[4] Glucocorticoid receptor expression is correlated negatively with neutrophilic recruitment and NETosis.[4] The uncontrolled and endogenous release of proinflammatory cytokines (called "cytokine storm") has been postulated to be responsible for some of the clinical manifestations and is associated with worse outcomes including death.[5]

However, the hyperinflammatory state is not a homogenous finding, and several studies have shown

that patients with severe COVID-19 disease had fewer, but distinct, cytokines compared with other causes of ARDS.[6,7]

Interventions that aim at down-regulating the inflammatory response in patients with COVID-19 may prevent disease progression and reduce both lung and systemic inflammatory related injury. The cytokine profile reported in patients with COVID-19 is within the broad range of regulation provided by corticosteroids.[8] Therefore, the subgroup of patients with markedly elevated levels of inflammatory markers is the one that is supposed to benefit most from corticosteroids.

To date, corticosteroids are the only drugs that have showed a statistically significant reduction in deaths in patients with COVID-19.[9] Corticosteroids are recommended for patients with COVID-19 with acute respiratory failure (ARF).[10] This recommendation is based on the RECOVERY trial that showed that a moderate dose of corticosteroid (6 mg of dexamethasone daily for 10 days) reduced mortality rates in hospitalized patients with COVID-19 and ARF who required respiratory support with supplemental oxygen or mechanical ventilation.[9] These beneficial findings are supported by three other trials of glucocorticoids for COVID-19, which stopped enrolment when the RECOVERY trial results were released.[11-13] Each of these trials showed some evidence of benefit, although none had completed enrolment. However, the data from RECOVERY trial also indicated that dexamethasone might increase mortality rates in hospitalized patients who did not require supplemental oxygen.[9]

In this issue of *CHEST*, Chen et al[14] provide new insights concerning the benefits of steroid treatment in selected critically ill patients with COVID-19. Their objective was to identify phenotypes that are more prone to benefit from steroid therapy. Two distinctive phenotypes were identified through the combinations of biologic parameters (biomarkers): 223 patients (52.1%) were classified in the hypoinflammatory phenotype, and 205 patients (47.9%) were classified in the hyperinflammatory phenotype. The hyperinflammatory phenotype was characterized by elevated levels of proinflammatory cytokines, higher rates of complications, and higher rate of mortality (71.2% vs 15.2%). Using forward stepwise modeling, the

three variables that contributed most to define the phenotypes were tumor necrosis factor-α, D-dimer, and neutrophil-lymphocyte ratio. After marginal structural modeling, the association between corticosteroid therapy and 28-day mortality rates was insignificant in patients with the hypoinflammatory phenotype (hazard ratio, 1.15, 95% CI, 0.45-2.94; $P = .76$). Interestingly, corticosteroid therapy was associated with a reduced 28-day mortality rate in patients with the hyperinflammatory phenotype (hazard ratio, 0.51; 95% CI, 0.34-0.78; $P = .0018$); regardless of the baseline severity of ARF and the use of invasive mechanical ventilation, the significance of the association was persistent.

The main strength of the study is the use of a biomarker-based parsimonious model to identify phenotypes in patients with COVID-19. The combination of biomarkers into clusters (phenotypes) is of paramount importance to determine the relationship between COVID-19 phenotypes and disease severity. Indeed, the hyperinflammatory phenotype showed differences in relevant clinical outcomes, such as death. Some of the biomarkers that are helpful to identify this phenotype, such as D-dimer and neutrophil-lymphocyte ratio, are easy to implement in clinical practice and commonly have been used. Even more relevant, the hyperinflammatory phenotype was associated with favorable response to corticosteroid treatment, furthering the path towards the definition of a specific endotype. Moreover, the role of potential confounders was well-defined and minimized through the use of a rigorous marginal structural modeling. The identification of biomarkers, phenotypes, and pathologic mechanisms in COVID-19 is critical for the identification of specific groups of patients who may benefit from corticosteroid therapy. Furthermore, the identification of subphenotypes in ARDS has shown to be associated with worse clinical outcomes, including death.[15]

The study of Chen et al[14] opens up new research priorities. First, temporal and quantitative changes of the inflammatory biomarkers during corticosteroid therapy should be verified in patients with COVID-19. Second, no uniform regimen of steroid therapy was used. The type of corticosteroid, the timing of corticosteroid initiation, the mode of administration, and the duration and consequent tapering of corticosteroid treatment are all factors that may play a relevant role and should be investigated. Third, phenotypes and endotypes should be validated in different cohort of patients and different health-care systems to confirm the reproducibility of the results. Finally, future randomized controlled trials must account for phenotypes and endotypes of diseases to eliminate all possible confounders. Such an approach may reveal subgroups of patients who could benefit with other therapies in COVID-19.

We are experiencing the first global pandemic since the dawn of precision medicine. Traditional approach to treatment is based on the evaluation of visible common clinical characteristics that facilitate a "one-drug-fits-all" model. Indeed, the administration of corticosteroids in patients with COVID-19 currently is based on the severity of the disease in terms of respiratory support. However, COVID-19 disease encompasses heterogeneous groups of patients that consist of varying unidentified phenotypes and endotypes. Heterogeneity in COVID-19 is able to obfuscate statistical analysis concerning clinical trials for potential therapeutic treatments and hinder the identification of different factors that modulate disease severity and response to treatment. The study of Chen et al[14] identifies a phenotype based on biomarkers, which is central for clinical research because it helps to rationalize experimental results and enhances reproducibility. The combination of biomarkers represents a measurable indicator that should be tested in randomized controlled trials to link an endotype with a phenotype. Definitions of phenotypes and endotypes that deconstruct COVID-19 diseases into groups based on distinct biologic and pathologic processes (endotypes) and clinical characteristics (phenotypes) will be the solid ground to design higher-yield clinical trials and tailor treatment.

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