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Anticytokine Therapies in Severe Coronavirus Disease 2019 Should Be Informed by Detailed Inflammatory Profiling and Specific Therapeutic Targets

To the Editor:

We read the article by Buckley et al (1), recently published in *Critical Care Explorations*, on the role of anticytokine therapies for severe coronavirus disease 2019 (COVID-19) with interest. Although we agree that anticytokine therapies may lead to improved outcomes in COVID-19 patients, we contend that current evidence from critically ill COVID-19 patients, which was recently published in this journal (2, 3), warrants against empiric targeting of interleukin 6 (IL-6) and suggests tumor necrosis factor (TNF) and serine proteases as more specific targets for anticytokine interventions.

As the authors suggest, COVID-19 is associated with an elevation in IL-6 levels (4, 5). However, the median values of IL-6 in severe COVID-19 are 10- to 40-fold lower than those in historic cohorts of acute respiratory distress syndrome (ARDS) (6). In keeping with the authors comments regarding the pleotropic nature of inflammatory mediators, we contend that empiric interventions targeting isolated inflammatory mediators, such as IL-6, may not be effective and could be potentially harmful. Instead, we should focus on detailed examination of the inflammatory profile of COVID-19 patients and its comparison with non-COVID-19 controls, assess the temporal evolution of inflammatory markers, and establish the link between different inflammatory profiles and clinical outcomes.

In our recent prospective study published in this journal, we used machine learning to demonstrate that top six analytes distinguishing COVID-19 positive ICU patients from COVID-19 negative ICU patients were TNF, granzyme B, heat shock protein 70 (HSP-70), IL-18, interferon-gamma-inducible protein 10, and elastase 2 (2). These preliminary data suggest that IL-6 may not be an appropriate target, especially considering that median levels of IL-6 in severe COVID-19 are lower than those in historic non-COVID ARDS cohorts (6).

Furthermore, in contrast to previous studies from sepsis and ARDS cohorts, COVID-19 patients in our study had persistently elevated levels of circulating TNF (2), suggesting altered upstream regulation of inflammation and highlighting the importance of assessing temporal trajectories of inflammatory markers. Equally intriguing was the role of serine proteases, including granzyme B and elastase 2. Granzyme B is located in lymphocytes (7) and would accumulate in lung early, whereas subsequent neutrophilic invasion would bring elastase 2 (8). Both serine proteases would potentially digest resident tissues and contribute to lung remodeling. Thus, a combination of TNF and serine protease inhibitors seems more relevant as potential therapeutic options than therapies targeting IL-6 response.

Linkage with clinical outcomes is also critical. In our first study in this journal (2), we demonstrate that HSP-70 measured on ICU day 1 accurately predicted mortality, whereas in our second study in this journal, we showed that proteome profiling in COVID-19 patients identified six proteins that predict mortality on the first day of an ICU admission with 100% accuracy (3). Although these are preliminary findings, they warrant further investigation as potential markers of disease severity and clinical outcomes both for prognostication purposes and as a means to stratify patients in future anticytokine clinical trials.

We applaud the authors for their comprehensive and well-written review on potential anticytokine therapies to improve outcomes of COVID-19. Although assessment of proposed empiric anticytokine therapies for clinical effectiveness in ongoing clinical trials is important, we want to highlight that detailed profiling of the inflammatory response in COVID-19 patients recently published in this journal is essential for identifying therapeutic targets that are specific to COVID-19 disease. Future clinical trials should establish whether inhibition of TNF and serine proteases (granzyme B and/or elastase 2) results in better clinical outcomes than anti-IL-6 treatments.

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