Clinical Infectious Diseases

EDITORIAL COMMENTARY

Paradoxes and Uncertainties of Immunomodulatory Treatments in the Fight Against Coronavirus Disease 2019

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Keywords. immunomodulation; COVID-19; steroids; IL-6.

In their article, "Immunomodulation as treatment for severe COVID-19: a systematic review of current modalities and future directions," Meyerowitz and colleagues provide a straightforward source of information for the clinician [1]. In a time when we are flooded with preprints and publications of varying quality, one of the most critical challenges is to separate the grain from the chaff. The authors have done this for us by reviewing hundreds of references and carefully selecting the most appropriate sources of information. Their article helps us forge our conclusions not only for the use of the different immunomodulatory treatments available but importantly also on the rationale of their use.

In this regard, it is refreshing that the authors highlight the importance of word choice when describing the immune response to coronavirus disease 2019 (COVID-19). How often have we read and heard from our colleagues and media outlets that COVID-19 is associated with a cytokine storm, bluntly implying an upregulation of all cytokines in response to the acute infection? Being more precise, the authors nicely emphasize that we instead observe an imbalance in the innate immune response and that we have to consider the complex network of interactions that evolves as the disease advances. A therapy that targets a single cytokine or pathway at any given time would not be sufficient to address the complexity of the elicited immune response.

Moreover, to characterize the inflammatory response to COVID-19, we are surveying what is detectable at the blood level and we are still partially blind as to what is happening at the site of inflammation in the lower respiratory tract. Similarly, we simply monitor the viral load in the upper respiratory tract but paradoxically are almost entirely unaware of the kinetics of viral load in the lower respiratory tract. For now, it will probably remain unclear which immunotherapeutic interventions will best impact the distinct immunopathological and thrombotic complications observed in the lungs. [2, 3]. In that regard, steroids and their pleiotropic effect on the immune response have been a logical option to test and have been shown to save the lives of hospitalized COVID-19 patients in need of oxygen therapy. This was the first good news of the year in the fight against COVID-19, and dexamethasone has now become part of the standard of care for patients who need supplemental oxygen. Furthermore, from a global public health standpoint, steroids have the incredible advantage of being easily available at a low cost, even in low- and middle-income countries. That being said, we still have to keep a close watch; we may regret that this finding is based primarily on a single study and that other similar trials have been stopped before reaching their enrollment target [4, 5].

In terms of suggested immunomodulatory treatment approaches, the authors highlight that interleukin (IL)-6 levels are associated with disease progression. Of note, similar levels are likely to be observed in other infections, and IL-6 is known to play an important role in autoimmune diseases such as rheumatoid arthritis. Nevertheless, these initial observations in COVID-19 patients have been judged to be sufficient to make a case for anti–IL-6R therapy; however, clinical studies to date have not shown a clear favorable effect. The overall benefit or harm offered by anti–IL-6R antibodies remains elusive, and we need confirmatory evidence. In the current pandemic, however, clinicians are often not waiting for results of randomized, controlled trials (RCTs) before weighing the best options for their patients, and thus off-label use of anti–IL-6R antibodies is common.

Another option suggested by the authors is to treat patients with type I interferons (IFN-alpha and -beta).

Received 30 November 2020; editorial decision 1 December 2020; published online 7 December 2020.

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Clinical Infectious Diseases® 2020;XX(XX):1–2

DOI: 10.1093/cid/ciaa1837

The rationale behind this approach is mainly to enhance the antiviral response that is induced by type I IFNs. However, to date, divergent results have arisen from various small RCTs when compared with the World Health Organization–led trial, and there is a need for more solid data before changing clinical practice. Many open questions remain, such as which IFN to give, when is the latest time after infection to do so, and what might be the best route of administration?

Immunomodulatory treatment could be administered early if it contributes to control of viral replication; however, currently it is primarily given during a later phase of the disease when, theoretically, the viral replication is supposed to be controlled and viral load has already substantially declined. On the other hand, the authors mention that the duration of viral shedding is longer in those patients who are exposed to steroids and possibly also in those patients exposed to anti–IL-6R. This is an additional paradox that again highlights the need for a better understanding of the kinetics of viral load in the lower respiratory tract.

These findings also raise the issue of how we will combine therapies. The redundancy and multiple interdependence of the different immune response pathways suggest that it is unlikely that a single drug with a very narrow effect on a specific pathway may do better than steroids. Given the current situation in which steroids are part of standard care, the next dilemma will be to show a supplementary effect of an immunomodulatory target therapy when added to standard steroid treatment and/or to design studies that compare any promising nonsteroidal drug candidate with a control group that does not receive steroids.

In addition to immunomodulatory interventions, we still need a specific severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antiviral treatment that can immediately control viral replication and be given orally early before hospitalization or as postexposure prophylaxis. We also expect that monoclonal antibodies may complete our armoury as they seem beneficial during the early stage of the disease [6]. In contrast, convalescent plasma has not shown clinical benefits in the late stage [7]. In the end, we may imagine that specific antiviral drugs combined with immunomodulation could improve patient care.

SARS-CoV-2 has taught us humility and fundamentally changed our perspective; COVID-19 is not just the business of infectious diseases specialists. Thanks to a multidisciplinary approach, steroids have been tested rapidly; it is likely that no clinical virologist would have done this without input from other fields. We reiterate the call of Meyerowitz and colleagues that as of now only high-quality RCTs should change treatment protocols as opposed to experimenting with various treatment cocktails in small populations, which generates more flawed data and uncertainty than help. We also have to remember that the very old patients are the most likely to die of COVID-19. Unfortunately, they are generally underrepresented in studies, and the impact of any immunomodulation on their aging immune system remains another field of uncertainty. All of this is easier said than done when intensive care units are overflowing, uncountable numbers of patients are dying, and the field is in a rush for quick and often high-profile publications. Before preparing for the next pandemic—as done by Meyerowitz and colleagues—use good clinical and research practices now to control the current one.

Note

Potential conflicts of interest. The authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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