To Toci or Not to Toci for COVID-19: Is That Still the Question?

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"I have great respect for the past. If you don't know where you've come from, you don't know where you're going. I have respect for the past, but I'm a person of the moment. I'm here, and I do my best to be completely centered at the place I'm at, then I go forward to the next place."

- Maya Angelou

Tocilizumab to treat a viral pneumonia: for infectious disease physicians, this is unorthodox and contrary to decades of experience. In general, we shy away from therapies that suppress immune responses for fear of exacerbating the underlying infection. While there are well-documented exceptions in which antimicrobial therapy PLUS anti-inflammatory therapy improve outcomes, such as pneumococcal meningitis and *Pneumocystis* pneumonia, anti-inflammatory therapy in the absence of pathogen-specific therapy makes us anxious. In critical care medicine, quelling inflammation is the holy grail, yet the quest for an anti-inflammatory remedy to sepsis and acute respiratory distress syndrome (ARDS) remains elusive. Despite major progress in understanding the pathophysiology of ARDS, no pharmacologic treatment, including corticosteroids and more targeted agents, has ever been shown to improve survival. So how did we arrive at a study of tocilizumab monotherapy for an acute viral pneumonitis resulting in ARDS? And what do we make of the provocative results presented by Somers and colleagues in this issue of *Clinical Infectious Diseases*,[1] in which there appears to be substantial improvement in survival after single-dose tocilizumab in mechanically ventilated patients with ARDS due to coronavirus disease 2019 (COVID-19)? To answer these questions, we must first take stock of where we came from, the moment we are in, and how to chart our future course.

The development of small molecule antiviral drugs is hampered by many challenges, including an often-limited spectrum of activity and rapid emergence of resistance. Although the

past 10 years have been encouraging with respect to development and approval of new antivirals for chronic infections like hepatitis C virus, this success is not mirrored for acute viral infections.[2] Great advances in our understanding of host-pathogen interactions, and bioengineering techniques to target these interactions, have enabled novel treatment approaches using host-directed therapy (HDT) to bypass many of the challenges with traditional antiviral development. The concept of HDT encompasses a range of approaches, such as therapies that augment host defense mechanisms (i.e., interferons for viral hepatitis) or modulate excessive inflammation (i.e., corticosteroids).[3]

Tocilizumab (Actemra), a humanized monoclonal antibody that functions as an interleukin 6 receptor (IL-6R) antagonist, is an example of HDT. Tocilizumab binds to both the membrane-bound and soluble forms of the human IL-6R, thereby interfering with pro-inflammatory signal transduction, primarily via the JAK/STAT pathway.[4] This drug was first approved for treatment of rheumatoid arthritis in 2010. Two years later, a young girl became critically ill with ARDS, multiorgan failure, and refractory hypotension unresponsive to corticosteroids shortly after infusion of investigational chimeric antigen receptor T-cells (CAR-T-cells) to treat acute lymphoblastic leukemia. Astute clinical observations of elevated serum IL-6 levels prompted off-label treatment with a single dose of tocilizumab, resulting in rapid clinical improvement.[5] This paved the path for regulatory approval of tocilizumab for the treatment of CAR-T-cell associated cytokine release syndrome (CRS) in 2017. Subsequent clinical experience indicates a low increased risk, if any, for secondary infections from tocilizumab-induced immunomodulation in the context of monthly or single-dose tocilizumab for rheumatoid arthritis[6] or CAR-T-cell associated CRS,[7] respectively.

As the COVID-19 pandemic surged in early 2020 due to outbreaks of infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), front-line healthcare providers were struck by the rapid deterioration in a subset of patients that resulted in ARDS,

cardiovascular collapse, and death. The urgency of confronting a devastating new disease prompted empiric use of readily available agents, including established antiviral medications and corticosteroids. Early observations suggested parallels to the hyperinflammatory state of CRS in critically ill patients with COVID-19. Correlations between elevated serum IL-6 levels and poor outcomes[8] solidified the collective interest of the medical establishment to recapitulate the success story of tocilizumab for CAR-T-cell associated CRS.

Now that we have established where we came from, one can understand the impetus to use tocilizumab in hospitalized patients with COVID-19 in the initial surge, despite lack of data from controlled trials. However, there are reasons for pause from clinical and biological perspectives. CAR-T-cell associated CRS is a sterile condition that presents as sepsis physiology with endothelial activation and capillary leak in its most severe form; ARDS occurs in a minority of cases.[9,10] In severe COVID-19, a cytopathic respiratory viral infection is the initial insult that triggers a hyperinflammatory response that promotes acute lung injury, a complex process involving multiple cell types and inflammatory mediators in addition to IL-6. The inflammatory profile in patients with severe COVID-19 is assumed to be the same as that in patients with severe CRS after CAR-T-cell therapy, but this has not been substantiated. Additionally, numerous studies demonstrate that IL-6 is an essential component of the adaptive immune response for recovery from viral infections, although overproduction of IL-6 may be detrimental to viral clearance and survival.[4]

Initial reports of patient outcomes after treatment with tocilizumab for COVID-19 were small, heterogenous, uncontrolled, and thus limited in providing meaningful conclusions. The study by Somers and colleagues rises to the challenge of addressing many of these issues in the context of a retrospective, real-world design.[1] Their study included mechanically ventilated patients with COVID-19 who did (N=78) and did not (N=76) receive a single dose of 8 mg/kg of tocilizumab, typically administered within 48 hours of intubation. Only 3% of patients in both

groups received a potentially effective antiviral agent (remdesivir). To account for treatment selection bias and imbalances in patient characteristics, the authors utilized rigorous methods, including propensity score inverse probability weighting of treatment with tocilizumab to create a pseudo-population that approximates randomized treatment assignment. In adjusted regression analyses, tocilizumab was associated with a 45% reduction in the hazard of death (95% CI, 10% to 67%). The authors also evaluated outcomes based on an ordinal illness severity scale that integrated secondary infections. Despite an increased incidence of subsequent infections (primarily ventilator-associated pneumonia) in the tocilizumab group (54% versus 26%), receipt of tocilizumab was associated with better outcomes (odds ratio per 1-level increase, 0.58; 95% CI, 0.36 to 0.94), and mortality was similar among tocilizumab-treated patients with and without superinfections. Although propensity score and regression analyses of observational datasets have important limitations, first and foremost that unmeasured confounding may still be present,[11] it is reassuring that the findings were consistent across models and sensitivity analyses.

Are these data enough to convince the skeptics and reassure the proponents of tocilizumab for early acute respiratory failure in patients with COVID-19? Other observational studies provide evidence that support both potential benefit and no benefit of tocilizumab in hospitalized patients with COVID-19, although this is the largest and most rigorous study in mechanically ventilated patients to date. This study adds strength to the potential utility of tocilizumab in hospitalized patients with COVID-19, although circumspection remains advisable—the experience in ARDS shows us time and time again that promising therapies are often quashed when put to the rigor of randomized controlled trials.

How do we move forward in providing the best care for patients with COVID-19 while we await results of ongoing randomized clinical trials to better define the effect of tocilizumab in this context? The work by Somers et. al., along with the report of similarly reduced risk for mortality

in mechanically ventilated patients with COVID-19 treated with dexamethasone (rate ratio, 0.64; 95% CI, 0.51 to 0.81) in a randomized study,[12] support the notion that some phenotypes of ARDS may be more likely to respond to anti-inflammatory agents.[13] Even if tocilizumab or other HDT are not ultimately shown to reduce mortality in randomized controlled trials, they may provide incremental benefit if given in combination with an antiviral agent at the right time, in the right patient. The impact of secondary infections resulting from these treatments, a potential source of considerable morbidity for critically ill patients, needs to be further elucidated. The path forward may require head-to-head comparisons that consider efficacy, safety, accessibility, and cost of these and other immunomodulatory therapies in various stages of clinical trials.

We are collectively in a moment of great uncertainty, which is reflected in the medical community's struggle to balance the emotional need for action with evidence-based medicine. The combination of an immunomodulatory agent with an effective antiviral that directly targets SARS-CoV-2 may be an approach that offers the most promise for patient benefit. In contrast to the words of Maya Angelou, the past 6 months have felt more like Lewis Carroll's sentiments that "If you don't know where you are going, any road will get you there." The way forward is now coming into better focus, but data from randomized trials are eagerly awaited, and there is much work left to do.

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