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Maintaining Momentum in Clinical Trials for Respiratory Viruses*

KEY WORDS: clinical trials; complement; COVID-19; pandemic

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The COVID-19 pandemic has resulted in an unprecedented need to develop novel therapeutics. In addition to antivirals targeting severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), substantial resources have been dedicated to finding host-directed therapies targeting the dysregulated immune response characteristic of severe and critical COVID-19. As a result, there has been an extraordinary need to rapidly design, develop, and implement the infrastructure needed for randomized clinical trials to provide definitive evidence for or against the putative efficacy of agents in either category against COVID-19. To date, only a few immunomodulators have been found to be effective in this regard, including dexamethasone, baricitinib, and, to a lesser extent, tocilizumab (1–3).

Part of the dysregulated immune response described in COVID-19 is an overactivation of myeloid cells and the complement system (4). It is hypothesized that high levels of soluble C5a result in the recruitment of myeloid cells to the lungs, the site of major injury in COVID-19. In this issue of *Critical Care Medicine*, Carvelli et al (5) report the results of a double-blinded, placebo-controlled randomized clinical trial evaluating the efficacy and safety of an anti-C5aR1 monoclonal antibody (avdoralimab) in patients with hypoxemia requiring greater than or equal to 5 L/min of oxygen. The study was divided into three different cohorts based on degree of oxygen requirement. The primary outcome for cohort 1 and 3 was World Health Organization ordinal scale status at Day 14 and 28; in cohort 2, it was ventilator-free days through day 28. Unfortunately, in none of these cohorts did randomization to avdoralimab result in an improvement in the primary outcome. Furthermore, avdoralimab did not appear to improve any of the second efficacy endpoints or exploratory biomarkers analyzed (such as interleukin-6, C5a, and C-reactive protein) and may even have worsened disease progression and mortality. Although the authors speculate that the reason avdoralimab did not improve outcomes was potentially due to immunosuppression leading to increased viral persistence or increased rates of bacterial or fungal infections, there was

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no evidence either of increased viral persistence in the blood of these patients or increased rates of secondary infections. However, it seems more likely that the primary pathology driving dysregulated myeloid responses in COVID-19 may not lie within the C5a-C5aR1 axis.

Although the results in the study by Carvelli et al (5) were negative regarding its primary and all secondary efficacy endpoints, the conclusions are important and do not diminish the value of the study. As a result of the unique nature of the COVID-19 pandemic and urgent need to identify effective therapeutics, many different immunomodulators were proposed to have benefit, some of which became popular with mainstream channels and others that remained in scientific evaluation (6). Unfortunately, much of the proposed benefit of these therapies was based on anecdotal evidence, in vitro plausibility, and small retrospective studies. As a result of the lack of evidence for definitive efficacy, clinicians at the bedside have often been left wondering what therapies are appropriate to prescribe to severely ill patients and which have just hypothetical benefit. To that end, the study by Carvelli et al (5) provides a definitive answer that moving forward with avdoralimab for a COVID-19 indication through additional clinical trials is simply not warranted. In an era in which multiple therapies are being proposed as therapeutics, definitive negative evidence is just as important as positive findings. This is especially true if the safety of unproven new therapeutics cannot be assured, in which case the guiding principle for clinicians is to do no harm.

There is no doubt that the COVID-19 pandemic has had devastating effects on morbidity and mortality as well as normal societal functions. At this time, however, the development of effective vaccines, rapid diagnostics, and improved therapeutics have allowed for some normalization of daily life, making it appropriate to evaluate how clinical trials were implemented during the pandemic. Outside of observational studies, two major types of clinical trials have been performed: large multicenter randomized clinical trials such as the Adaptive COVID-19 Treatment Trial, Accelerating COVID-19 Therapeutic Interventions and Vaccines, and Randomized Evaluation of COVID-19 Therapy series of studies and smaller, often single-center, investigator-initiated studies (2, 3, 7, 8). The larger multicenter randomized clinical trials have the goal of taking promising therapies following an agent prioritization process and evaluating them for definitive evidence of efficacy. In contrast, the smaller single-center studies are often intended to evaluate therapies at an earlier stage based upon solid preclinical mechanistic hypotheses and assessing them for preliminary evidence of safety and efficacy.

Over the past 3 years, substantial resources have been used to build the organization and infrastructure necessary to perform large phase 3 multicenter randomized clinical trials, many of which continue to study therapies in COVID-19 (9). Moving forward, it is imperative that we maintain the networks, resources, and infrastructure required to rapidly mobilize and implement clinical trials as other new and emerging pathogens become evident. Just as SARS-CoV-2 rapidly spread around the global, we remain under constant threat of the next global pandemic arising from potential pathogens such as pandemic influenza, other zoonoses, or yet undiscovered pathogens. The clinical trial infrastructure should have ample dexterity to shift rapidly between pathogens being targeted and therapeutics being evaluated. One such platform is the Strategies and Treatments for Respiratory Infections and Viral Emergencies (STRIVE) protocol being established by the National Institute of Allergy and Infectious Diseases (NIAID). STRIVE is a master protocol with the intent to evaluate the safety and efficacy of therapeutics in patients admitted to the hospital for acute respiratory infection. This master adaptive protocol allows for individual study-specific patient populations, samples sizes, and primary outcomes and is intended to rapidly assess a multitude of proposed treatments in series or combination against the prevailing standard of care for a variety of respiratory pathogens. The key to success of master protocols like this will be to ensure appropriate sustainable funding and infrastructure along with a commitment from partnering clinical trial sites to be ready and willing to engage in clinical trials using the platform during both pandemic and nonpandemic times.

Although large platforms are intended to provide definitive evidence for or against efficacy, they generally provide limited information on disease pathogenesis overall and must prioritize a small number of agents. In this context, there remains a need to continue to have smaller, single-center, randomized clinical trials enrolling a smaller number of patients that can vet other therapeutics having strong rationale supporting their efficacy and that might later progress to larger platform trials if warranted. Understanding that steps need to be taken to ensure trials do not directly compete, these smaller clinical trials typically have an advantage in that they often allow for more detailed characterization of disease pathogenesis

and mechanism(s) of action by embedding more detailed collection of patient information directly integrated with real-time evaluation of patient samples using multiomic approaches. As was done in the study by Carvelli et al (5), evaluating biomarkers can also provide key information on potential efficacy and possibly reveal mechanisms by which therapeutics may improve outcomes.

Last, we must also evaluate the process in which therapeutics are selected for inclusion in clinical trials. Traditionally, therapeutics have navigated through rigorous sets of preclinical, small animal, and large animal models in the relevant disease they are targeting to establish preliminary evidence of effectiveness prior to entering human clinical trials. The urgent need for therapeutics targeting COVID-19 resulted in a model whereby FDA-approved agents known to be safe in humans were identified and implemented in clinical trials after evaluation by scientific selection committees, sometimes based more on hypothetical rather than proven mechanisms of action. The quickly evolving pandemic forced this change, but it is imperative that we seek to continuously re-evaluate this process. In the future and as time and resources (including well-established animal models) permit, therapeutic prioritization should highlight preclinical and mechanistic insights that may increase the likelihood of success. Additionally, we need to take the lessons learned from studying the most promising therapeutics against COVID-19 and apply that knowledge to future outbreaks involving other respiratory pathogens, especially if there is evidence of overlapping pathogenesis. This will require keeping a facile clinical trials infrastructure in place to rapidly bring relevant stake holders back together on an emergency basis to evaluate and prioritize therapeutic options in a future pandemic.

The COVID-19 pandemic has taught us meaningful lessons about preparedness as it relates to emerging infections, and the current outbreak of Monkeypox is a reminder that global dissemination of infectious diseases is a constant threat. Moving forward, it is essential that we take the significant progress made in clinical trial design and infrastructure and build on it, so we are ready to rapidly answer research and efficacy questions regarding novel therapeutics for future emerging infections. Without these frameworks in place, we will stumble at the starting line of the next pandemic, undoubtedly leading to patients again receiving inappropriate and untested therapies contributing to loss of life that could have been averted by early identification and testing of effective therapeutics.

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