Aviptadil for COVID-19: A Case Study and Call to Action About the Challenges of Research During a Global Pandemic*

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With evolution from COVID pandemic into COVID endemic, we ask how we have improved care and survival for those infected with this novel pathogen and how we can do better with the next threat. Although rates of hospitalization and death have remained relatively low during the recent Omicron waves, case fatality rates are still at least 40% higher than those seen with seasonal influenza (1), with disproportionate impacts on the elderly and immunocompromised, further underscoring the urgent need to continue to study and report on the efficacy of new treatments for COVID-19.

In this issue of *Critical Care Medicine*, Youssef et al (2) share the findings from one such study: a multicenter randomized, placebo-controlled, clinical trial of IV synthetic vasoactive intestinal peptide (Aviptadil) for adults with severe COVID-19 disease. Patients requiring supplemental oxygen delivered by nasal cannula at rates not less than 20 L/min, noninvasive ventilation, or mechanical ventilation were randomized in a 2:1 ratio to either 3 days of escalating doses of IV Aviptadil or placebo. The study's primary endpoint was survival with freedom from respiratory failure at day 60. Key secondary endpoints included mortality at 60 days, the Pao_2/Fio_2 ratio, and concentrations of the inflammatory cytokine interleukin (IL)–6. Analyses focused on a modified intention to treat population (i.e., those randomized minus those deemed ineligible or who withdrew consent before treatment) and were adjusted for mode of oxygen delivery at baseline (i.e., high-flow nasal cannula or mechanical ventilation).

Between May and December 2020, the study team enrolled 196 participants and had no loss to follow-up through 60 days. Viewed through a conservative statistical lens, this was a "negative" study as the odds of reaching the primary endpoint were not significantly different between those who were and were not randomized to Aviptadil after controlling for mode of oxygen delivery at baseline. However, several secondary endpoints and subgroup analyses did suggest a benefit for Aviptadil. In particular, when the primary composite endpoint was broken down into its components, there was a statistically significant mortality benefit, with a two-fold increase in survival after controlling for mode of oxygen delivery at baseline status. Furthermore, in a subgroup analysis of those mechanically ventilated at the time of enrollment, there was a 10-fold increase in the odds of survival (albeit with wide CIs). The discordance between the primary endpoint analysis and the 60-day survival analysis reflects persistent respiratory failure among some treated with Aviptadil, a finding that will warrant close attention in future studies and cohorts. Additional analyses found early improvements in the Pao_2/Fio_2 ratio and IL-6 concentrations among

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those who received Aviptadil. These "intermediate" endpoints provide important mechanistic and biologic plausibility to support the improved clinical outcomes in the cohort.

This trial also presents a useful case study for examining the challenges of conducting clinical trials during a fast-moving global pandemic. These challenges include 1) a rapidly evolving evidence base, 2) heterogeneity in study populations, 3) selection of appropriate study endpoints, and 4) a lag time from study completion to publication.

First, the challenge of time and timing. In a pre-COVID world, clinical trials were developed, carried out, and analyzed over years, with painstaking consideration given to every aspect of the trial from enrollment through to dissemination. In contrast, the rapidly evolving evidence base around care and treatment of COVID-19 has meant that many trials are outdated by the time they are published. For example, in this trial, two thirds of patients received remdesivir, half received corticosteroids, and only one-sixth received tocilizumab—treatments that are all now recommended as part of routine care for most critically ill patients. Thus, although this trial was conducted during the early days of the pandemic, its publication raises the question of how we now incorporate Aviptadil into practice. Are these findings generalizable to patients critically ill with COVID-19 "today"? Preparing for the next pandemic will require a fundamental shift in how the biomedical community approaches clinical trials. We must pivot from conducting "one-off" trials investigating a focused hypothesis to establishing and supporting broad-based research platforms, as have already been successfully leveraged by the Randomised, Embedded, Multi-factorial, Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP RECOVERY and Randomised Evaluation of COVID-19 Therapy (REMAP-CAP) groups (3, 4). By allowing for rapid assessment of new agents across multiple sites, in addition to streamlined study procedures, monitoring, and data collection, these platforms ensure both speed and feasibility during an ongoing pandemic. Adaptive designs and Bayesian analytic methods further enable early identification of promising data signals (5). The RECOVERY trial leveraged a partial factorial design to evaluate treatments both in isolation and in combination, whereas the REMAP-CAP study incorporated Bayesian approaches to facilitate adaptive randomization. These more flexible, adaptive designs and analyses help to ensure that our most valuable resources of time and patients willing to participate in clinical research are not squandered. Looking ahead, it will be critical for global funders to invest in such platforms to ensure their sustainability and readiness to respond to the next pandemic.

Second, there is the challenge of patient selection. As is the case with other critical illnesses (and some would argue all human diseases), the host immune response to COVID-19 can be quite heterogeneous. This heterogeneity makes it challenging to prospectively identify which patients are most likely to have a positive response to a particular agent. This uncertainty, in turn, directly impacts sample size and analytic considerations. These challenges were reflected in the study by Youssef et al (2) by the multiple adjustments made in consultation with the data monitoring committee and U.S. Food and Drug Administration (FDA) to the sample size and analytic plan, including the addition of a covariate accounting for care at a tertiary versus community hospital and an increase in the target enrollment to account for improved survival among patients treated with high-flow nasal cannula. Similar challenges likely underlie the differing fates of tocilizumab and sarilumab, two FDA-approved anti–IL-6R antibodies that were both studied as a treatment for COVID-19. In the case of tocilizumab, the seminal trial that factored heavily into its FDA Emergency Use Authorization (EUA) enrolled patients with both hypoxia and an elevated CRP (6). In contrast, although sarilumab did improve survival in a trial that enrolled critically ill patients (4), another study that enrolled hospitalized patients who required any amount of oxygen supplementation did not improve outcomes and the agent was not granted an EUA (7). Future trials need to anticipate patient heterogeneity and subphenotypes of disease by proactively planning for biologically plausible subgroup analyses (8). Meanwhile, point-of-care technologies are rapidly advancing and may soon enable biomarker-based adaptive randomization allowing for more precise enrollment of patients with particular subphenotypes.

A related challenge is that of establishing appropriate study endpoints and outcomes. Although the primary endpoint for the study by Youssef et al (2) was initially survival, it was later modified to be a composite primary outcome of being alive and free of

respiratory failure. With the benefit of hindsight, this change likely resulted in the negative outcome for the primary endpoint. Hopefully, as we look ahead to the next pandemic, there can be discussions between regulatory agencies (e.g., FDA and the European Medicines Agency), funders, and researchers that incorporate lessons learned from this pandemic to establish criteria for designating study endpoints when faced with future pandemics. The adoption of more flexible, nontraditional endpoints, such as hierarchical composite endpoints, has the potential to improve power and efficiency in future clinical trials (9).

Yet another tension highlighted by this trial is the inherent lag between study enrollment and the publication of study results. This tension was magnified exponentially during the fast-moving early months of the COVID-19 pandemic, when journals, including this one, worked tirelessly to screen and review thousands of publications in an attempt to separate the wheat from the chaff. This natural delay in publication and dissemination raises the challenge of trying to figure out how to incorporate new research findings into practice and new drugs into our arsenal. Although the proliferation and increasing acceptance of preprints has helped somewhat, there will always be a tenuous balance between rigorous peer review and rapid dissemination.

And so where do we go from here? How do we continue to support high-quality trials for COVID-19 and ensure that we, as a field of researchers and clinicians, are better prepared to act quickly and decisively when the next global pandemic strikes? Just as COVID-19 has catapulted vaccine technology into the future with the widespread adoption of messenger RNA–based vaccines and dramatically accelerated our understanding of host-pathogen interactions, the pandemic has accelerated the adoption and implementation of innovative approaches to clinical trials. Although none of the challenges described above are new, they were all intensified by the magnitude and time pressures of the COVID-19 pandemic. The trial by Youssef et al (2) is encouraging and suggests that Aviptadil warrants consideration as another agent for patients critically ill with COVID-19. At the same time, and taking a step back from the particulars of the agent, it also opens the door to a much-needed examination of the challenges of conducting research during a pandemic. The pendulum of evidence-based practice has decisively swung from anecdote to the double-blind, placebo-controlled, randomized clinical trial over the last half century. Although the merits of the randomized clinical trial cannot be disputed, it is also important to acknowledge the substantial time and resources to conduct such "gold standard" trials during a pandemic, when time and resources are in short supply. Now is the time to engage in thoughtful debate about how to engineer speed and flexibility into the collective research enterprise and ensure that we are better prepared for next time.

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