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Viewpoint

Oh, the Frustration of Antibodies!

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ABSTRACT: The COVID-19 pandemic has been humbling for the biomedical community, pointing out as much about what we do not know as what we do. Among these learnings are lessons about immune-based measures to prevent or treat a new biothreat. This article summarizes lessons learned from two experimental approaches for passive immunity, convalescent plasma and monoclonal antibody therapy. Two early reports of outcomes, both of which appeared within hours of one another, reveal the importance of blending past learning with a forward-looking approach. These also present cautionary lessons as the world looks to new vaccines to help eradicate this deadly scourge.

KEYWORDS: *COVID-19, monoclonal antibody, convalescent plasma, vaccine, SARS-CoV2*

The past few days have seen the publication (or more accurately, the pre-publication) of two reports filled with controversial and frankly confusing data about the potential for antibody therapy of COVID-19. First, a report emerged from India of a randomized controlled trial of convalescent plasma (CP).[1] This study conveyed mixed data, interpreted by critics as a confirmation of why the FDA was overly hasty in granting an emergency-use authorization for this therapy.[2] At the same time, the defenders of convalescent plasma pointed out evidence of its promise.[3] This head-scratcher was followed within hours by a press release announcing "proof-of-concept data" that a COVID-19 monoclonal antibody product being developed by Eli Lilly showed considerable promise but only at an intermediate dose.[4]

WHAT IS GOING ON HERE?

While more data will undoubtedly resolve the situation eventually, such findings are nothing surprising to those of us who have developed antibody therapeutics. As a brief background, antibodies are remarkable protein-based components of the immune system, which have evolved to help fight pathogens over the eons and which can function in many ways. Indeed, some of the perplexing data might ultimately shed some light upon a little-discussed mechanistic basis for tackling COVID-19. Let us look at each of the confusing reports with a bit more detail.

The study released by the Indian Council of Medical Research evaluated the use of CP in a group of 464 moderately ill patients with confirmed COVID-19.[1] These subjects were randomized into two groups, one of which received the best standard of care, while the other received CP collected from patients who had recovered from COVID-19. These results failed to identify an impact of COVID-19 CP upon overall survival or disease progression, yet the findings were not entirely negative as this same study revealed that patients receiving CP demonstrated improved overall symptoms, blood oxygenation, and, indeed, higher rates of viral clearance.

Michael Joyner, the lead author on an earlier Mayo Clinic study that ultimately led to the controversial decision by the FDA to approve CP for the treatment of COVID-19 seemed buoyed by the positive aspects of the Indian study, emphasizing the positive and describing it as a "cup-half full" approach.[3] He also pointed out that the study was limited by two features. First, Joyner indicated that "Most of the plasma had low titers of antibodies..." and these "...were given relatively late during the course of the disease—a median of 8 days after onset of symptoms." The Mayo study revealed that the benefits of CP were observed when treatment began earlier (within 7 days of diagnosis).[5]

One might conclude that there are no conclusions. That might be a bit pessimistic. One thing which can be agreed upon is that confounding factors for CP have been the variability in antibody levels and the need to standardize the amount of antibody.

With this in mind, we turn to the other study. This study involved an experimental monoclonal antibody, and surely, one might presume the dosing levels of a monoclonal antibody lack the variability of CP and thus would yield more conclusive outcomes about the promises of antibody therapy (or perhaps lack thereof).

The Eli Lilly results evaluated monoclonal antibody treatment for patients suffering from mild-to-moderate COVID-19 that had not yet been hospitalized.[4] Lilly reported that treatment with a neutralizing monoclonal antibody product (LY-CoV555) reduced viral load in treated patients, but only at a moderate dosing level of 2800 mg per patient. Neither the low (700 mg) nor the high (7000 mg) treatment

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levels had any effect on viral load. Nonetheless, these groups were pooled to compare antibody-treated patients with placebo controls, and Lilly reported that despite the lack of evidence that the antibody decreased viral burden they did note a 72% risk reduction as evidenced by lower hospitalization of the antibody-treated patients.

Despite the global impatience to put COVID-19 behind us and the fretful loss of life from the pandemic, these findings are frustrating but not particularly surprising. Both studies are comparatively small, each having just over 400 patients in total. Much larger studies will be needed to demonstrate whether or not there is a statistical benefit. For CP in particular, the variability in antibody levels can be particularly problematic, which may ultimately demonstrate the need to pool and standardize these materials in the future.

Focusing on the Eli Lilly findings, where the superiority of the moderate dosing levels to remain consistent, this could reflect a blessing for science and a curse for this particular product. Specifically, a Goldilocks-like dosing schema is nothing new for antibodies, as antibodies function to kill cells via the complement system (an ancient mechanism in which proteins in the blood are induced to kill antibody-targeted cells) or via cell-mediated killing (known by immunologists as antibody-dependent cellular cytotoxicity or ADCC). Too little antibody means not enough molecules are present to mediate killing (a good thing from the standpoint of protecting bystander cells). At the other extreme, too much antibody means that only one arm (of the two) can bind to a particular target.

A Goldilocks effect (first and more appropriately attributed to the Swedish immunologist, Örjan Ouchterlony) arises when both arms of the Y-shaped antibody are able to bind a target and kill it. Consequently, the rather paradoxical findings with LY-CoV555 might ultimately reveal an opportunity to seek out and eliminate cells harboring SARS-CoV2. Unfortunately, this same outcome would likely doom the study drug itself, as practical implementation of LY-CoC555 would be limited to a window of drug exposure, which would complicate its potential deployment.

For both projects, it is far too early to make conclusions either way. We are still in a steep (perhaps even vertical) learning curve with COVID-19 in general, and in particular, in our understanding of how to combat this disease using passive (antibody-based) or active (vaccine-based) immunotherapy. Yet, these results can show some of the frustrations (and opportunities) that are particularly frustrating for projects associated with antibody development. Such knowledge will be even more crucial as we move toward vaccine development. The key features for a vaccine include both efficacy and feasibility, but less spoken about is durability, the ability to maintain defenses against SARS-CoV2 months and years later. Nonetheless, these two studies of passive immunotherapy will be remembered as necessary stepping stones in the development of treatment and preventative measures to win the war against SARS-CoV2.

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