Realizing the Potential of Anti–SARS-CoV-2 Monoclonal Antibodies for COVID-19 Management

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The phases of SARS-CoV-2 infection may be viewed along a spectrum.[1] Following exposure, patients may have asymptomatic infection in which they test positive for the virus by reverse transcriptase–polymerase chain reaction (RT-PCR) but have no clinical evidence of disease. A subgroup of patients progress to developing symptomatic infection, usually within 12 days. Patients with symptomatic COVID-19 range from having mild or moderate disease, typically managed in the outpatient setting, to severe or critical COVID-19, which requires hospitalization. Those with mild or moderate COVID-19 often have high nasopharyngeal SARS-CoV-2 levels, and it is in this phase that antiviral therapy, such as anti–SARS-CoV-2 monoclonal antibodies, appears to be most beneficial. Monoclonal antibodies are currently used for postexposure prophylaxis and for treatment of symptomatic SARS-CoV-2 infection. In this issue of *JAMA*, an analysis of individuals with asymptomatic infection by O'Brien et al[2] provides insights into this phase of SARS-CoV-2 infection and the potential role of monoclonal antibodies in its management.

Anti–SARS-CoV-2 monoclonal antibodies target the viral spike protein. SARS-CoV-2 enters cells through an interaction between the spike protein and angiotensin-converting enzyme 2 on the host cell. Host antibodies against the spike protein prevent binding of the virus to host cells and represent one of the primary immune responses against SARS-CoV-2.[3,4] Patients who develop endogenous antibodies against SARS-CoV-2 soon after symptom onset have better clinical outcomes than those with delayed antibody responses,[5] suggesting that passive immunotherapy may be beneficial in treating COVID-19. This hypothesis has been confirmed in phase 3 clinical trials demonstrating that administration of anti–SARS-CoV-2 monoclonal antibodies to high-risk nonhospitalized patients with mild or moderate COVID-19 resulted in relative risk reductions ranging from approximately 70% to 85% (absolute risk reduction ranging from 2% to 6%) in the rate of hospitalization or death.[6-8] The US Food and Drug Administration has issued Emergency Use Authorizations for several monoclonal antibodies (bamlanivimab-etesevimab, casivirimab-imdevimab, and sotrovimab) for treatment of this patient population. In the phase 3 treatment trial of casivirimab and imdevimab among outpatients with COVID-19, intravenous infusion of the monoclonal antibodies, compared with placebo, led to an approximately 70% relative reduction in hospitalization and all-cause mortality, with absolute rates of 1.0% vs 3.2% in the 1200-mg treatment and placebo groups, respectively.[7]

In addition to their role in treating COVID-19, casirivimab-imdevimab and bamlanivimab-etesevimab are authorized for postexposure prophylaxis in individuals who are at high risk of progression because they are not fully vaccinated or are immunocompromised and not expected to mount an adequate immune response to vaccination. In a phase 3 placebo-controlled postexposure prophylaxis trial among household contacts of people with a recently positive SARS-CoV-2 test, casirivimab and imdevimab administered subcutaneously significantly reduced symptomatic COVID-19 among those who were SARS-CoV-2 RT-PCR negative and antibody negative at baseline.[9] Symptomatic infection with SARS-CoV-2 developed in 11 (1.5%) of 753 participants in the casirivimab and imdevimab group vs 59 (7.8%) of 752 participants in the placebo group (relative risk reduction of 81.4%).

Although monoclonal antibodies are authorized for postexposure prophylaxis and treatment of symptomatic patients, it has been unclear whether they confer benefit in those with asymptomatic SARS-CoV-2 infection. In the previously mentioned postexposure prophylaxis trial of casirivimab and imdevimab,[9] some household contacts were found to be SARS-CoV-2 RT-PCR positive but asymptomatic. O'Brien et al[2] now report the results of a randomized phase 3 trial of casirivimab and imdevimab in these individuals. The investigators enrolled 314 individuals aged at least 12 years between July 2020 and January 2021. The enrollment of the infected household contact must have been within 96 hours of the collection of the positive SARS-CoV-2 sample. Participants received subcutaneous casirivimab and imdevimab or placebo. The primary end point was the proportion of seronegative participants who developed symptomatic COVID-19. Overall, 66% of participants were seronegative and of these, 71% had at least 1 risk factor for severe COVID-19. Among those who were RT-PCR positive and seronegative at baseline, symptomatic COVID-19 developed in 42.3% (44/104) of those who received placebo and 29.0% (29/100) of those who received casirivimab and imdevimab (relative risk reduction, 31.5%; P = .04). When symptoms started 3 days or longer after treatment (giving the antibodies more time to work), risk reduction with casirivimab and imdevimab was 76% (5 of 100 individuals in the casirivimab and imdevimab group vs 22 of 104 in the placebo group). Even among those who developed symptoms, treatment decreased duration of symptoms by an average of 5.6 days (21.7 days vs 27.3 days). There was also more rapid decline in viral shedding in participants treated with casirivimab and imdevimab.

In addition to the clinical data, this study provides insights into the biology of SARS-CoV-2 infection. First, not all

individuals who were RT-PCR positive developed symptomatic COVID-19; in the placebo group, less than 50% developed symptoms. Second, baseline serostatus strongly predicted progression from asymptomatic infection to symptomatic disease; among placebo recipients, 42% (44/104) of those who were seronegative and 13% (5/38) of those who were seropositive developed symptoms. Third, individuals who were seronegative at baseline cleared the virus more slowly than those who were seropositive. These observations suggest that antibodies have an important role in preventing symptomatic infection and in clearing the virus in those who are infected.

The interpretation of this study should be tempered by several caveats. Although monoclonal antibodies are generally used in individuals at high risk of severe COVID-19, the population in this study was not particularly vulnerable: the mean age was 41 years; 30% had no risk factors for severe disease; and, of the remainder, the most common risk factor was being overweight (which confers less risk than other factors). Participants were also enrolled prior to the emergence of the Delta and Omicron variants; casirivimab and imdevimab retain activity against Delta but not against Omicron.[10] In addition, variant-specific differences in the incubation period and viral loads[11,12] might alter the efficacy of monoclonal antibodies. While prevention of symptomatic infection has benefits, the primary goal of monoclonal antibody therapy is to prevent progression to severe disease; however, this trial was unable to assess this outcome because there were only 3 hospitalizations (all in the placebo group). Also, this study was conducted prior to widespread COVID-19 vaccination; whether monoclonal antibodies have the same benefit in people who have breakthrough infection after vaccination is not known.

It is noteworthy that participants in this trial received casirivimab and imdevimab by subcutaneous injection. Although robust phase 3 clinical trial data have demonstrated that subcutaneous casirivimab and imdevimab treatment is efficacious for postexposure prophylaxis,[9] evidence in support of subcutaneous delivery for treatment of COVID-19 is limited. The FDA authorized subcutaneous administration of casirivimab and imdevimab as an alternative to intravenous delivery for treatment of individuals with symptomatic COVID-19 based on studies of viral load reduction and pharmacokinetics.[13] The study by O'Brien et al[2] provides evidence that subcutaneous administration of casirivimab and imdevimab has efficacy in infected individuals. However, high serum monoclonal antibody levels are achieved more quickly after intravenous administration than following subcutaneous injection; it is unknown whether intravenous administration might have led to even greater efficacy for individuals with asymptomatic SARS-CoV-2 infection.

What are the current roles for anti–SARS-CoV-2 monoclonal antibodies and how might they be used in the future?

At this time, anti–SARS-CoV-2 monoclonal antibodies are authorized for postexposure prophylaxis and for treatment of nonhospitalized high-risk patients with mild to moderate COVID-19. If, in the future, casirivimab and imdevimab therapy is authorized for use in people who are infected but do not have symptoms, this monoclonal antibody combination could potentially be used in high-risk situations, such as for immunosuppressed individuals who are RT-PCR positive but asymptomatic. In immunocompetent patients, monoclonal antibodies are likely to be reserved for symptomatic individuals as long as there continue to be supply and logistical constraints. However, casirivimab and imdevimab activity is compromised by the Omicron variant, and it is unknown whether the results of this study can be extrapolated to other monoclonal antibody therapies.

In terms of future roles for monoclonal antibodies, the long-acting combination of tixagevimab and cilgavimab is now authorized for preexposure prophylaxis,[14] which will be particularly important in people who are immunocompromised and not able to mount an immune response to COVID-19 vaccines. At the opposite end of the spectrum, anti–SARS-CoV-2 monoclonal antibodies improve outcomes in patients hospitalized with COVID-19 who are seronegative (ie, they do not have endogenous antibodies against the virus).[15] To realize this benefit, however, a rapid and reliable serologic test is needed to determine which hospitalized patients are seronegative, because those who are seropositive do not benefit from receiving exogenous monoclonal antibodies. In addition, the use of anti–SARS-CoV-2 monoclonal antibodies will need to be reassessed with the advent of efficacious and more convenient oral regimens for COVID-19—ritonavir-boosted nirmatrelvir and molnupiravir (the latter is considered an alternative to other, more efficacious treatment options).[16,17] Moreover, treatment-emergent resistance remains a threat,[18] and vigilance is needed to track new variants that may not be susceptible to monoclonal antibodies.

Extraordinary progress has occurred in expanding the role of anti–SARS-CoV-2 monoclonal antibodies for COVID-19, but several remaining questions must still be addressed. Does treatment of SARS-CoV-2 prevent onward transmission (as has been shown for HIV)? In addition to preventing acute complications, does treatment ameliorate postacute sequelae of SARS-CoV-2? How might the logistical challenges and supply constraints in delivering monoclonal antibodies be overcome? Do anti–SARS-CoV-2 monoclonal antibodies impair development of immune responses after COVID-19 vaccination? How can global equity be achieved in providing these and other effective medications? The answers to these and other questions are critical to realizing the full potential of anti–SARS-CoV-2 monoclonal antibodies for COVID-19 and to informing the optimal approach to future pandemics.

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