Editor's Note

Neutralizing Monoclonal Antibody for Mild to Moderate COVID-19

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In this issue of *JAMA*, Gottlieb et al[1] report the findings of the ongoing BLAZE-1 (Blocking Viral Attachment and Cell Entry with SARS-CoV-2 Neutralizing Antibodies) trial, a randomized, phase 2/3 clinical trial of antispike neutralizing monoclonal antibody treatment among 577 outpatients with mild or moderate coronavirus disease 2019 (COVID-19). This report represents the final analysis of the phase 2 portion of this trial and included 5 cohorts (3 groups with varying doses of bamlanivimab monotherapy, 1 group with a combination therapy of bamlanivimab and etesevimab, and a placebo group). The findings for the difference between each of the 3 monotherapy groups compared with the placebo group for the primary end point of change in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) log viral load at day 11 from baseline were not statistically significant, but were statistically significantly different for the primary end point for the combination therapy group compared with the placebo group.

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In a prior publication from this trial, Chen et al[2] reported findings from an interim analysis for the 3 monotherapy cohorts (no combination group) and the placebo group. The results from that study differ from the final analyses reported in the current study.[1] In the earlier publication, the 2800 mg dose of bamlanivimab, compared with placebo, achieved statistical significance for the primary outcome of the mean change in viral load from baseline at day 11, whereas the 700 mg and 7000 mg doses did not[2]; the effect sizes for all comparisons were different from the final analysis by Gottlieb et al.[1]

Why are the results different? In the earlier publication, follow-up for the placebo group was incomplete at the time of the database lock on September 5, 2020. In the final analysis reported in the current article,[1] the database was locked on October 6, 2020, and the longer follow-up for the placebo group, which is now complete, resulted in changes in the primary outcome among that group. The comparison of the monotherapy groups against the final results for the placebo group led to changes in the effect sizes, and the loss of previously reported statistical significance in the group that received 2800 mg of bamlanivimab.[2]

In addition to reporting different results than the prior interim analysis, the current study raises timely questions about the indications for use of monoclonal antibodies. The US Food and Drug Administration has issued Emergency Use Authorizations for both bamlanivimab and for the combination of casirivimab and imdevimab for outpatients with mild to moderate symptoms of COVID-19 and risk factors for progression to severe disease (such as advanced age, obesity, diabetes, chronic kidney disease, and immunosuppression).

Even though the BLAZE-1 study used an objective and measurable primary end point (change in SARS-CoV-2 log viral load from baseline to day 11), this end point does not translate easily into tangible clinical outcomes. Viral load decreases naturally during illness, and statistically significant differences in this outcome may occur only if treatment is given early during the course of illness. Rather, the prespecified secondary outcomes of COVID-19–related hospitalizations or emergency department visits likely are most meaningful to patients and families. As reported by Gottlieb et al,[1] the proportion of patients with COVID-19–related hospitalizations or emergency department visits was 5.8% (9 events) for placebo, 1.0% (1 event) for 700 mg of bamlanivimab, 1.9% (2 events) for 2800 mg of bamlanivimab, 2.0% (2 events) for 7000 mg of bamlanivimab, and 0.9% (1 event) for the combination therapy.

Cases of COVID-19 in the US continue to surge[3]; each day brings new records for hospitalizations and deaths with concerns that emerging genetic variants may further hasten spread[4] while vaccination efforts to date have been disappointing. During normal times, an interim analysis of an ongoing clinical trial usually would not be published, but these are not normal times. Even though monoclonal antibodies likely improve clinical outcomes in selected patients, the studies needed to answer remaining questions on the utility of treatment (which patients can benefit and in what circumstance) are unlikely to become available in a timely manner.

As has been the case throughout the pandemic, clinicians face an ever-changing treatment narrative and must make decisions based on the best information available. While the world waits for widespread administration of effective vaccines and additional data on treatments, local efforts should work to improve testing access and turnaround time and reduce logistical barriers to ensure that monoclonal therapies can be provided to patients who are most likely to benefit.[5]

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