Not All Monoclonal Antibodies for COVID-19 Are Created Equal

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As the COVID-19 pandemic continues, SARS-CoV-2 variants with potential for increased transmissibility and severity of illness [1, 2], such as the B.1.1.7 (alpha), B.1.617.2 (delta), and P.1 (gamma) variants, have sustained transmission in the community and disproportionately affect unvaccinated persons.[3] Other than providing supportive care, counseling on COVID-19 transmission risk reduction, and monitoring for disease progression[4], the only therapeutics for outpatient management of COVID-19 are neutralizing monoclonal antibodies directed to SARS-CoV-2 spike protein, made available through FDA emergency use authorization.[5-8] Four products have been made available for the treatment of mild-moderate COVID-19 in persons at high risk for severe disease. Emergency use authorization of bamlanivimab (approved 11/9/2020), revoked 4/16/2021)[5, 9], casirivimab-imdevimab (approved 11/21/2020)[6], bamlanivimab-etesevimab (approved 2/9/2021)[7], and sotrovimab (approved 5/26/2021)[8] was based on early clinical trials data demonstrating reductions in SARS-CoV-2 viral load[5-7, 10, 11]; hospitalizations and emergency department and/or medically attended visits[5-8, 10-12]; and deaths[7] in those who receive therapy versus placebo early in the course of clinical symptoms. To date, there have been no comparative trials of the different monoclonal antibody preparations, and, because of this, there have been no clear differences in indication or treatment outcomes among these agents. To the same end, the EUA eligibility criteria are the same for each product.

In this issue of the *Journal of Infectious Diseases*, Ganesh et al provide important post-clinical trial experience with the first neutralizing monoclonal antibody treatments for COVID-19, available through FDA EUA, and the first study comparing outcomes of persons who receive bamlanivimab versus casirivimab-imdevimab.[13] In this observational, retrospective study design, 3596 adult patients with laboratory-confirmed mild-moderate COVID-19 and ≤ 10 days of symptoms met EUA eligibility criteria for monoclonal antibody treatment and received an infusion either bamlanivimab or casirivimab-imdevimab, based on product availability at the infusion facility. All patients had a last one underlying condition that placed them at risk for progressing to severe COVID-19, and 55.3% had multiple comorbidities as measured by a Monoclonal Antibody Screening Score (MASS) that assigned weighted points based on number and relative risk of EUA high risk eligibility

criteria met by the patients.[14, 15] For the primary study outcome, there were lower rates of 28-day all-cause hospitalization in persons who received casirivimab-imdevimab compared to those who received bamlanivimab (2.83% v. 4.34, p=0.05); however, antibody treatment groups were not comparable in terms of underlying high risk medical conditions. Patients who received bamlanivimab were more likely to have hypertension (53.3% v. 48.3%, p=0.01) and a higher burden of comorbid medical conditions as indicated by distribution of the MASS between the antibody treatment groups (p=0.008). Ultimately, in the proportional hazards regression model, bamlanivimab-treated patients had a higher likelihood of hospitalization versus casirivimab-imdevimab-treated patients (unadjusted HR=1.5, 95% CI 1.0- 2.4, p=0.05), but when adjusted for the MASS, this did not reach statistical significance (adjusted HR 1.4, 95% CI 0.9-2.2, p=0.12). In the proportional hazards regression model, those in the bamlanivimab-treatment group also had a higher likelihood of COVID-19-related 28-day hospitalization compared to those treated with casirivimab-imdevimab (unadjusted HR 1.7, 95% CI 1.0-3.1, p=0.05), but this also did not reach statistical significance once adjusted for the MASS (adjusted HR 1.6, 95% CI 0.8-2.7, p=0.13). There were no significant differences between the treatment groups in secondary outcomes such as rates of ED visits, admissions to the ICU or deaths.

The Mayo Clinic experience adds to the growing body of reports demonstrating reduced hospitalization rates in persons who received a neutralizing monoclonal antibody infusion for COVID-19. Other real-world studies have demonstrated hospitalization risk reduction of 50% in persons treated with either bamlanivimab or casirivimab-imdevimab and 64% in persons treated with bamlanivimab compared to historical and contemporary controls, respectively.[16, 17] The Mayo cohort and other reported real-world outcomes compare favorably with clinical trials data, with relative hospitalization risk reduction of 67% and 70% with bamlanivimab in all v. high risk subjects[5], 50% and 67% with casirivimab-imdevimab in all v. high risk subjects[6], 87% with bamlanivimab-etesevimab[7], and 85% with sotrovimab.[8]

The current and other real-world study results are especially promising given that they were achieved in patient cohorts with higher co-morbidity burden compared to participants of the early bamlanivimab and casirivimab-imdevimab clinical trials. However, it remains uncertain if these

results are generalizable in patients who have significant underlying medical co-morbidities and, perhaps, this is an area in which differences in efficacy may emerge among the available neutralizing antibodies. In the current study, high co-morbidity burden, as measured by the MASS, was associated with 28-day all-cause hospitalization rate. Additionally, chronic kidney disease, immunocompromised status, cardiovascular disease, and chronic lung disease were associated with all-cause hospitalization, whereas higher body mass index was associated with lower risk for hospitalization. Similarly, Kumar and colleagues identified higher median comorbidity burden (measured by a cumulative priority system sum), presence of chronic kidney disease, age >55 years with hypertension, age >55 years with cardiovascular disease, and age >55 years with chronic lung disease as univariate predictors of 30-day hospitalization.[17] In two small series reporting outcomes of organ transplant recipients with COVID-19 treated with bamlanivimab monotherapy, higher rates of hospitalization (16.7% in both) were observed. [18, 19]

Clinical trials and real-world studies were conducted prior to the emergence of variants such as Beta (B.1.351), Delta (B.1.617.2), Gamma (P.1), and Zeta (P.2). Each of these variants carries one or more amino acid substitutions in the receptor binding domain (RBD) of the SARS-CoV-2 spike protein.[1] These circulating variants present the greatest threat to the efficacy of COVID-19 monoclonal antibody therapies, and it is in this context that differential activity of the available monoclonal antibodies is emerging. With B.1.35, P.1, and P.2, the E484K substitution results in loss of neutralizing activity of bamlanivimab and reduced activity of bamlanivimab-etesevimab.[20, 21] The Delta variant, B.1.617.2, possessed two RBD substitutions, E484Q and L452R, that render bamlanivimab and bamlanivimab-etesevimab inactive.[22] Because of concerns for loss of neutralizing activity potentially leading to treatment failures, the FDA revoked the EUA for bamlanvimab; additionally, bamlanivimab-etesevimab is no longer recommended for use in the U.S. because of variants with reduced susceptibility.[9, 23]

Casirivimab-imdevimab and sotrovimab have retained activity against all circulating variants of SARS-CoV-2 and remain recommended treatments for mild-moderate COVID-19.[20-23] Casirivimab and imdevimab bind to non-overlapping epitopes of the RBD[6], and this confers some

protection from a single mutation resulting in loss of activity. For example, B.1.351 and P.1 variants, casirivimab has reduced activity, but the activity of imdevimab is preserved.[20, 21] While sotrovimab is infused as a monotherapy, this antibody binds to a more conserved region of the spike protein RBD[8], and, thus, less vulnerable to substitutions that occur in the RBD.

The study reported by Ganesh et al adds to the growing body of evidence that outside of clinical trials these monoclonal therapies, when given early and to specific patient subgroups, offer an effective means of keeping patients out of the hospital and from progressing to severe COVID-19. The current study highlights differences in outcome with these therapies based on multiple comorbidities, which may allow clinicians to focus therapy on these higher risk groups. Limitations remain in these studies, which lack traditional control groups and have not accounted for the spread of monoclonal antibody resistant variants. Future studies should focus on newer monoclonal antibodies more resistant to viral change, comparisons of treated and untreated and untreated populations and the utility of these therapies in inpatient populations and as a prophylactic measure. The Mayo Clinic experience adds to the growing evidence that monoclonal antibody therapy is effective for outpatient management of SARS-CoV2 infection and clinicians should be reassured that these therapies work and that they should offer them to their eligible patients.

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