Curbing the Delta Surge: Clinical Outcomes After Treatment With Bamlanivimab-Etesevimab, Casirivimab-Imdevimab, or Sotrovimab for Mild to Moderate Coronavirus Disease 2019

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Abstract

Objective: To describe and compare the clinical outcomes of bamlanivimab-etesevimab, casirivimab-imdevimab, and sotrovimab treatment of mild to moderate coronavirus disease 2019 (COVID-19) during the severe acute respiratory coronavirus 2 (SARS-CoV-2) B.1.617.2 Delta surge.
Methods: This is a retrospective study of high-risk patients who received bamlanivimab-etesevimab, casirivimab-imdevimab, and sotrovimab for mild to moderate COVID-19 between August 1, 2021, and December 1, 2021. Rates of severe disease, hospitalization, intensive care unit admission, and death were assessed.
Results: Among 10,775 high-risk patients who received bamlanivimab-etesevimab, casirivimab-imdevimab, or sotrovimab for mild to moderate COVID-19 during the Delta surge, 287 patients (2.7%) developed severe disease that led to hospitalization, oxygen supplementation, or death within 30 days after treatment. The rates of severe disease were low among patients treated with bamlanivimab-etesevimab (1.2%), casirivimab-imdevimab (2.9%), and sotrovimab (1.6%; *P*<.01). The higher rate of severe outcomes among patients treated with casirivimab-imdevimab may be related to a significantly lower COVID-19 vaccination rate in that cohort. Intensive care unit admission was comparable among patients treated bamlanivimab-etesevimab, casirivimab-imdevimab, or sotrovimab (1.0%, 1.0%, and 0.4%, respectively).
Conclusion: This real-world study of a large cohort of high-risk patients shows low rates of severe disease, hospitalization, intensive care unit admission, and mortality after treatment with bamlanivimab-etesevimab, casirivimab-imdevimab, and sotrovimab for mild to moderate COVID-19 during the SARS-CoV-2 Delta surge.

S ince November 2020, neutralizing monoclonal antibodies directed against the spike protein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have been authorized to treat high-risk patients with mild to moderate coronavirus disease 2019 (COVID-19).[1-3] The use of these experimental therapies is supported by separate emergency use authorizations (EUAs) from the US Food and

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Drug Administration (FDA).[4,5] Randomized clinical trials have shown that bamlanivimab-etesevimab (Eli Lilly), casirivimab-imdevimab (Regeneron), and sotrovimab (Glaxo Smith Kline) treatment of patients with mild to moderate COVID-19 were associated with improved clinical and virologic outcomes.[1-3]

In real-world clinical settings, retrospective studies have consistently shown that the use of anti-spike neutralizing monoclonal antibodies for the treatment of high-risk patients with mild to moderate COVID-19 resulted in significantly lower rates of hospitalization when compared with propensity-matched untreated controls.[6-8] However, these studies were conducted during the period before the SARS-CoV-2 B.1.617.2 (Delta) surge. Studies have reported that the SARS-CoV-2 B.1.617.2 (Delta) variant is much more transmissible and causes more severe illness when compared with the previous variants.[9-14] Bamlanivimab-etesevimab, casirivimab-imdevimab, and sotrovimab were determined in experimental studies to maintain efficacy against SARS-CoV-2 B.1.617.2 (Delta).[15] However, studies are needed to directly compare the effectiveness of bamlanivimab-etesevimab, casirivimab-imdevimab, and sotrovimab treatment in the real-world clinical setting.

In this study, we sought to characterize the relative efficacy by comparing the rates of severe outcomes after bamlanivimab-etesevimab, casirivimab-imdevimab, or sotrovimab treatment. This retrospective study was conducted among high-risk patients with mild to moderate COVID-19 from August 1, 2021, to December 1, 2021, a period in the pandemic dominated by SARS-CoV-2 B.1.617.2 (Delta) variant of concern.[16]

METHODS

Setting

Mayo Clinic is an integrated health care delivery network serving more than 1 million patients each year across southern Minnesota, northeastern Iowa, western Wisconsin, and the metropolitan areas of Jacksonville, Florida, and Phoenix, Arizona. On November 7, 2020, Mayo Clinic established its Monoclonal Antibody Treatment (MATRx) program to administer anti-spike monoclonal antibodies to high-risk patients with mild to moderate COVID-19. The MATRx program, protocols, and procedures have been described previously.[17]

For this study, only patients treated in Minnesota and Wisconsin were included. By limiting the geography, we could directly compare the efficacy of the three monoclonal antibody products given similar circulating variants in these communities.[16] At the time of this study, the predominant circulating variant was SARS-CoV-2 B.1.617.2 (Delta).[16]

Study Population and Design

This was a retrospective study among adult patients, 18 years of age or older, who were identified from the Mayo Clinic electronic health records as having received treatment with anti-spike neutralizing monoclonal antibodies from August 1, 2021, to December 1, 2021. All high-risk adult patients with mild to moderate COVID-19 treated with anti-spike neutralizing monoclonal antibodies during the study period were included. Although high-risk adolescents aged 12 to younger than 18 years received anti-spike monoclonal antibody therapies, they were not included in this study because they used different eligibility criteria. All patients in Minnesota and Wisconsin were screened by a single multidisciplinary MATRx team and followed the same algorithm throughout the study period. For this study, the population was divided into three cohorts (bamlanivimab-etesevimab, casirivimab-imdevimab, or sotrovimab cohort) based on the specific neutralizing monoclonal antibody received.

Anti–Spike Monoclonal Antibodies

Anti-spike neutralizing monoclonal antibodies were distributed to Minnesota and Wisconsin infusion facilities by the federal government. According to the Department of Health and Human Services, the

SARS-CoV-2 B.1.617.2 (Delta) was susceptible to bamlanivimab-etesevimab, casirivimab-imdevimab, or sotrovimab, allowing the use of any of these products interchangeably without concerns for viral resistance. The specific neutralizing monoclonal antibody administered to an eligible patient was based solely on the available product at the infusion facility during the date of treatment. There were no clinical criteria to favor one product over another. All patients received education about the specific neutralizing monoclonal antibody product, the potential benefits and adverse effects, and the EUA and investigational status. All patients provided consent for treatment with the anti-spike neutralizing monoclonal antibody products. The products available during this study were bamlanivimab-etesevimab (700-mg / 1400-mg dose), casirivimab-imdevimab (600-mg / 600-mg dose), and sotrovimab (500-mg dose), all administered as a one-time infusion.

Clinical Eligibility Criteria and Risk Factor Scores

Adult patients were eligible to receive anti-spike neutralizing monoclonal antibodies if they had mild to moderate COVID-19, confirmed by a positive SARS-CoV-2 polymerase chain reaction or antigen test, and were within 10 days of symptom onset. In compliance with the FDA EUA criteria, patients had at least one of the following criteria: age 65 years or older, body mass index (BMI) greater than 25 kg/m^2, immunocompromised status, pregnancy, hypertension, diabetes mellitus, chronic kidney disease, chronic lung disease, cardiovascular disease, sickle cell disease, neurodevelopmental disorders, or medico-technological dependence.[18]

In November 2020, our program developed a Monoclonal Antibody Screening Score (MASS).[19-21] The MASS score assigned points to each of the initial eligibility criteria set forth by the FDA in November 2020, as follows: age 65 years or older (2 points), BMI greater than or equal to 35 kg/m^2 (1 point), diabetes mellitus (2 points), chronic kidney disease (3 points), cardiovascular disease in a patient 55 years of age or older (2 points), chronic respiratory disease in a patient 55 years of age or older (2 points), hypertension in a patient 55 years of age or older (1 point), and immunocompromised status (3 points). For this study, we used MASS as the measure of high-risk characteristics.

Outcome

The primary outcome of this study was the proportion of patients who developed severe outcomes within 30 days after anti-spike neutralizing monoclonal antibody infusion. Severe outcome was defined according to the WHO ordinal scale of 4 (hospitalized and oxygen supplementation by mask or nasal prongs) or greater (which included those who required invasive mechanical ventilation, extracorporeal membrane oxygenation, and those who died); this primary outcome is in contrast to all-cause hospitalization in randomized clinical trials.[2,22,23] In addition, we assessed the proportion of patients who required an intensive care unit (ICU) level of care and overall mortality at day 30 as secondary outcomes.

Ethical Considerations

This study was conducted in accordance with the aim of the Strengthening Research of Observational Epidemiologic Studies. The Mayo Clinic Institutional Review Board reviewed this study and designated it with an exempt status. Only patients with research authorization were included.

Statistical Analysis

The baseline demographics, clinical characteristics, and outcomes of patients who received infusions with bamlanivimab-etesevimab, casirivimab-imdevimab, or sotrovimab were described using standard descriptive statistics including mean, median, and IQR. As appropriate, outcomes were compared across groups using a Kruskal-Wallis rank sum test, Fischer exact test or Pearson's χ^2 test, as appropriate and adjusted for multiple comparisons. Statistical significance is set at $P<.05$.

TABLE 1. Demographic and Clinical Characteristics of 10,775 High-Risk Patients Treated With Anti–SARS-CoV-2 Monoclonal Antibodies During the Delta Surge, Minnesota and Wisconsin, August 1, 2021, to December 1, 2021[a,b]

Characteristics	Bamlanivimab-etesevimab (n=494)	Casirivimab-imdevimab (n=9206)	Sotrovimab (n=1072)	All patients (n=10,775)
Age, median (IQR), y	57.8 (42.1-67.8)	56.8 (41.8-68.3)	53.7 (40.6-66.0)	56.6 (41.7-68.1)
Male	227 (46.0)	4228 (45.9)	464 (43.3)	4919 (45.7)
White	466 (94.3)	8615 (93.5)	1014 (94.6)	10095 (93.7)
Non-Hispanic	458 (92.7)	8641 (93.8)	1018 (95.0)	10117 (93.9)
Charlson comorbidity index, median (IQR)	0 (0-1.0)	0 (0-1.0)	0 (0-1.0)	0 (0-1.0)
Monoclonal antibody screening score, median (IQR)	2.0 (1.0-4.0)	2.0 (0-4.0)	2.0 (0-4.0)	2.0 (0-4.0)
Body mass index, median (IQR), kg/m^2	28.8 (26.6-32.6)	28.5 (25.5-32.0)	28.8 (25.8-32.6)	28.6 (25.5-32.1)
Cardiovascular disease	74 (15.0)	1563 (17.0)	144 (13.4)	1781 (16.5)
Chronic kidney disease	8 (1.6)	170 (1.8)	26 (2.4)	204 (1.9)
Chronic lung disease	40 (8.1)	946 (10.3)	78 (7.3)	1064 (9.9)
Diabetes mellitus	73 (14.8)	1361 (14.8)	175 (16.3)	1609 (14.9)
Hypertension	157 (31.8)	2854 (31.0)	265 (24.7)	3276 (30.4)
Immunocompromised status	35 (7.1)	937 (10.2)	111 (10.4)	1083 (10.1)

[a]SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
[b]Values shown are n (%) or median (IQR).

RESULTS

Patient Population

A total of 10,775 high-risk patients with mild to moderate COVID-19 received treatment with bamlanivimab-etesevimab (n=494), casirivimab-imdevimab (n=9209), or sotrovimab (n=1072) during the study period. The differences in the total number of treated patients per cohort reflect the drug supply in our infusion facilities, as allocated by the government. The population's median age was 56.6 years (range, 18-102 years; IQR, 41.7-68.1 years). Female patients accounted for 54.3% of the cohort. The population was predominantly White (93.7%) and non-Hispanic (93.9%). The median BMI was 28.6 (IQR, 25.5-32.1) kg/m^2. The most common medical comorbidities were hypertension (30.4%), cardiovascular disease (16.5%), diabetes mellitus (14.9%), immunocompromised status (10.1%), and chronic lung disease (9.9%). The majority (n=6376; 59.2%) have received primary COVID-19 vaccination series, defined as two doses of an mRNA vaccine or a single dose of an adenovirus-vector vaccine. Table 1 describes the demographic and clinical characteristics of the three treatment cohorts.

Severe Outcomes and Mortality

During the 30 days after anti-spike neutralizing monoclonal antibody infusion, 287 patients (2.7%) progressed clinically to develop severe COVID-19 and required hospitalization in our system; the majority (n=186 [64.8%]) were not fully vaccinated. One hundred four patients (1.0%) required ICU-level care; the majority (n=74 [69.1%]) were not fully vaccinated. Thirteen patients (0.1%) had requirement of invasive mechanical ventilation as their worst outcome; the majority (n=11 [84.6%]) were not fully vaccinated.

Twenty-five patients (0.2%) died (WHO ordinal scale 8) by day 30 after anti-spike neutralizing monoclonal antibody infusion. All deaths occurred in patients who have not been fully vaccinated (Supplementary

TABLE 2. Clinical Outcomes by Day 30 After SARS-CoV-2 Monoclonal Antibody Infusion in 10,775 High-Risk Patients With Mild to Moderate COVID-19 During the Delta Surge, August 1, 2021, to December 1, 2021, Mayo Clinic in the Midwest[a,b]

Outcome	Bamlanivimab-etesevimab n=494	Casirivimab-imdevimab n=9209	Sotrovimab n=1072	P[c]
Severe COVID-19	6 (1.2)	264 (2.9)	17 (1.6)	<.01
Required ICU-level intervention	5 (1.0)	95 (1.0)	4 (0.4)	.09
All-cause mortality	0 (0.0)	24 (0.3)	1.0 (0.1)	.53
Vaccination status[d]	320 (64.8)	5391 (58.5)	665 (62.0)	<.01

[a]COVID-19, coronavirus disease 2019; ICU, intensive care unit; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
[b]Values are n (%).
[c]P value calculated by Fischer exact test or Pearson's χ^2 test for vaccination status, as appropriate, and adjusted for multiple comparisons.
[d]Fully vaccinated status indicates completion of primary series consisting of receipt of two doses of mRNA vaccine or a single dose of an adenovirus vector vaccine.

Tables 1 and 2, available online at http://www.mayoclinicproceedings.org). Eight of 25 deaths were due to progressive respiratory failure from COVID-19 pneumonia. The remaining 17 deaths were due to bacterial sepsis (n=4), progression of metastatic cancer (n=3), myocardial infarction (n=2), pulmonary embolism (n=2), stroke (n=1), severe complicated pancreatitis (n=1), or not reported (n=4).

Neutralizing Monoclonal Antibody–Specific Outcomes

The rates of progression to severe disease was 1.2% among patients treated with bamlanivimab-etesevimab (95% CI, 0.7%-1.7%), 2.9% among patients treated with casirivimab-imdevimab (95% CI, 2.7%-3.0%), and 1.6% among patients treated with sotrovimab (95% CI, 1.2%-2.0%). However, it was significantly higher among those who received casirivimab-imdevimab (P<.01) (Table 2). There were no significant differences in ICU admission, invasive mechanical ventilation, and death among the three neutralizing monoclonal antibody cohorts.

The time to anti-spike neutralizing monoclonal antibody infusion was similar among all treatment cohorts (median of 2 days; IQR, 1-3 days from a positive diagnostic test among all three antibody products; P=.40). Likewise, the comorbidity risk scores, as measured by MASS (median score of 2.0; IQR, 0-4.0 among all three antibody products; P=.53), and Charlson comorbidity index (median index of 0; IQR, 0-1.0) were not significantly different among the three treatment cohorts. However, the proportions of patients who completed primary COVID-19 vaccination series (defined as having received two doses of an mRNA vaccine or a single dose of adenovirus vector vaccine) were significantly different among bamlanivimab-etesevimab, casirivimab-etesevimab, and sotrovimab (64.8% vs 58.5% vs 62.0%, respectively; P<.01 by Pearson's χ^2 test) (Table 2). In a subgroup analysis that was limited to fully vaccinated individuals (n=6376) (Supplemental Tables 1 and 2), there was no significant difference in the rates of severe disease among patients who were treated with bamlanivimab-etesevimab, casirivimab-imdevimab, or sotrovimab (1.2% vs 1.7% vs 0.6%, respectively; P=.07 by Fisher exact test).

DISCUSSION

The enhanced transmissibility of SARS-CoV-2 B.1.617.2 Delta variant resulted in a surge of COVID-19 cases during the latter half of 2021, with corresponding increase in severe disease that required hospitalization.[9] While SARS-CoV-2 B.1.617.2 Delta disproportionately affected unvaccinated persons, it also affected those who have received their primary COVID-19 vaccination series.[19] High

risk individuals with multiple medical comorbidities have been described to remain at an increased risk of severe breakthrough COVID-19, even after receiving vaccination with two doses of mRNA vaccine or a single dose of an adenovirus vector vaccine.[19]

With its increased pathogenicity, SARS-CoV-2 B.1.617.2 Delta resulted in overburdened hospitals caring for patients with severe and, at times, critical illness.[19] Hence, there was a major effort among health care facilities to reduce hospitalization rates by providing early treatment of high-risk patients with bamlanivimab-etesevimab, casirivimab-imdevimab, and sotrovimab in the outpatient setting.[6-8,19,20] Our program treated more than 10,000 patients with neutralizing monoclonal antibodies during the 4-month study period (at the height of the Delta surge, and before the emergence of SARS-CoV-2 B.1.1.529 Omicron variant). In an earlier study of 630 patients during the start of the Delta surge in July 2021, we observed a significant reduction in hospitalization (odds ratio, 0.138) among patients treated with casirivimab-imdevimab compared with untreated patients.[19] Extrapolating from this initial study, we can assume that by preventing high-risk patients from progressing to severe and critical disease, the early treatment with anti-spike neutralizing monoclonal antibodies in our cohort may have mitigated the anticipated increase in hospitalizations during the Delta surge in our communities.

Earlier comparative studies suggested potential differences in clinical outcomes between different anti-spike monoclonal antibody products.[7,14] In a study of 3596 high-risk patients treated from November 2020 to February 2021, we observed a slightly better (although not statistically significant) outcome among patients treated with casirivimab-imdevimab when compared with bamlanivimab monotherapy.[7] During the period dominated by the wild-type and SARS-CoV-2 B.1.1.7 (Alpha) variant of concern, we observed that bamlanivimab-etesevimab treatment was significantly better in preventing severe disease than casirivimab-imdevimab.[14]

Investigators from other centers are similarly assessing the real-world comparative efficacy of different neutralizing monoclonal antibody products in their patient cohorts.[24] In our present study, we observed that although treatment with any of the three neutralizing monoclonal antibody products resulted in low rates of severe disease, the cohort of patients treated with casirivimab-imdevimab had a numerically higher rate of severe disease progression when compared with those treated with bamlanivimab-etesevimab or sotrovimab. This observation could not be accounted for by differences in time to infusion or baseline medical comorbidities because these variables were not significantly different among the three treatment cohorts.

The higher rate of severe disease among patients treated with casirivimab-imdevimab could potentially be due to the lower rate of COVID-19 vaccination rates in this cohort. Indeed, most patients with worst outcomes in this study (eg, those who required ICU-level care, invasive mechanical ventilation, or extracorporeal membrane oxygenation) were unvaccinated against COVID-19. Likewise, all deaths in our treated cohort occurred among high-risk unvaccinated persons. Moreover, in a subgroup analysis that included only vaccinated patients, there was no longer a significant difference in the rate of severe outcomes among the three treatment cohorts. Accordingly, this observation implies the protection afforded by active immunization and the potential for cumulative effectiveness of anti-spike neutralizing monoclonal antibodies among high-risk vaccinated persons with breakthrough infections. Although this study did not account for the impact of vaccination rates at the population-level in our communities, our patient-level observations emphasize the need to promote COVID-19 vaccination to reduce the risk of severe outcomes.

Study Limitations

This study has numerous limitations including those inherent to its retrospective and observational design. Some variables

such as vaccination status and clinical outcomes may not have been captured in our study if patients sought medical care in other centers. This limitation on outcomes assessment is mitigated by the close follow up of high-risk patients enrolled in a remote monitoring program that followed patients through the typical period for disease progression.[25] Viral genetic sequencing was not performed to determine the specific variant in this study, so we can only assume that our cases were predominantly due to SARS-CoV-2 B.1.617.2 Delta based on data tracking reported by the US Centers for Disease Control and Prevention.[16] Likewise, we are not able to determine if severe cases that did not respond to the neutralizing monoclonal antibody treatment were caused by the more resistant AY.1 and AY.2 lineages.[26] The imbalance in the total number of patients per cohort and the lack of treatment randomization are limitations beyond our control because this program was dependent solely on federal drug allocation. The population was largely non-Hispanic white persons who sought care at a large academic medical center, and the results of this study may not be generalizable to communities of underrepresented populations.[21] The MATRx clinical program proactively screened eligible patients which resulted in a rapid time to neutralizing monoclonal antibody treatment, and the outcomes of this study may not reflect the programs with different protocols and infrastructure. This study also has no control group of untreated patients, but this design was intentional because the aim was not to assess efficacy (compared with no treatment) but mainly to compare clinical outcomes of the three neutralizing monoclonal antibody products. The clinical efficacy of the three monoclonal antibody products has been independently proven in rigorous randomized placebo-controlled clinical trials.[1-3] Subsequent retrospective studies have likewise shown their effectiveness compared with untreated patients in real-world settings.[6-8,19,20] These aforementioned limitations are counterbalanced by the large cohort of patients treated during a pandemic period dominated by a single variant of concern (based on state health department and US Centers for Disease Control and Prevention tracking) and the standard protocol for treatment that was coordinated by a single treatment team. The standard approach to proactive screening and treatment led to comparable baseline demographic and clinical characteristics among the three groups, including a similarly rapid time to neutralizing monoclonal antibody infusion after COVID-19 diagnosis.

CONCLUSION

This study of 10,775 high-risk patients with mild to moderate COVID-19 during the SARS-CoV-2 B.1.617.2 Delta surge showed that early treatment with bamlanivimab-etesevimab, casirivimab-imdevimab, or sotrovimab resulted in lower than anticipated rates when compared with historical data on progression to severe disease, ICU admission, and death among untreated patients. Our real-world clinical outcomes complement and confirm the experimental pseudovirus and live virus data that suggested the effectivity of the three neutralizing monoclonal antibody products against the SARS-CoV-2 B.1.617.2 Delta variant. Although the differences in the rates of severe outcomes among the three anti-spike monoclonal antibody products were small, high-risk patients treated with casirivimab-imdevimab had a numerically higher rate of severe outcomes, and this could be associated with the lower overall rate of vaccination in this cohort. This observation emphasizes the need to promote active immunization to mitigate the clinical impact of COVID-19, especially among high-risk persons. Comparative studies that assess the relative clinical efficacy of various anti-spike neutralizing monoclonal antibodies are suggested as they are useful for monitoring real-world outcomes, confirming experimental data, and guiding treatment decisions.

POTENTIAL COMPETING INTERESTS

The authors report no potential competing interests.

SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mayoclinicproceedings.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

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