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BRIEF REPORT

Comparable Outcomes for Bebtelovimab and Ritonavir-Boosted Nirmatrelvir Treatment in High-Risk Patients With Coronavirus Disease-2019 During Severe Acute Respiratory Syndrome Coronavirus 2 BA.2 Omicron Epoch

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The effectiveness of bebtelovimab in real-world settings has not been assessed. In this retrospective cohort study of 3607 high-risk patients, bebtelovimab was used more commonly than nirmatrelvir-ritonavir for treatment of coronavirus disease 2019 (COVID-19) among older patients, immunosuppressed patients, and those with multiple comorbid conditions. Despite its use in patients with multiple comorbid conditions, the rate of progression to severe disease after bebtelovimab (1.4% [95% confidence interval, 1.2%–1.7%]) was not significantly different from that for nirmatrelvir-ritonavir treatment (1.2% [.8%–1.5%]). Our findings support the emergency use authorization of bebtelovimab for treatment of COVID-19 during the Omicron epoch dominated by BA.2 and subvariants.

Keywords. SARS-CoV-2; bebtelovimab; COVID-19; hospitalization; monoclonal antibodies; nirmatrelvir; Paxlovid; ritonavir.

Early treatment of coronavirus disease-2019 (COVID-19) with neutralizing anti-spike monoclonal antibodies is recommended for high-risk persons to reduce the risk of hospitalization and death [1]. Randomized clinical trials and retrospective studies have consistently confirmed their effectiveness in preventing hospitalization and death [2–4]. However, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has evolved into variants of concern characterized by spike mutations that allow the virus to escape neutralization by bamlanivimab-etesevimab, casirivimab-imdevimab, and sotrovimab [5]. In February 2022, the US Food and Drug Administration (FDA) granted an emergency use authorization (EUA) for bebtelovimab based on in vitro pseudovirus experiments that demonstrated activity against Omicron BA.2 and subvariants but with only a limited set of clinical data [6]. In the absence of robust clinical data, bebtelovimab was designated as an alternative therapy for patients unable to receive intravenous remdesivir or oral nirmatrelvir-ritonavir [1].

The effectiveness of bebtelovimab in real-world settings has not been assessed. In this retrospective study, we assessed the characteristics and outcomes in high-risk outpatients who received bebtelovimab for COVID-19 during a period dominated by SARS-CoV-2 Omicron BA.2 and subvariants. We compare their outcomes with those in patients treated with ritonavir-boosted nirmatrelvir, an antiviral drug that significantly reduces hospitalization and death among high-risk persons [7].

METHODS

Setting

Mayo Clinic is an integrated healthcare delivery network serving >1 million patients annually across Minnesota, Iowa, Wisconsin, Florida, and Arizona. On 7 November 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 elsewhere [8]. In collaboration with site-specific COVID-19 Clinical Care Teams, MATRx screened patients with a positive SARS-CoV-2 polymerase chain reaction or antigen test result to assess their eligibility for outpatient therapeutics. Eligible patients were proactively contacted and consented to receive treatment with nirmatrelvir-ritonavir, remdesivir, or bebtelovimab

Study Population and Design

This was a retrospective study of adult patients, aged ≥18 years, who were identified from the electronic health records as having received treatment with bebtelovimab or nirmatrelvir-ritonavir since Omicron BA.2 emerged as the predominant variant on 20 March 2022. Intravenous remdesivir was available as an option, but the logistics of once-daily infusion for 3 days made it less desirable for patients and providers. For this study, only patients who had a follow-up period of ≥30 days by 14 June 2022 were included.

Treatment Options

Bebtelovimab was given as single intravenous infusion of 175 mg over 1 minute within 7 days of symptom onset. Oral

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nirmatrelvir (one or two 150-mg pills, depending on renal function) coformulated with ritonavir (one 100-mg pill) was given twice daily for a total of 5 days. All treatments were administered under the EUA guidance. All patients received information and education about all treatment options, the potential benefits and adverse effects, and the EUA status of both products. Treatment decision was based on patient factors (eg, renal or liver function), drug factors (eg, drug-drug interactions), and patient preference after a shared decision making process.

Clinical Eligibility Criteria and Risk Scores

Adult patients were eligible to receive treatment if they had mild to moderate COVID-19 confirmed by SARS-CoV-2 polymerase chain reaction or antigen test and were within 5 days (for nirmatrelvir-ritonavir) or 7 days (for bebtelovimab) of symptom onset. In compliance with the US FDA EUA criteria, patients had ≥1 of the following criteria: age ≥65 years, body mass index >25 (calculated as weight in kilograms divided by height in meters squared), immunocompromised status, pregnancy, hypertension, diabetes mellitus, chronic kidney disease, chronic lung disease, cardiovascular disease, sickle cell disease, neurodevelopmental disorders, or medicotechnological dependence [9]. In November 2020, our MATRx program developed a Monoclonal Antibody Screening Score (MASS), as described elsewhere [9]. MASS was used as a clinical prioritization tool during periods of scarcity when there was an imbalance in the demand and supply [9]. For this study, we used MASS as a composite measure of high-risk characteristics, in addition to Charlson Comorbidity Index.

Outcome

The primary outcome was the proportion of patients who progressed to severe outcome within 30 days. A severe outcome was defined according to the World Health Organization Ordinal Scale of 4 (hospitalized and oxygen supplementation by mask or nasal prongs) or greater (which included those who required invasive mechanical ventilation or extracorporeal membrane oxygenation and those who died). Mild COVID-19 incidentally diagnosed at hospital admission for a non–COVID-19 indication was not considered a severe outcome unless it progressed to severe disease. The proportions of patients who required an intensive care unit level of care and the all-cause mortality rate were assessed 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 (STROBE). The Mayo Clinic Institutional Review Board reviewed this study and granted exempt status. Only patients with research authorization were included.

Statistical Analysis

Baseline patient demographics, clinical characteristics, and outcomes were assessed using standard descriptive statistics, including mean, median, and interquartile range. Groups were compared using Kruskal-Wallis rank sum, Fisher exact, or Pearson χ^2 tests, as appropriate. Analyses were performed using an RStudio integrated development environment [10]. Charlson Comorbidity Index features were computed using the comorbidity package (version 1.0.2) [11]. Statistical significance is set at $P < .05$.

RESULTS

The patient population consisted of 3607 high-risk patients with a median age of 66.2 years (interquartile range, 52.5–74.7 years); the majority (54.1%) were ≥65 years old, female (58.4%), white (94.9%), and non-Hispanic (96.0%). The most common comorbid conditions were hypertension (46.3%), diabetes mellitus (19.4%), and immunosuppressed status (16.3%).

The population was divided into bebtelovimab (n = 2833) and the nirmatrelvir-ritonavir (n = 774) cohorts. Significant differences were observed between the cohorts in almost all medical comorbid conditions (Table 1). Overall, the bebtelovimab cohort was older and had a higher number of comorbid conditions, as reflected by MASS and Charlson Comorbidity Index. In particular, the bebtelovimab cohort had significantly higher proportions of cardiac disease, lung disease, kidney disease, rheumatologic disease, cancer, and immunocompromised status than the nirmatrelvir-ritonavir cohort. The most common immunocompromising conditions were receipt of drugs for inflammatory and autoimmune conditions, cancer, and transplantation. In contrast, the nirmatrelvir-ritonavir cohort had a higher median body mass index and a higher proportion of diabetes mellitus. Both cohorts had similarly high rates of having completed primary COVID-19 vaccination.

Fifty (1.4%) of 3607 patients progressed to severe outcome by 30 days after treatment (Table 2). Rates of severe disease did not differ significantly between the bebtelovimab (1.4% [95% confidence interval, 1.2%–1.7%]) and nirmatrelvir-ritonavir (1.2% [.8%–1.5%]) cohorts. The rate of admission to the intensive care unit was 0.4%, which was comparable between the bebtelovimab (0.5%) and nirmatrelvir-ritonavir (0.3%) cohorts. Six patients (0.2%) died by day 30 owing to respiratory failure from COVID-19 (n = 2), cardiac causes (n = 2), or progression of metastatic cancer (n = 2).

DISCUSSION

Two noteworthy observations deserve emphasis from our real-world analysis of outpatient COVID-19 therapeutics during the Omicron period dominated BA.2 and subvariants. First, this study highlights important differences in the characteristics

Table 1. Demographic and Clinical Characteristics in 3607 High-Risk Outpatients Treated With Bebtelovimab or Nirmatrelvir-Ritonavir for Mild to Moderate Coronavirus Disease 2019, Severe Acute Respiratory Syndrome Coronavirus 2 Omicron BA.2 Subvariant Epoch

Characteristic	Patients, No. (%)[a]		*P* Value
	Bebtelovimab (n = 2833)	Nirmatrelvir-Ritonavir (n = 774)	
Age, median (IQR), y	66.7 (53.6–74.9)	62.2 (49.5–73.8)	<.01
Age >65 y	1581 (55.8)	370 (47.8)	<.01
Male sex	1183 (41.8)	318 (41.4)	.74
White race	2713 (95.8)	710 (91.7)	<.01
Body mass index, median (IQR)[b]	27.5 (24.6–30.5)	28.2 (25.3–31.2)	<.01
Charlson Comorbidity Index, median (IQR)	1.0 (0.0–2.0)	0.0 (0.0–1.0)	<.01
MASS, median (IQR)[c]	4.0 (2.0–6.0)	3.0 (1.0–4.0)	<.01
Congestive heart failure	217 (7.7)	38 (4.9)	<.01
Chronic kidney disease	71 (2.5)	6 (0.8)	<.01
Chronic lung disease	457 (16.1)	78 (10.1)	<.01
Diabetes mellitus	527 (18.6)	174 (22.5)	.02
Hypertension	1309 (46.2)	361 (46.8)	.78
Immunocompromised status[d]	566 (20.0)	21 (2.7)	<.01
Cancer	388 (13.7)	66 (8.5)	<.01
Rheumatologic disease	171 (6.0)	22 (2.8)	<.01
Full vaccination status[e]	2624 (92.6)	716 (92.5)	.46

Abbreviations: IQR, interquartile range; MASS, Monoclonal Antibody Screening Score.

[a]Data represent no. (%) of patients unless otherwise specified.

[b]Body mass index was calculated as weight in kilograms divided by height in meters squared.

[c]The MASS was calculated as follows: age ≥65 years (2 points), body mass index ≥35 (1 point), diabetes mellitus (2 points), chronic kidney disease (3 points), cardiovascular disease in a patient ≥55 years old (2 points), chronic respiratory disease in a patient ≥55 years old (2 points), hypertension in a patient ≥55 years old (1 point), and immunocompromised status (4 points).

[d]The most common immunocompromising conditions were receipt of immunosuppressive drugs for autoimmune, inflammatory, or rheumatologic conditions (10.9%), chemotherapy for solid or hematologic cancer (4.6%), and organ transplantation (4.2%). Patients with AIDS accounted for only 0.4%.

[e]Full vaccination status is defined as 2 doses of a messenger RNA vaccine or a single dose of adenovirus-vector coronavirus disease 2019 vaccine. Booster doses were not included in the definition.

Table 2. Rates of Severe Disease, Intensive Care Unit Admission, and Death by Day 30 Among 3607 High-Risk Outpatients Treated With Bebtelovimab or Nirmatrelvir-Ritonavir During the Severe Acute Respiratory Syndrome Coronavirus 2 Omicron BA.2 Epoch

Outcome	Patients, No. (%)		*P* Value
	Bebtelovimab (n = 2833)	Nirmatrelvir-Ritonavir (n = 774)	
Severe outcome[a]	41 (1.4)	9 (1.2)	.55
ICU admission	14 (0.5)	2 (0.3)	.38
Death	6 (0.2)	0 (0.0)	.20

Abbreviation: ICU, intensive care unit.

[a]Severe outcome is defined according to the World Health Organization classification of 4 (hospitalization and oxygen supplementation) or higher (including death).

of patients who were treated with bebtelovimab compared with those who received oral nirmatrelvir-ritonavir. Patients who received bebtelovimab infusion were significantly older and had a higher number of medical comorbid conditions. Second, despite having more high-risk characteristics, the bebtelovimab cohort had a low rate of severe disease progression, which was comparable to that in patients treated with nirmatrelvir-ritonavir.

Ritonavir-booster nirmatrelvir is recommended as a first-line outpatient treatment for mild to moderate COVID-19 [1]. This authorization was based on a randomized placebo-controlled trial among unvaccinated high-risk patients showing that nirmatrelvir-ritonavir was associated with 89% relative risk reduction in hospitalization and death by day 29 [7]. In that trial conducted before SARS-CoV-2 Omicron, the rates of hospitalization or death by day 29 were 0.8% among those who received nirmatrelvir-ritonavir compared with 7.0% among those who received placebo. The rate of severe outcome in our study of mostly vaccinated patients with multiple high-risk comorbid conditions was 1.2%. The effectiveness of nirmatrelvir-ritonavir in reducing rates of severe COVID-19 and death has been demonstrated in older patients, immunosuppressed patients, and those with cardiovascular diseases [12]. However, many high-risk patients possessed characteristics (eg, kidney or liver disease) or were taking medications (eg, tacrolimus or amiodarone) that would contraindicate or caution against the use of nirmatrelvir-ritonavir. For these patients in our program, bebtelovimab was preferentially used because of the excellent outcomes with previous anti-spike monoclonal antibodies [2–4].

However, there are currently no peer-reviewed published data on the efficacy of bebtelovimab. In a preprint report of the phase 2 BLAZE-4 trial, the use of bebtelovimab with or without bamlanivimab-etesevimab was associated with greater viral clearance and faster resolution of symptoms compared with placebo. However, the rates of COVID-19 hospitalization or death by day 29 were similar [13]. In the FDA document, the rate of severe outcome after bebtelovimab (with or without bamlanivimab-etesevimab) treatment was 3%, which was lower compared to rates in placebo cohorts in previous clinical trials [6]. The observed 1.4% rate of severe outcome after bebtelovimab in our study is reassuring and supports its continued use even among the immunocompromised and highest-risk groups of patients with COVID-19 due to Omicron BA.2 and subvariants.

While we aimed to compare outcomes between bebtelovimab and nirmatrelvir-ritonavir, this was not as straightforward because there were significant differences in characteristics between the 2 cohorts. Bebtelovimab was used more often among patients with a higher number of comorbid conditions, including chronic kidney, cardiac, or lung disease and immunosuppressed status. Historically, possession of ≥1 of these

comorbid conditions translated to a higher risk of severe disease despite anti-spike monoclonal antibody treatment. Even without adjustment for these higher-risk comorbid conditions, it was reassuring that the outcome with bebtelovimab was comparable to that with nirmatrelvir-ritonavir. Only 1.4% of 2833 high-risk patients progressed to severe disease by day 30 after bebtelovimab infusion. This low rate is consistent with our program's previous observations with bamlanivimab with or without etesevimab, casirivimab-imdevimab, or sotrovimab before the Omicron BA.2 surge [14].

The findings of the current study should be interpreted in the context of several limitations. Because of a retrospective design, some outcomes may not have been captured in patients who sought subsequent care in other centers. The outcome did not include incidental diagnosis of mild COVID-19 among high-risk patients hospitalized for a non–COVID-19 diagnosis. The imbalance in the number and characteristics of patients between the 2 groups and the lack of treatment randomization are limitations beyond our control. The population were predominantly non-Hispanic white persons who sought care at an academic center, and our results may not be generalizable to communities of underrepresented populations.

This study has no control group of untreated high-risk patients, which made it impossible to measure the relative efficacy. As more treatment options became available, it was difficult to identify a contemporaneous cohort of untreated patients with comparable high-risk characteristics. Hence, the study design was aimed mainly to describe (and compare) the outcomes in the 2 treatment options for high-risk patients during a period dominated by BA.2 and subvariants. Finally, viral sequencing was not performed, so we can only assume, based on data tracking reported by the Centers for Disease Prevention and Control, that our cases were due to SARS-CoV-2 BA.2 Omicron. These limitations were counterbalanced by a large cohort of high-risk patients managed by a centralized team, which allowed for a comparative analysis of outcomes between 2 outpatient therapies during the Omicron BA.2 epoch.

In conclusion, the current study is the first to compare the outcomes of treatment with bebtelovimab or nirmatrelvir-ritonavir in real-world settings dominated by SARS-CoV-2 Omicron BA.2 and subvariants. Our observations suggest that bebtelovimab is a valuable option for high-risk patients, especially but not only those for whom nirmatrelvir-ritonavir may be a problematic choice. The clinical outcomes in this study support the EUA of bebtelovimab for early treatment of high-risk persons with mild to moderate COVID-19 during the Omicron epoch dominated by BA.2 and subvariants. SARS-CoV-2 Omicron continues to evolve, and the BA.5 subvariant has emerged as the dominant variant. Omicron BA.4 and BA.5 may escape neutralization of antibodies generated from vaccination and prior natural infection [15]. While pseudovirus experiments suggest that bebtelovimab neutralizes BA.4 and BA.5 subvariants, [5] we encourage continued real-time monitoring of its effectiveness in the clinical setting as these novel variants emerge.

Notes

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Potential conflicts of interest. R. R. R. received grants from Gilead, Regeneron, Roche, and nFerence (funds provided to the institution), participated on a data and safety monitoring board for Novartis, and serves as board of director for the American Society of Transplantation. J. C. O. is supported by grants from nFerence and is a paid consultant for Elsevier and Bates College. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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