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MAJOR ARTICLE

Comparative Efficacy of Early COVID-19 Monoclonal Antibody Therapies: A Retrospective Analysis

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Background. Bamlanivimab and casirivimab/imdevimab are monoclonal antibody (mAb) treatments used for mild to moderate coronavirus disease 2019 (COVID-19) in high-risk patients. To date, there are few data summarizing real-world evidence comparing the 2 mAbs. Additionally, there are insufficient data to guide administration timing relative to symptom onset. The purpose of this study was to evaluate 30-day failure rates for each agent and to identify the relationship between symptom onset and efficacy.

Methods. We performed a retrospective cohort study of a 6-month period at a large community medical center. Consecutive outpatients diagnosed with COVID-19 disease by nasopharyngeal (NP) polymerase chain reaction (PCR) testing received either bamlanivimab 700 mg or casirivimab/imdevimab 1200 mg/1200 mg. Each patient was followed for a total of 30 days. Three independent, blinded physicians performed adjudication for revisit reasons. The primary outcome was therapy-related failure, defined as COVID-19-related hospital admission within 30 days of infusion. Multivariable logistic regression was performed to adjust for confounders that may have influenced hospital admission in either group.

Results. During the period from November 2020 to May 2021, 183 patients were treated with bamlanivimab and 270 with casirivimab/imdevimab. The mean age was ~67 years and body mass index 30 kg/m^2. Thirty-day admission for therapy-related failure rates were 4.8% and 13.7% for casirivimab/imdevimab and bamlanivimab, respectively (P = .001). No significant differences were found between early (<3 days of symptom onset) and late administration of either mAb.

Conclusions. There was a higher failure rate with bamlanivimab vs casirivimab/imdevimab. No difference in efficacy was found between early vs late administration of either mAb.

Keywords. antispike protein; coronavirus; comparative efficacy; COVID-19; protein therapeutics; SARS-CoV-2.

In response to the coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, several monoclonal antibodies (mAbs) targeting viral entry were developed and approved under Emergency Use Authorizations (EUAs). These mAbs include bamlanivimab (EUA now revoked), casirivimab with imdevimab, and bamlanivimab with etesivimab. The mechanisms of action of these agents are related to their ability to bind to the spike protein of SARS-CoV-2, thus preventing attachment to the human angiotensin-converting enzyme 2 (ACE2) receptor. The result is decreased entry into host cells, thereby reducing viral load. The indications for administering 1 of the mAbs include treatment of mild to moderate COVID-19 in outpatients with a high risk for progressing to severe disease and hospitalization [1–3].

Bamlanivimab was the first mAb widely available for COVID-19, receiving EUA approval in November 2020. After the EUA was issued, warnings of clinical worsening after administration and new hypersensitivity symptoms were added to the bamlanivimab labeling. A 1000–2000-fold reduction in susceptibility to 4 SARS-CoV-2 variants was later identified, and clinicians were notified of the potential implications of this concern [1]. By April 2021, the Food and Drug Administration (FDA) revoked bamlanivimab's EUA over increasing the frequency of resistant SARS-CoV-2 variants [1]. Subsequently, bamlanivimab plus etesivimab received EUA approval based on a phase III study [4]. The combination product has improved susceptibility to SARS-CoV-2 variants; however, diminished susceptibility to the SARS-CoV-2 B.1.351 (Beta), P.1 (Gamma), B.1.427/B.1.429 (Epsilon), and B1.526 (Iota) variants has been reported [3]. Another combination mAb cocktail, casirivimab with imdevimab, received EUA approval shortly after bamlanivimab. Escape SARS-CoV-2 variants were identified for both individual components, but in combination, all variants tested retained susceptibility [2]. Lastly, sotrovimab received an EUA in September 2021; it has activity against many

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variants of SARS-CoV-2 but was not available at the time of this study [5].

Collectively, there is insufficient real-world evidence comparing the differences between these mAbs on hospital admission rates, including influencing factors such as patient characteristics and adverse drug reactions (ADRs). While data exist supporting early administration of antiviral therapies in other illnesses (ie, influenza), it is unclear if the timing of administration of antispike mAbs impacts efficacy in SARS-CoV-2 infection. The rapid evolution of SARS-CoV-2 variants warrants a rapid identification of clinical response rates considering patients' risk factors for disease progression and vaccination status. The primary objective of this study was to evaluate 30-day hospital admission due to therapy-related failure (worsening of SARS-CoV-2 infection or ADRs) in patients with mild to moderate COVID-19 who received either bamlanivimab or casirivimab with imdevimab as part of routine care. The secondary objectives were to evaluate mAb administration timing and patient-reported symptom onset with respect to response to therapy, factors influencing revisits, and ADRs between groups.

METHODS

We performed a single-center retrospective cohort study at a community teaching hospital to evaluate 2 mAbs used for COVID-19. All consecutive patients who received either bamlanivimab or casirivimab/imdevimab infusions from November 2020 through May 2021 were identified in the electronic medical record (EMR) system, Allscripts Sunrise Clinical Manager. For context, during the pandemic, an outpatient infusion center was set up in the emergency department. Local clinicians could refer patients to the infusion center. Patient selection for mAb administration was protocolized and based on the EUA criteria, except for the symptom onset requirement [1–3]. The hospital's COVID-19 mAb infusion protocol at the time of study completion required that each patient had evidence of a positive SARS-CoV-2 result, a symptom onset of ≤7 days, and did not require oxygen supplementation at baseline. Once initial criteria were met, other criteria were imposed by age. All patients ≥65 years of age were eligible as long as they did not have a terminal illness, end-stage dementia, or an advanced directive indicating a do not hospitalize request. Patients age ≥55 years had to meet 1 of the following criteria: body mass index ≥35 kg/m^2, glycosylated hemoglobin A1C ≥7.5%, estimated glomerular filtration rate <50 mL/min, coronary artery disease with 2 medications or ejection fraction <40%, chronic obstructive pulmonary disorder on chronic bronchodilator therapy, or active immunosuppression or immunosuppressive therapy. Any patient age <55 years was evaluated on a case-by-case basis. Patient demographics, laboratory results, and hospital repeat visit data were collected using the EMR. We used the height and weight obtained at patient triage upon presentation for the infusion to calculate body mass index for all patients. Multiple imputation was used for missing heights [6]. Medical history was obtained via chart review, including time from COVID-19 symptom onset to mAb infusion, smoking status, and comorbidities. All hospital revisits within 30 days after administration of mAb were evaluated. Revisits included emergency department utilization, admission under observation status, and hospital admission. Three blinded physicians with different areas of expertise (family medicine, emergency medicine, infectious diseases) independently adjudicated all patient revisits to determine the cause of revisits. Clinicians were provided 3 categories for revisits to choose from (1) COVID-19 related, (2) adverse drug reaction related to mAb, (3) both 1 and 2, and (4) unrelated to COVID-19. Physicians were given full access to patient and medical information, but were not allowed to share the results of their analysis. The final revisit disposition was based on majority agreement between the 3 assessments.

Patients received either bamlanivimab 700 mg or casirivimab/imdevimab 1200 mg/1200 mg over 60 minutes, with a postinfusion observation of at least 1 hour as part of routine care in the emergency department. Bamlanivimab was used exclusively until January 2021, when casirivimab/imdevimab became the mAb of choice at our institution due to the concern for emerging variants and lack of supporting evidence for bamlanivimab monotherapy.

The primary outcome of this study was hospital admission due to therapy-related failure, defined as a hospital admission related to COVID-19 or mAb ADR within 30 days of infusion for patients who received bamlanivimab infusion and those who received casirivimab/imdevimab infusion [7]. We performed a prespecified stratified analysis based on COVID-19 symptom history (administration of mAb >3 and ≤3 days after patient-reported symptom onset) to evaluate mAb administration timing and patient-reported symptom onset with respect to response to therapy. In addition, we focused on the identified patient populations (body mass index ≥35 kg/m^2 and age ≥65 years of age) associated with hospital admission due to therapy-related failure. This study was granted approval and waiver of consent by the Robert Wood Johnson University Hospital Somerset Institutional Review Board (IRB 21-07).

All data were summarized using descriptive statistics. Categorical data were presented as proportions and compared with the chi-square test. The normality of continuous data was evaluated by visual inspection of histograms and the Kolmogorov-Smirnov test. Parametric data were assessed using the independent sample *t* test, and nonparametric data with the Mann-Whitney *U* test. Significance testing was performed with a 2-sided alpha of .05. Confounding variables were identified based on biological plausibility, bivariate analysis, and previous evidence. All variables (age, available comorbidities) with $P < .1$ in bivariate analysis were tested as

covariates in multivariable logistic regression, and those with a $P < .05$ were retained in the final model. All data were analyzed with SPSS, version 26.0 (IBM Corporation, Armonk, NY, USA).

Patient Consent

The Institutional Review Board at Robert Wood Johnson University Hospital Somerset determined that informed consent for participation was not required in this minimal risk study. All data were anonymized before analysis.

RESULTS

A total of 453 consecutive patients meeting criteria received an mAb infusion indicated for the treatment of mild to moderate COVID-19: 183 patients treated with bamlanivimab and 270 treated with casirivimab/imdevimab. Patient characteristics were similar between groups. Patients were mainly White, with a mean length of symptoms of 3.7 days, aged ~65 years, and had a mean body mass index (BMI) of 30.6 kg/m^2. Few patients had a history of malignancy (bamlanivimab vs casirivimab/imdevimab: 5, 2.7%, vs 17, 6.3%; $P = .118$) or rheumatologic disease (bamlanivimab vs casirivimab/imdevimab: 3, 1.6%, vs 13, 4.8%; $P = .117$). Only 1 individual with HIV was identified in the bamlanivimab group. A summary of patient characteristics can be found in Table 1.

In the group of patients treated with bamlanivimab, 113 (61.7%) had a history of symptoms for ≥3 days. Patient characteristics between early and late symptom onset were similar in the overall population. Patients who received bamlanivimab had a mean age of 67 years and a BMI of 29.5 kg/m^2. One hundred ninety (70.4%) of the casirivimab with imdevimab patients had a history of symptoms for ≥3 days. Characteristics were similar between early and late symptom onset and were representative of the overall population. A comparison of patient characteristics between those receiving early vs late administration of casirivimab with imdevimab or bamlanivimab can be found in Supplementary Table 1.

For the primary outcome, there was a statistically significant decrease in 30-day hospital admission for therapy-related failure in patients who received casirivimab/imdevimab (25/270, 4.8%) vs bamlanivimab (30/183, 13.7%; odds ratio [OR], 0.36; 95% CI, 0.17–0.75; $P = .001$). In addition, hospital admission for any cause (COVID-19-related and non-COVID-19-related) was greater in patients who received bamlanivimab (Table 2). There was 1 (0.4%) ADR-related hospital revisit (for weakness and vomiting) in the casirivimab/imdevimab group compared with 7 (3.8%) in the bamlanivimab group ($P = .009$). ADRs reported in the bamlanivimab group included vomiting, electrocardiogram changes, lethargy, confusion, dizziness, numbness and tingling, and altered mental status. Of all patients who reported an ADR, 5 required hospitalization, and all received bamlanivimab. Refer to Table 2 and Supplementary Table 1 for more detailed information.

Among bamlanivimab recipients, duration of symptoms before infusion of ≥3 or <3 days did not affect therapy-related failure (late vs early: 15% vs 11.4%; OR, 1.47; 95% CI, 0.57–3.81;

Table 1. Comparison of Patient Characteristics Among Patients Treated With Casirivimab With Imdevimab or Bamlanivimab

	Casirivimab With Imdevimab (n = 270)	Bamlanivimab (n = 183)	*P* Value
Age, mean ± SD, y	63.4 ± 13.0	66.9 ± 12.9	.005
Days from onset, mean ± SD	3.84 ± 2.2	3.48 ± 2.2	.090
BMI, mean ± SD, kg/m^2	31.3 ± 7.9	29.5 ± 6.8	.017
Female, No. (%)	149 (55.2)	91 (49.7)	.253
Caucasian, No. (%)	204 (75.6)	171 (93.0)	<.001
Hispanic, No. (%)	38 (14.1)	22 (12.0)	.527
Oxygen saturation room air, mean ± SD, %	96.2 ± 2.1	96.6 ± 2.0	.044
Required oxygen, No. (%)	3 (1.1)	8 (4.4)	.057
Systolic blood pressure, mean ± SD, mmHg	141.2 ± 21.6	138.9 ± 24.3	.289
Diastolic blood pressure, mean ± SD, mmHg	79.1 ± 10.0	77.1 ± 11.4	.289
Temperature, mean ± SD, °F	98.7 ± 1.02	98.6 ± .90	.477
Active smoker, No. (%)	21 (7.8)	9 (4.9)	.235
Chronic pulmonary disease, No. (%)	31 (11.5)	25 (13.7)	.489
Diabetes, No. (%)	68 (25.3)	55 (3.2)	.248
Heart failure, No. (%)	8 (3.0)	10 (5.5)	.222
Hypertension, No. (%)	99 (36.7)	82 (44.8)	.083
Obese, No. (%)	140 (51.9)	75 (41.0)	.023
Charlson-Deyo comorbidity index			.081
≤2	254 (94.1)	164 (89.6)	
>2	16 (5.9)	19 (10.4)	

Abbreviation: BMI, body mass index.

Table 2. Comparison of Hospital Admissions and Revisits Between Patients Treated With Casirivimab Plus Imdevimab or Bamlanivimab

	Casirivimab Plus Imdevimab (n = 270)	Bamlanivimab (n = 183)	Unadjusted OR (95% CI)	*P* Value	Adjusted[b] OR (95% CI)	*P* Value
Admission for therapy-related failure[a]	13 (4.8)	25 (13.7)	0.32 (0.16–0.64)	.001	0.36 (0.17–0.75)	.006
Admission for SARS-CoV-2 infection	13 (4.8)	21 (11.5)	0.39 (0.19–0.80)	.010	0.45 (0.21–0.95)	.035
Admission for mAb adverse drug reaction	0 (0)	5 (2.7)	-	-	-	-
Any admission	24 (8.9)	32 (17.5)	0.46 (0.26–0.81)	.007	0.53 (0.29–0.97)	.040
Revisit for therapy-related failure[a]	19 (7.0)	30 (16.4)	0.38 (0.20–0.71)	.002	0.42 (0.22–0.81)	.009
Revisit for SARS-CoV-2 infection	18 (6.7)	23 (12.6)	0.50 (0.26–0.95)	.032	0.57 (0.29–1.11)	.098
Revisit for mAb adverse drug reaction	1 (0.4)	7 (3.8)	0.09 (0.01–0.77)	.027	0.09 (0.01–0.71)	.023
Any revisit	38 (14.4)	40 (21.9)	0.59 (0.36–0.96)	.032	0.66 (0.40–1.10)	.114
ED revisit for therapy-related failure[a]	6 (1.9)	4 (2.2)	0.84 (0.22–3.19)	.803	0.78 (0.20–3.01)	.720
ED revisit for SARS-CoV-2 infection	5 (1.9)	2 (1.1)	1.71 (0.33–8.90)	.525	1.67 (0.32–8.85)	.546
ED revisit for mAb adverse drug reaction	1 (0.4)	2 (1.1)	0.34 (0.30–3.74)	.375	0.23 (0.02–2.80)	.251
Any ED revisit	14 (5.2)	8 (4.4)	1.20 (0.49–2.91)	.693	1.14 (0.46–2.80)	.778

Abbreviations: ED, emergency department; mAb, monoclonal antibody; OR, odds ratio; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a]Includes admission for both SARS-CoV-2 infection and adverse drug reactions within 30 days of mAb infusion.

[b]Adjusted for age and comorbidity index.

P = .424). Similarly, the duration of symptoms before infusion did not affect the failure rate among casirivimab/imdevimab recipients (late vs early: 3.7% vs 7.5%; OR, 0.69; 95% CI, 0.20–2.39; *P* = .561). Revisits for any reason, COVID-19 worsening, and ADRs did not differ between early and late administration for either mAb (Table 3; Supplementary Table 2).

In the special population analysis, 111 and 122 patients were treated with bamlanivimab and casirivimab/imdevimab, respectively, aged 65 years and older. Age ≥65 was significantly associated with a higher rate of treatment failure only for casirivimab/imdevimab (9% vs 1.4%; *P* = .004). There were no statistically significant differences between BMI ≥35 and <35 kg/m^2 for either mAb (Supplementary Table 3).

DISCUSSION

In this study, the primary outcome of hospital admission due to therapy-related treatment failure was significantly decreased by 65% in patients who received casirivimab/imdevimab vs bamlanivimab. The mAb of choice at our institution was changed from bamlanivimab to casirivimab/imdevimab in January 2021. The change was made based on evolving concerns for variants of SARS-CoV-2 that had been recently described with mutations that reduced the activity of mAb therapy for SARS-CoV-2. Specifically, variants with the E484K mutation have a loss of activity for bamlanivimab of >2360-fold [1–3]. Our region began to see isolates with the mutation with origins in New York (B1.526; Iota) in November 2020, South Africa (B1.351; Beta) in February 2021, and Brazil (P1; Gamma) in March 2021. Given the recognition of the greater potency of casirivimab/imdevimab for variant isolates, our findings suggest that there may have been a greater prevalence of variants circulating at the time of the study than previously understood or a relative lack of potency of bamlanivimab compared with casirivimab/imdevimab.

We recognize that at present the Omicron (B.1.1.529) variant has been identified as a variant of concern (VOC), with limited to no data regarding the efficacy of the monoclonal antibody treatments used in this study [8]. We would also like to point out that as of January 24, 2022, the FDA has recommended against use of either casirivimab/imdevimab or the combination agent bamlanivimab/etesevimab in cases where the Omicron variant is highly suspected [9]. Regardless, we do not anticipate any effect of the B.1.1.529 variant on the study, considering that the first cases were identified after completion [8]. This development highlights the need for rapidly available variant testing in confirmed COVID-19 cases. Further research on the effectiveness of available monoclonal antibodies in this new variant is required.

Finally, a significant difference in any hospital admission between the 2 groups was identified. Whether admission for a new acute or chronic illness was secondary to SARS-CoV-2 infection worsening as a result of mAb failure is difficult to establish; however, the possibility exists. Contrary to this postulation are the results from a study that identified a decrease in hospitalizations for acute and chronic illnesses during the COVID-19 pandemic, suggesting that patients may not seek medical attention as often due to concerns for the virus [10].

However, patients who receive mAb infusions may be more likely to present for exacerbation of other illnesses because of their self-awareness of risk. This postulation requires confirmation in future studies.

The revisit rate in the special populations analysis for bamlanivimab was surprising because the BLAZE-1 trial cited a lower revisit rate of 4% postinfusion for 95 patients age 65 years and older or with a BMI ≥35 kg/m^2 [4]. Our study found substantially higher revisit rates in both of these populations. One likely explanation for this is a lack of overall effectiveness of bamlanivimab in this study, leading to a lack of difference in outcomes by age or weight. A recent real-world study, performed in the same geographical area, of patients age ≥65 years or with a BMI ≥35 kg/m^2 treated with bamlanivimab had an admission rate of 7.3% and an adjusted odds ratio similar to this study of 0.583. However, it is important to note that this study includes outpatient infusion centers, whereas our institution does not offer this option [11].

A phase III study of casirivimab with imdevimab, R10933-10987-COV-2067, enrolled 799 patients within 3 days of symptom onset with a median age of 42 years (7% of patients were age ≥65 years). In their high-risk patient analysis, 151 patients were treated with casirivimab/imdevimab and had a composite hospital admission/emergency department revisit rate of 3% [2]. Again, our study had a substantially higher revisit rate. Finding a significant difference in the failure rate of patients age 65 years and older treated with casirivimab/imdevimab and not with bamlanivimab again speaks to the lack of efficacy of bamlanivimab during this time frame. This difference in results is unclear but may be related to differences in populations in clinical trials vs real-world use [12]. The current analysis and the R10933-10987-COV-2067 study included patients with a symptom onset ≤7 days and had similar entry criteria. The study has not been published in full; therefore, the ability to compare study populations at this time is limited.

We did not observe any differences in revisit outcomes based on the length of symptom history. If BAM were active, we would have expected benefit for earlier treatment with an antiviral as seen with the use of oseltamivir for influenza and acyclovir or its analogs in herpes virus infection [13, 14]. The preliminary results of a recent study (COV-2609) looking at prophylactic use of casirivimab/imdevimab in household contacts demonstrated 100% efficacy in preventing infection, demonstrating the activity of this mAb combination early [15].

Another important observation in our analysis was the greater proportion of White patients who received bamlanivimab (95%) vs carisimab with imdevimab (75%). Racial disparities in the receipt of antispike protein antibodies has been previously reported [16]. Our observation that the disparity was more evident with bamlanivimab suggests that minority groups may have had less access to antispike protein antibodies early on. Additional research is warranted to identify factors contributing to this disparity.

As with any observational study, there are some inherent limitations. First, as a single-center study, the external validity may be influenced by prescribing patterns. For example, we utilized a cutoff for mAb eligibility of 7 days after symptom onset, vs the EUA, which stated 10 days. However, our criteria for the use of mAbs closely mirrored the EUA criteria, attenuating this concern. Our study relied on the physician documentation in the electronic health record and patient-reported symptom onset, which carry the concern of reporter bias. We also relied on revisit to the same hospital for our end point. If a patient had presented to another hospital, we would not have captured the outcome. There is no reason to suspect that this occurred differentially between groups. The study highlights the importance of monitoring viral variants in circulation before deciding which therapeutic modalities are optimal. Significant strengths of the study included the short time frame, allowing comparison in similar populations. The same clinicians were responsible for prescribing the mAb as we had a dedicated COVID-19 response team, and the SARS-CoV-2 variant prevalence was evolving at the time of the study.

In this single-center cohort, casirivimab/imdevimab was more effective in preventing COVID-19-related revisits than

Table 3. Comparison of Hospital Admissions Between Patients Treated With Casirivimab Plus Imdevimab or Bamlanivimab Stratified by Administration Early vs Late Administration Relative to Patient-Reported Symptom Onset

	≥3 Days of Symptoms (n = 190)	<3 Days of Symptoms (n = 80)	Unadjusted OR (95% CI)	*P* Value	Adjusted[a] OR (95% CI)	*P* Value
Casirivimab plus imdevimab						
Admission for therapy-related failure[b]	7 (3.7)	6 (7.5)	0.47 (0.15–1.45)	.190	0.69 (0.20–2.39)	.561
Any admission	14 (7.4)	10 (12.5)	0.56 (0.24–1.31)	.181	0.79 (0.30–2.10)	.625
Bamlanivimab						
Admission for therapy-related failure[b]	17 (15.0)	8 (11.4)	1.37 (0.56–3.37)	.490	1.47 (0.57–3.81)	.424
Any admission	22 (19.5)	10 (14.3)	1.45 (0.64–3.28)	.371	1.55 (0.66–3.68)	.318

Abbreviations: mAb, monoclonal antibody; OR, odds ratio; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a]Adjusted for age and comorbidity index.

[b]Includes admission for both SARS-CoV-2 infection and adverse drug events within 30 days of mAb infusion.

bamlanivimab, likely due to greater potency for SARS-CoV-2 variants. Additionally, we failed to detect a difference in failure rate based upon early vs late administration, an unusual finding for antiviral therapy for COVID-19 disease. The implications of these findings support that close monitoring of viral evolution is essential with such therapy because viral variant evolution and dissemination can occur quickly. Limited capacity for variant testing could delay recognizing the emergence of mAb resistance in the community. Further observation for other variants that may require alternatives to currently available mAbs will be critically important.

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