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Clinical data to support the use of bamlanivimab for the treatment of outpatients with mild to moderate coronavirus disease-19 (COVID-19) are needed.

2335 Patients who received single-dose bamlanivimab infusion between November 12, 2020, and February 17, 2021, were compared with a propensity-matched control of 2335 untreated patients with mild to moderate COVID-19 at Mayo Clinic facilities across 4 states. The primary outcome was the rate of hospitalization at days 14, 21, and 28.

The median age of the population was 63 years; 47.3% of the bamlanivimab-treated cohort were 65 years or more; 49.3% were female and 50.7% were male. High-risk characteristics included hypertension (54.2%), BMI greater than or equal to 35 (32.4%), diabetes mellitus (26.5%), chronic lung disease (25.1%), malignancy (16.6%), and renal disease (14.5%). Patients who received bamlanivimab had lower all-cause hospitalization rates at days 14 (1.5% vs. 3.5%; risk ratio [RR], 0.41), 21 (1.9% vs. 3.9%; RR, 0.49), and 28 (2.5% vs. 3.9%; RR, 0.63). Secondary exploratory outcomes included lower intensive care unit (ICU) admission rates at days 14 (0.14% vs. 1%; RR, 0.14), 21 (0.25% vs.1%; RR, 0.25), and 28 (0.56% vs.1.1%; RR. 0.51) and lower […]

Intravenous bamlanivimab use associates with reduced hospitalization in high-risk patients with mild to moderate COVID-19

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BACKGROUND. Clinical data to support the use of bamlanivimab for the treatment of outpatients with mild to moderate coronavirus disease-19 (COVID-19) are needed.

METHODS. 2335 Patients who received single-dose bamlanivimab infusion between November 12, 2020, and February 17, 2021, were compared with a propensity-matched control of 2335 untreated patients with mild to moderate COVID-19 at Mayo Clinic facilities across 4 states. The primary outcome was the rate of hospitalization at days 14, 21, and 28.

RESULTS. The median age of the population was 63 years; 47.3% of the bamlanivimab-treated cohort were 65 years or more; 49.3% were female and 50.7% were male. High-risk characteristics included hypertension (54.2%), BMI greater than or equal to 35 (32.4%), diabetes mellitus (26.5%), chronic lung disease (25.1%), malignancy (16.6%), and renal disease (14.5%). Patients who received bamlanivimab had lower all-cause hospitalization rates at days 14 (1.5% vs. 3.5%; risk ratio [RR], 0.41), 21 (1.9% vs. 3.9%; RR, 0.49), and 28 (2.5% vs. 3.9%; RR, 0.63). Secondary exploratory outcomes included lower intensive care unit (ICU) admission rates at days 14 (0.14% vs. 1%; RR, 0.14), 21 (0.25% vs.1%; RR, 0.25), and 28 (0.56% vs.1.1%; RR. 0.51) and lower all-cause mortality at days 14 (0% vs. 0.33%), 21 (0.05% vs. 0.4%; RR,0.13), and 28 (0.11% vs. 0.44%; RR, 0.26). Adverse events were uncommon with bamlanivimab, occurring in 19 of 2355 patients, and were most commonly fever (n = 6), nausea (n = 5), and lightheadedness (n = 3).

CONCLUSIONS. Among high-risk patients with mild to moderate COVID-19, treatment with bamlanivimab was associated with a statistically significant lower rate of hospitalization, ICU admission, and mortality compared with usual care.

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Introduction

Control of the severe acute respiratory syndrome–coronavirus 2 (SARS-CoV-2) pandemic requires prevention, early diagnosis, and effective treatment. Enhanced testing has allowed for early identification of infected individuals who do not yet require hospitalization, but are at high risk for complications. Most treatments authorized or approved in 2020 were targeted at late-stage disease and critical illness, but new treatments are emerging to intervene earlier in the course of illness for high-risk individuals. One treatment option for these individuals is antispike neutralizing monoclonal antibody, which received emergency use authorization (EUA) by the US FDA. Bamlanivimab was authorized on November 9, 2020, the combination of casirivimab-imdevimab on November 21, 2020, and the combination of bamlanivimab-etesevimab on February 9, 2021 (1–3). These monoclonal antibodies inhibit the interaction of SARS-CoV-2 spike protein with ACE-2 receptors, thereby preventing viral attachment and infectivity (4). On April 16, 2021, the FDA revoked the EUA for bamlanivimab monotherapy at the request of the manufacturer with a specific strategy to transition therapeutic focus to combination therapy of bamlanivimab and etesevimab, driven by concerns over emerging resistance patterns in SARS-CoV-2 variants (5).

A phase 2 placebo-controlled trial showed decreased emergency department visits and hospitalizations among patients administered bamlanivimab (6), leading to it being granted an EUA by the FDA (1). However, the utilization of bamlanivimab was initially

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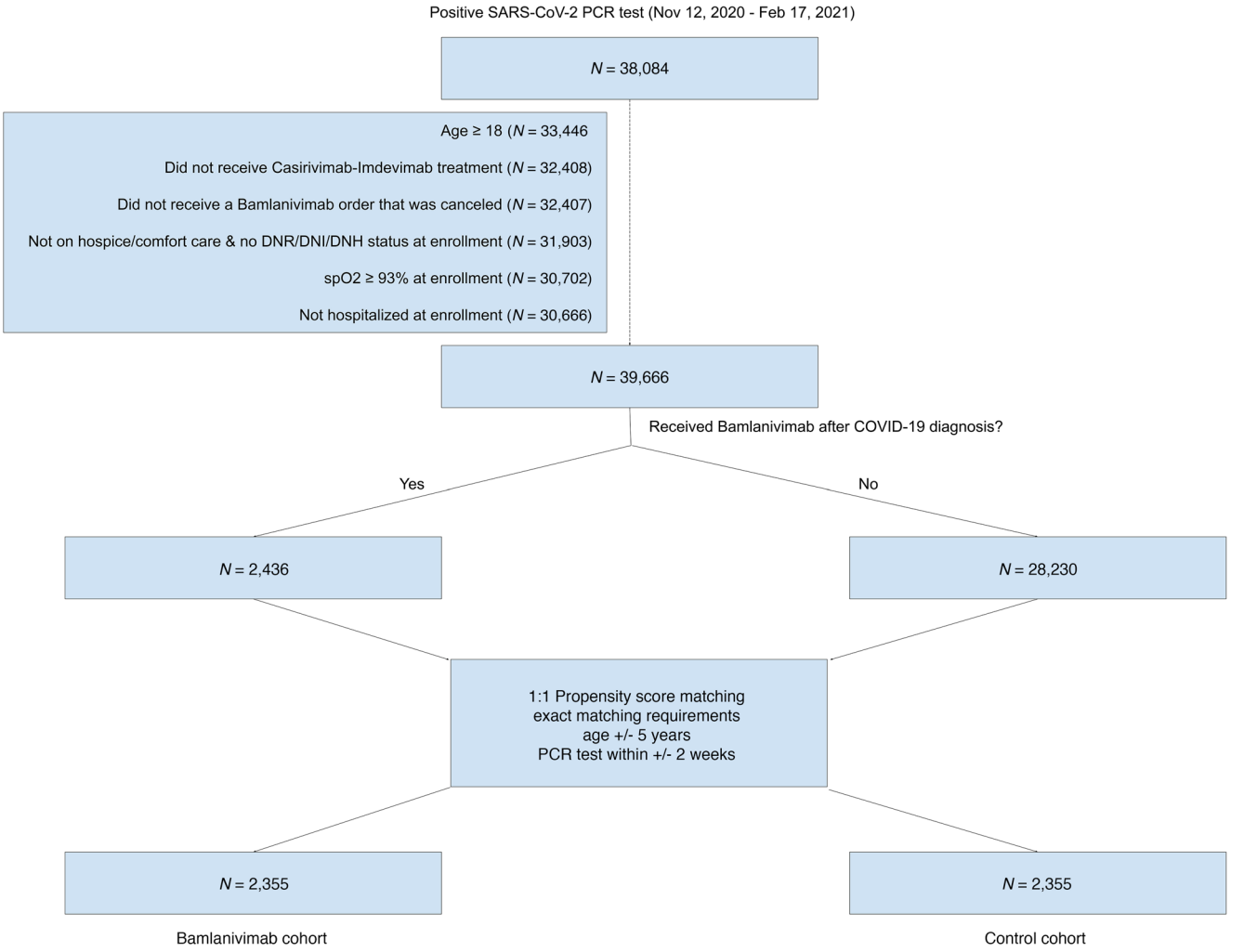

Figure 1. Study population, participant selection, and propensity matching.

slow, owing partly to the complexities of implementing outpatient infusion centers for infectious patients (7). Further, some patients were wary of investigational treatment and clinicians were skeptical in recommending these therapies due to limited clinical evidence and initial lack of endorsement by national societies (8–10).

Upon the issuance of the EUA, institutions across the US established infusion facilities for the administration of monoclonal antibodies (11–14). The Mayo Clinic developed its dedicated infusion facilities and assembled multidisciplinary teams to coordinate monoclonal antibody infusions to patients with coronavirus disease-19 (COVID-19) who were eligible under the EUA (7, 15). This study was conducted to analyze the association of bamlanivimab monotherapy with clinical outcomes in high-risk patients with mild to moderate COVID-19.

Results

Patient population

Of the 33,446 adult patients with positive SARS-CoV-2 PCR test, the participant selection algorithm (Figure 1) resulted in 2 cohorts that were balanced for relevant demographic and clinical covariates: (a) bamlanivimab-treated patients (n = 2335) and (b) control patients (n = 2335), who did not receive monoclonal antibodies (Table 1). Appropriate matches could not be found for 101 bamlanivimab-treated patients. which led to a decrease in size of our bamlanivimab cohort from 2436 to 2335. Unmatched data are shown in Supplemental Table 2, and the effect of propensity score matching on these variables is shown in Supplemental Table 3 (supplemental material available online with this article; https://doi.org/10.1172/JCI151697DS1). All covariates showed standardized differences of less than 0.1, confirming that the cohorts were reasonably balanced for reliable downstream comparisons (Table 1). The success of balancing was also confirmed by comparing the age distribution (Supplemental Figure 3) and the prevalence of each categorical covariate (Supplemental Figure 4) in the 2 cohorts before and after propensity matching. Distribution of test results across the 2 cohorts is shown in Supplemental Figure 5.

The mean time from PCR date to bamlanivimab infusion was 2. 8 days (median, 2 days; Supplemental Figure 4).The most common comorbidities were hypertension (54.2%), diabetes mellitus (26.5%), chronic lung disease (25.1%), renal disease (14.5%),

Table 1. Clinical characteristics of bamlanivimab and control cohorts

	Before matching			After matching		
Clinical covariate	Bamlanivimab cohort (*n* = 2436)	Control cohort (*n* = 28,230)	Standardized difference	Bamlanivimab cohort (*n* = 2335)	Control cohort (*n* = 2335)	Standardized difference
Age (yr)						
Median	64	44		63	63	
IQR	(52, 72)	(30, 57)		(52, 72)	(52, 71)	
<65 years old	1274 (52.3%)	24,566 (87.0%)	0.99	1,230 (52.7%)	1274 (54.6%)	0.04
65–75 years old	734 (30.1%)	2347 (8.3%)	0.74	716 (30.7%)	662 (28.4%)	0.05
>75 years old	428 (17.6%)	1317 (4.7%)	0.56	389 (16.7%)	399 (17.1%)	0.01
Sex						
Female	1201 (49.3%)	14,476 (51.3%)	0.04	1,152 (49.3%)	1,154 (49.4%)	0.00
Male	1235 (50.7%)	13,746 (48.7%)	0.04	1,183 (50.7%)	1,181 (50.6%)	0.00
Race						
Native American	4 (0.2%)	115 (0.4%)	0.04	4 (0.2%)	5 (0.2%)	0.01
Asian	37 (1.5%)	633 (2.2%)	0.05	36 (1.5%)	37 (1.6%)	0
Black/African American	49 (2.0%)	761 (2.7%)	0.04	48 (2.1%)	55 (2.4%)	0.02
White/Caucasian	2270 (93.2%)	23,302 (82.5%)	0.29	2174 (93.1%)	2164 (92.7%)	0.02
Other[A]	56 (2.3%)	1091 (3.9%)	0.08	53 (2.3%)	64 (2.7%)	0.03
Unknown	20 (0.8%)	2328 (8.2%)	0.28	20 (0.9%)	10 (0.4%)	0.05
Ethnicity						
Hispanic	121 (5.0%)	1969 (7.0%)	0.08	114 (4.9%)	118 (5.1%)	0.01
Non-Hispanic	2270 (93.2%)	23,359 (82.7%)	0.28	2176 (93.2%)	2192 (93.9%)	0.03
Unknown	45 (1.8%)	2,902 (10.3%)	0.29	45.0 (1.9%)	25.0 (1.1%)	0.07
BMI (kg/m^2)						
Underweight (<18.5)	7 (0.3%)	116 (0.4%)	0.02	6 (0.3%)	10 (0.4%)	0.03
Normal weight (18.5 to <25)	245 (10.1%)	3011 (10.7%)	0.02	241 (10.3%)	246 (10.5%)	0.01
Overweight (25 to <30)	504 (20.7%)	4154 (14.7%)	0.17	488 (20.9%)	476 (20.4%)	0.01
Obese, class 1 (30 to <35)	419 (17.2%)	3330 (11.8%)	0.17	410 (17.6%)	456 (19.5%)	0.05
Obese, class 2 (35 to <40)	383 (15.7%)	1552 (5.5%)	0.42	357 (15.3%)	379 (16.2%)	0.03
Obese, class 3 (≥40)	443 (18.2%)	1208 (4.3%)	0.62	399 (17.1%)	380 (16.3%)	0.02
Unknown	435 (17.9%)	14,859 (52.6%)	0.71	434 (18.6%)	388 (16.6%)	0.05
Comorbidity						
Hypertension	1353 (55.5%)	4878 (17.3%)	0.98	1265 (54.2%)	1286 (55.1%)	0.02
Chronic pulmonary disease	635 (26.1%)	3085 (10.9%)	0.47	585 (25.1%)	572 (24.5%)	0.01
Diabetes mellitus without complications	381 (15.6%)	1034 (3.7%)	0.58	352 (15.1%)	345 (14.8%)	0.01
Cancer (local)	375 (15.4%)	1062 (3.8%)	0.56	342 (14.6%)	337 (14.4%)	0.01
Peripheral vascular disease	372 (15.3%)	1138 (4.0%)	0.52	341 (14.6%)	301 (12.9%)	0.05
Renal disease	369 (15.1%)	1027 (3.6%)	0.56	339 (14.5%)	280 (12.0%)	0.07
Diabetes mellitus with complications	295 (12.1%)	694 (2.5%)	0.55	267 (11.4%)	213 (9.1%)	0.08
Liver disease (mild)	255 (10.5%)	911 (3.2%)	0.38	230 (9.9%)	204 (8.7%)	0.04
Congestive heart failure	248 (10.2%)	707 (2.5%)	0.45	219 (9.4%)	166 (7.1%)	0.08
Cerebrovascular disease	223 (9.2%)	759 (2.7%)	0.37	209 (9.0%)	167 (7.2%)	0.07
Myocardial infarction	149 (6.1%)	434 (1.5%)	0.34	134 (5.7%)	88 (3.8%)	0.09
Connective tissue disease	144 (5.9%)	406 (1.4%)	0.34	133 (5.7%)	123 (5.3%)	0.02
Cancer (metastatic)	73 (3.0%)	263 (0.9%)	0.2	67 (2.9%)	70 (3.0%)	0.01
Liver disease (moderate/severe)	19 (0.8%)	91 (0.3%)	0.08	18 (0.8%)	17 (0.7%)	0
HIV/AIDS	6 (0.2%)	17 (0.1%)	0.07	5 (0.2%)	3 (0.1%)	0.02
Immunosuppressant use	165 (6.8%)	354 (1.3%)	0.98	143 (6.1%)	116 (5.0%)	0.05
Time from PCR date to infusion (days)						
Mean	2.8			2.8		
Median (range)	2.0 (0,10)			2.0 (0,10)		

[A]Other race categories include the following: Samoan, Guamanian or Chamorro, Native Hawaiian/Pacific Islander, other Pacific Islander, unable to provide, and other.

Table 2. Hospitalizations, ICU admissions, and mortality for bamlanivimab-treated and untreated control cohort

Outcome	Bamlanivimab (*n* = 2335)	Control (*n* = 2335)	Risk difference (95% CI)	Risk ratio (95% CI)	Fisher's exact *P* value[A]	log-rank *P* value
Number of patients with follow-up data						
14 day	2126	2145				
21 day	1983	1989				
28 day	1789	1832				
Hospitalizations						
14 day	31/2126 (1.5%)	76/2145 (3.5%)	2.1% (1.2%, 3%)	0.41 (0.28, 0.63)	<0.001	<0.001
21 day	38/1983 (1.9%)	77/1989 (3.9%)	2% (0.91%, 3%)	0.49 (0.34, 0.73)	<0.001	
28 day	44/1789 (2.5%)	72/1832 (3.9%)	1.5%(0.33%, 2.6%)	0.63 (0.44, 0.91)	0.01	
ICU admissions						
14 day	3 (0.14%)	22 (1%)	0.88% (0.43%, 1.3%)	0.14 (0.05, 0.48)	<0.001	0.06
21 day	5 (0.25%)	20 (1%)	0.75% (0.26%, 1.2%)	0.25 (0.11, 0.69)	0.004	
28 day	10 (0.56%)	20 (1.1%)	0.53% (−0.055%, 1.1%)	0.51 (0.25, 1.10)	0.10	
Mortality						
14 day	0 (0%)	7 (0.33%)	0.33% (0.085%, 0.57%)	0.00 (0.00, 1.18)	0.02	0.06
21 day	1 (0.05%)	8 (0.4%)	0.35% (0.057%, 0.65%)	0.13 (0.03, 1.00)	0.04	
28 day	2 (0.11%)	8 (0.44%)	0.32% (−0.014%, 0.66%)	0.26 (0.07, 1.23)	0.11	

[A]*P* values for the null hypothesis that the odds ratio is 1.

malignancy (16.6%), peripheral vascular disease (14.6%), liver disease (9.6%), congestive heart failure (9.0%), and immunosuppressive drug use (6.1%).

Primary outcome

All-cause hospitalization. All-cause hospitalization rates were significantly lower in the bamlanivimab group than the propensity-matched cohort at days 14 (1.5% vs. 3.5% [difference, 2.1%; 95% CI: 1.2%–3.0%]; risk ratio [RR], 0.41; 95% CI, 0.28–0.63), 21 (1.9% vs. 3.9% [difference, 2.0%; 95% CI, 0.91%–3.0%]; RR, 0.49; 95% CI, 0.34–0.73), and 28 (2.5% vs. 3.9% [difference, 1.5%; 95% CI, 0.33%–2.6%]; RR, 0.63; 95% CI, 0.44–0.91) (Table 2). Bamlanivimab-treated patients had significantly more hospitalization-free days at all time points compared with the propensity-matched cohort (Table 3). Kaplan-Meier survival analysis showed significant separation in rates of hospitalization-free survival between the bamlanivimab-treated and propensity-matched controls (log-rank test $P = 0.01$; Figure 2).

Secondary outcomes

Intensive care unit admissions. All-cause intensive care unit (ICU) admission rates were lower in bamlanivimab-treated patients compared with the propensity-matched cohort at days 14 (0.14% vs. 1% [difference, 0.88%; 95% CI, 0.43%–1.3%]; RR, 0.14; 95% CI, 0.05–0.48), 21 (0.25% vs. 1% [difference, 0.75%; 95% CI, 0.26%–1.2%]; RR, 0.25; 95% CI, 0.11–0.69), and 28 (0.56% vs. 1.1% [difference, 0.53%; 95% CI, −0.06%–1.1%]; RR, 0.51; 95% CI, 0.25–1.10) (Table 2). Bamlanivimab-treated patients had significantly more ICU-free days at days 14 and 21 compared with the propensity-matched cohort (Table 3). Ventilator days were similar between the 2 cohorts, with mechanical ventilation required in 1 of 10 ICU-admitted patients in the bamlanivimab group and 2 of 19 ICU-admitted patients in the control group.

Survival. Patients treated with bamlanivimab had lower all-cause mortality compared with the propensity-matched cohort at days 14 (0% vs. 0.33% [difference, 0.33%; 95% CI, 0.09%–1.1%]; RR,0.00; 95% CI, 0.00–1.18), 21 (0.05% vs. 0.4% [dif-

Table 3. Hospitalization-free days and ICU-free days for bamlanivimab-treated vs. untreated control group

Outcome	Bamlanivimab (*n* = 2335)		Control (*n* = 2335)		Absolute difference (95% CI)	Mann-Whitney *P* value	Two-way mixed ANOVA *P* value
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)			
Hospital-free days							
14 day	13.9 (0.6)	14 (14, 14)	13.8 (1.3)	14 (14, 14)	0.1 (0.1, 0.2)	<0.001	0.01
21 day	20.9 (0.8)	21 (21, 21)	20.7 (1.8)	21 (21, 21)	0.2 (0.1, 0.3)	<0.001	
28 day	27.9 (0.9)	28 (28,28)	27.7 (2.3)	28 (28,28)	0.2 (0.1, 0.3)	0.01	
ICU-free days							
14 day	14.0 (0.1)	14 (14, 14)	13.9 (0.6)	14 (14, 14)	0.1 (0.0, 0.1)	<0.001	0.005
21 day	21.0 (0.1)	21 (21, 21)	20.9 (1.1)	21 (21, 21)	0.1 (0.0, 0.1)	0.003	
28 day	28.0 (0.2)	28 (28,28)	27.9 (1.6)	28 (28,28)	0.1 (0.1, 0.2)	0.07	

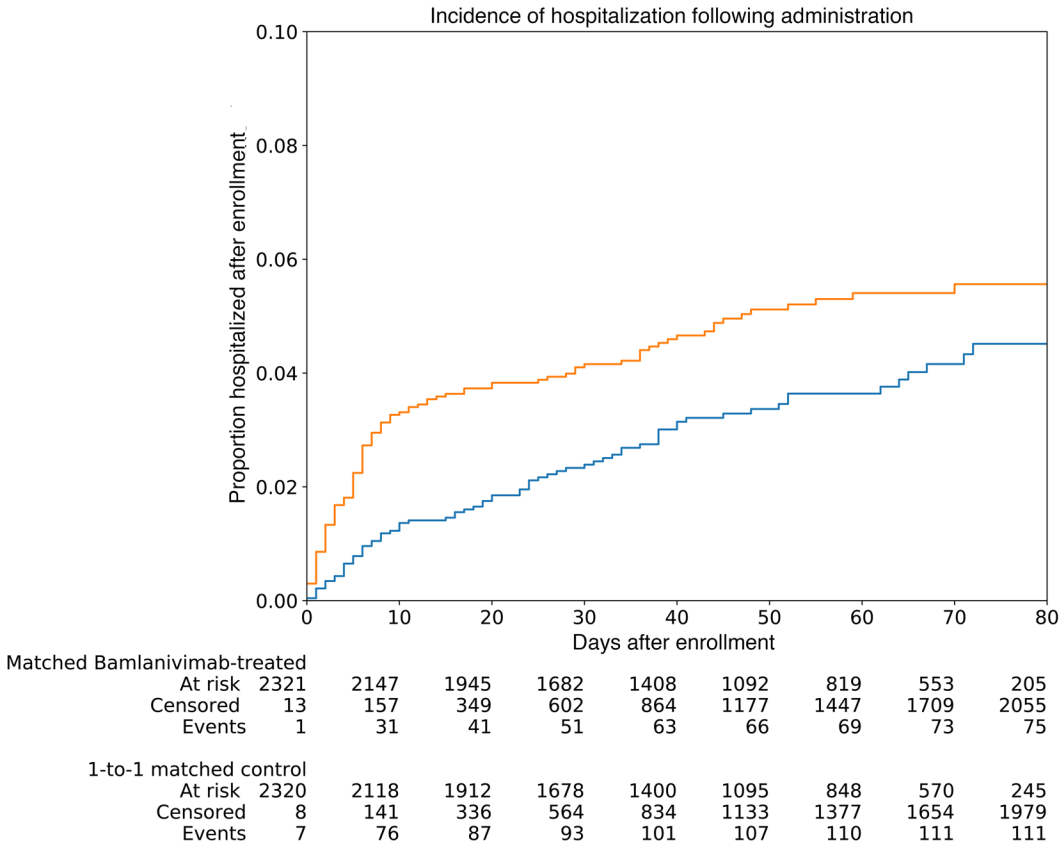

Figure 2. Cumulative incidence of hospitalization over time in bamlanivimab-treated and propensity-matched untreated control population. Bamlanivimab cohort median observed follow-up time = 27.0 days, IQR = (48.0, 70.0); 1-to-1 matched control median observed time = 28.0 days, IQR = (47.0, 70.0). Orange line, untreated matched controls; blue line, bamlanivimab-treated patients.

ference, 0.35%, 95% CI, 0.06%–0.65%]; RR,0.13; 95% CI, 0.03–1.00), and 28 (0.11% vs. 0.44% [difference, 0.32%, 95% CI, 0.01%–0.66%]; RR, 0.26; 95% CI, 0.07–1.23). Only 2 bamlanivimab-treated patients (among 1789 patients with at least 28 days of follow-up) died, on days 20 and 25, of causes unrelated to COVID-19. In the untreated cohort, 7 of 8 deaths were attributable to COVID-19.

Sensitivity analyses

Falsification outcome. Supplemental Table 5 shows the results comparing the negative outcomes in the original and propensity-matched cohorts. Prior to matching, the difference in cancer screening rates between the treated and untreated cohorts was statistically significant (Fisher's exact test, $P = 0.002$), but after matching, the difference in rates was not statistically significant (Fisher's exact test, $P = 0.67$). In addition, in both cases, the difference in rates was not statistically significant after controlling for residual confounding factors via logistic regression. This demonstrated that the matching procedure was effective in controlling for potential confounding factors that may lead the treated or untreated cohorts to be enriched for non–COVID-19–related end points.

Intention-to-treat sensitivity analysis. There were 183 additional patients with cancelled orders for bamlanivimab included in the intended-to-treat analysis. After 1:1 propensity matching, there were 2509 patients in the bamlanivimab intended-to-treat cohort and 2509 patients in the control cohort. Supplemental Table 6 shows the results comparing the hospitalization, ICU admission, and mortality outcomes of these cohorts. The 14-day and 21-day outcomes for hospitalization and ICU admission remained statistically significant for this comparison. These results suggested that it is unlikely that treatment cancellation bias has strongly influenced the study findings.

Adverse events

Adverse events were reported in 19 patients, with fever and chills ($n = 6$), nausea and vomiting ($n = 5$), and lightheadedness ($n = 3$) being most common. Rash, chest pain, confusion, weakness (2 each) and diarrhea, headache, cough, facial swelling, and dyspnea (1 each) were also observed. No one had anaphylaxis. All adverse events were mild and did not require hospitalization.

Impact of therapy

Based on this study, it is estimated that, in the first 28 days of follow-up of 1789 patients, there were 358 hospital days, 179 ICU days, and 6 lives saved.

Discussion

This retrospective study shows that bamlanivimab monotherapy was associated with a statistically significant ($P = 0.01$) decrease in

the rate of all-cause hospitalization at 28 days after infusion, with greater effects demonstrated at 14 and 21 days. Our findings are consistent with the emerging real-world data from other centers describing the clinical benefit of antispike neutralizing antibodies in patients with mild to moderate COVID-19 (12–14).

Among high-risk patients 65 years and older and those with BMI greater than or equal to 35 who participated in the phase 2 randomized clinical trial, the rate of hospitalization and medically attended visit was 4% among bamlanivimab-treated patients compared with 15% among those who received placebo (6). Our reported rates in this study are numerically lower, especially among the untreated propensity-matched control group (6). This difference could have been due to the different time point of enrollment, as the current cohort represents a contemporary population among whom the care of COVID-19 patients has improved. The lower rate of hospitalization in the untreated cohort lessened the anticipated magnitude of impact of bamlanivimab therapy. Nonetheless, this study observed that bamlanivimab was markedly associated with reduction in all-cause hospitalizations, by 57% at day 14 and 31% by day 28. In a separate initial analysis, patients who accepted antispike monoclonal antibody therapy had lower hospitalization rates when compared with those who declined the offer for treatment. However, the initial study observed significant differences in sociodemographic and medical comorbidities between the treated and untreated populations (12). Thus, rigorous propensity matching is essential in assessing efficacy outcomes of neutralizing monoclonal antibodies outside of randomized controlled trials.

This study suggests that bamlanivimab-treated patients were less likely to progress to critical illness; this is supported by the lower rates of ICU admission and mortality, notable in a cohort that included only the high-risk population (16, 17). By virtue of the strict FDA EUA criteria, 100% of the bamlanivimab-treated population had at least 1 risk factor for progression to severe COVID-19 (6). Furthermore, our patient population contained patients with transient nonsustained SpO_2 of 93% on room air, a population who would have been excluded from the BLAZE-1 trial (6). As prior studies have suggested that patients with medical comorbidities are at higher risk of severe and critical illness, early treatment with bamlanivimab may have mitigated this progression (11, 18, 19).

Due to the evolution of SARS-CoV-2 variants, bamlanivimab is no longer authorized for use as monotherapy. Despite this, the results of this study, which showed the real-world efficacy of bamlanivimab monotherapy in the prevention of hospital admission and other serious clinical outcomes, provides proof of concept that treatment with neutralizing antibodies is an effective strategy for mitigating the current COVID-19 pandemic. The observations in this study could serve as a model that may be translatable to the use of other monoclonal antibody combination therapies that are still available.

Limitations. This study has several limitations. First, this was an observational cohort study, which precludes the causal inference that can result from a randomized clinical trial. However, performing a randomized trial was not feasible due to the ethical implications of withholding a drug authorized for emergency use in the treatment of high-risk patients. Propensity score matching was performed in an attempt to reduce confounding bias. Furthermore, two sensitivity analyses demonstrated that the matching procedure was effective in controlling for potential confounding variables. Second, this study had a retrospective design and may not have captured all the clinical outcomes of patients who may have received subsequent care in other institutions. This limitation is mitigated by the extensive outpatient remote monitoring and follow-up program (17). Also, only patients with documented follow-up were included in the analysis of outcomes at days 14, 21, and 28. Third, this study focused on bamlanivimab monotherapy and did not include patients who received casirivimab and imdevimab or bamlanivimab and etesevimab combination therapy. The clinical outcomes reported here therefore only apply to one specific monoclonal antibody, for which the EUA has been revoked secondary to resistance patterns of emerging SARS-CoV-2 variants in the community (5). Fourth, the study population was predominantly White, and further studies will need to be performed to validate the findings in other populations. Fifth, the outcomes data were derived from a single multisite healthcare system that proactively screened and obtained consent from eligible patients, leading to rapid infusion of monoclonal antibody, and thus, the results may not be generalizable to other systems with different practices. Sixth, despite the large patient population and the statistical significance, the magnitude of some findings is small. In particular, the differences in ICU-free and hospitalization-free days are small when considered at the patient level. However, this small difference can be magnified when considered at the larger population level.

Conclusions. Among high-risk patients with mild to moderate COVID-19, treatment with bamlanivimab compared with usual care was associated with a statistically significant ($P = 0.01$) lower rate of hospitalization at 28 days. A marked decrease was observed in the rates of ICU admissions and mortality. While bamlanivimab monotherapy is no longer authorized, the observations in this study provide proof that treatment with neutralizing antibodies is effective clinically in reducing hospitalization, ICU admission, and mortality in patients with mild to moderate COVID-19.

Methods

Monoclonal antibody treatment program. The Mayo Clinic Monoclonal Antibody Treatment (MATRx) program was established on November 7, 2020, and the first patients were infused with bamlanivimab (700 mg intravenously as a single dose over an hour) on November 19, 2020. The details of this program have been reported (7). A multidisciplinary team reviewed all patients 18 years old or older identified from an electronic registry of positive SARS-CoV-2 PCR tests and self- and clinician-referred patients. Under the EUA existing at the time, adult patients were eligible for bamlanivimab if they had mild to moderate COVID-19, were within 10 days of symptom onset, and met at least 1 of the following criteria: age of 65 years or older, BMI of 35 or higher, diabetes, chronic kidney disease, immunosuppressive medication use, or an immunocompromising condition. Patients 55 years and older qualified if they had hypertension, cardiovascular disease, or chronic lung disease. Pediatric patients 11 to 17 years old were eligible for treatment based on a separate EUA criteria and are not included in this study. The MATRx team members attempted to contact eligible patients for education and consent.

Study design and participants. The study enrolled adult (≥18 years old) patients identified from the Mayo Clinic electronic health record (EHR) database with positive SARS-CoV-2 PCR tests between November 12, 2020, and February 17, 2021. The start date, November 12, 2020, was selected as it was the earliest test date for a patient who was infused with bamlanivimab monotherapy. The study end date was selected as the most recent date with data available. The participant selection algorithm (Figure 1) resulted in 2 cohorts balanced for relevant demographic and clinical covariates: (a) treated patients who received bamlanivimab infusion and (b) control patients who did not receive bamlanivimab after COVID-19 diagnosis.

Participant selection and propensity score matching. The study population was selected from the pool of adult patients with COVID-19 who met the following criteria: (a) had not received casirivimab and imdevimab at any time during the study period, (b) did not have a cancelled bamlanivimab order, (c) were not on hospice or comfort care, (d) did not have do-not-intubate (DNI), do-not-resuscitate (DNR), or do-not-hospitalize (DNH) status, (e) had minimum SpO_2 of 93% or more, and (f) were not currently hospitalized at the time of positive PCR test or bamlanivimab infusion. For each patient in the treated cohort, the enrollment date was defined as the date of bamlanivimab infusion. A histogram of infusion dates relative to PCR diagnosis dates is provided in Supplemental Figure 1.

Propensity score matching was performed to select matched controls balanced on covariates that may influence bamlanivimab administration (Table 1 and ref. 20). Propensity scores were computed for each patient by fitting an L1-regularized logistic regression model to predict which of the 2 cohorts the patient was in, as a function of the covariates detailed in the next section (21). To identify a matched control for each treated patient, a set of control patients with the same age (±5 years) and PCR diagnosis date (±7 days) was considered, and the patient with the closest propensity score was selected if the propensity score difference was less than the selected threshold. If the control patient (a) had a minimum SpO_2 of less than 93%, (b) was hospitalized, (c) had active DNR, DNI, or DNH status, (d) was receiving only palliative or comfort care, or (e) was deceased on or before the date of study enrollment, then a new control patient (the next nearest neighbor by propensity score) was selected. This process was repeated until an eligible match was found. If an eligible match was not found, the search was expanded to the set of control patients with age ±5 years and PCR diagnosis dates ±14 days relative to the bamlanivimab patient. If the expanded search did not find any control patients, the bamlanivimab-treated patient was dropped from the analysis. The caliper threshold was set to 0.1× pooled SD of the propensity scores in the logit space. For each control patient, the study enrollment date was defined based on the number of days between the positive PCR test and bamlanivimab infusion for the matched treated patient (Supplemental Figure 2 and refs. 22, 23).

Demographic and clinical covariates. To perform propensity matching described above, demographic and clinical covariates that could influence the likelihood of bamlanivimab administration were considered (Table 1). Demographic covariates considered included age, sex, race, and ethnicity. Race and ethnicity were determined based on patient-entered responses to multiple choice questions with fixed categories and were considered in this study in order to control for social determinants of health and other potential confounding factors. Clinical covariates were derived from the Charlson Comorbidity Index (https://www.mdcalc.com/charlson-comorbidity-index-cci) and were identified for each patient on the basis of ICD-9 and ICD-10 codes recorded in the 5 years prior to the SARS-CoV-2 PCR testing date (Supplemental Table 1).

Other covariates considered during the propensity score matching included hypertension, BMI, immunosuppressive medication usage, and location of infusion. Hypertension status was determined using ICD-10 codes recorded in the 5 years prior to the PCR testing date (Supplemental Table 1). BMI was calculated using most recently recorded weight (between 1 year before and 1 week after COVID-19 diagnosis) and height (between age 18 and 1 week after COVID-19 diagnosis). Immunosuppressive medication usage was determined using medication orders active or completed in the year prior to the PCR testing date up to the end of the study period (Supplemental Table 4). This study included participants from 4 major sites: Scottsdale, Arizona; Jacksonville, Florida; Rochester, Minnesota; and other Mayo Clinic Health Systems sites. Location of infusion was incorporated into the covariate balancing analysis post hoc. Due to the small number of sites, this variable was modeled as a fixed effect (24).

Outcomes. The clinical outcomes that were assessed between the bamlanivimab-treated and control cohorts at days 14, 21, and 28 after study enrollment were rates of hospitalization, ICU admission, and death and number of hospital- and ICU-free days (hospital-free and ICU-free days were defined as the number of days the patient was alive and outside the hospital and ICU, respectively). Hospitalization rate was the primary outcome of interest. To determine the outcome for each cohort, only patients with sufficient follow-up data relative to the end study date (February 17, 2021) were considered. For example, to determine the 14-day outcomes for each cohort, only patients with enrollment dates on or prior to February 3, 2021, were included.

Statistics. Prior to the statistical analysis, missing values were imputed. Among all of the covariates, the only ones with missing data were race (0.8%), ethnicity (1.8%), and BMI (17.9%; see Table 1). For covariates with missing data, the missing values were categorized as unknown.

The effectiveness of covariate balancing between bamlanivimab-treated and control cohort was assessed using the standardized difference (22, 23). To compare the rates of hospitalization, ICU admission, and death at the defined time points after study enrollment, the percentage of patients positive for each outcome relative to the total number of patients with follow-up in each cohort was calculated. For each of these outcome variables, risk ratios as well as Fisher's exact test *P* values were computed from the percentage of patients positive for each outcome. In addition, 95% CIs for the risk ratios were computed using the Δ method approximation. The logistic regression models to compute the propensity scores were implemented using the statsmodels package (version 0.10.0) in Python (25). To test the robustness of study findings, post hoc negative outcome and intention-to-treat sensitivity analyses were conducted, as described below.

In order to account for death as a competing risk for the hospitalization and ICU outcome measures, we also considered hospital-free and ICU-free days alive as outcome variables. To compare hospital-free and ICU-free days at the defined time points after study enrollment, the mean number of hospital-free and ICU-free days among patients with follow-up were calculated for each cohort, along with their 95% CI. The differences in means (95% CI)

were calculated, and significance was assessed with a Mann-Whitney *U* test. Because of the potential for type 1 error due to multiple comparisons, analysis of the secondary outcomes should be interpreted as exploratory. For each of the statistical tests, a 2-sided *P* value of less than 0.05 was considered statistically significant. Analysis was performed with the aid of the scipy package (version 0.25.6) in Python (26).

Hospitalization-free survival was also assessed at daily intervals with a Kaplan-Meier analysis and a corresponding log-rank test. Specifically, the proportions of patients in each cohort (among those with follow-up) who were not hospitalized on each day after study enrollment were compared (Supplemental Table 3 and Figure 2). Survival analysis was performed using the lifelines package (version 0.25.6) in Python (27).

Post hoc statistical tests were done to account for the fact that the end points were measured at multiple time points. For each of the survival-type outcomes (hospital admission, ICU admission, and mortality), the *P* values from 28-day capped log-rank tests between the propensity matched cohorts were reported. These tests are used to assess whether or not the hospital admission rates, ICU admission rates, and mortality rates were significantly different between the matched cohorts within the 28 day follow-up period. The log-rank tests were performed using the lifelines (version 0.25.6) package in Python. For each of the numeric outcomes (number of hospital-free days and number of ICU-free days), we report *P* values from 2-way mixed ANOVA tests, using treatment (bamlanivimab or control) as the between-subjects factor and time point (14, 21, or 28 days) as the within-subjects factor (28). Mixed ANOVA tests were performed using the pingouin (version 0.3.11) package in Python, with the Greenhouse-Geisser correction applied afterwards to adjust for violations of the sphericity assumption.

Sensitivity analysis. Two post hoc sensitivity analyses were performed to test the robustness of the findings. First, in order to test the sensitivity of the study findings to potential unobserved confounding variables, the statistical analysis was repeated on a negative outcome suspected to be unrelated to COVID-19 disease or treatment. For this post hoc sensitivity analysis, cancer screening was considered as the negative outcome. In particular, the negative outcome was defined as +1 for patients with an ICD-10 diagnostic code for cancer screening (Z12.*) 15 to 42 days following their PCR diagnosis date and 0 otherwise. Patients with PCR diagnosis dates after February 8, 2021, were excluded from this sensitivity analysis due to lack of 42-day follow-up data.

Second, an intention-to-treat sensitivity analysis was conducted to compare the outcomes between all patients who received an order for bamlanivimab versus the control group. In this analysis, all patients with cancelled orders for bamlanivimab were considered in addition to the bamlanivimab-treated patients, subjected to the same inclusion criteria. For each of the patients with cancelled bamlanivimab orders, the relative infusion dates were randomly sampled from the distribution of relative infusion dates for the actual bamlanivimab-treated cohort, ensuring that the infusion dates were within the study period. A 1:1 propensity matching was performed between the bamlanivimab intended-to-treat cohort and the control cohort, following the same procedure as in the primary analysis. The rates of hospitalization, ICU admission, and mortality for the matched cohorts were compared for the 14-, 21-, and 28-day time horizons.

Study approval. This retrospective study was approved by the Mayo Clinic Institutional Review Board. Informed consent was waived and patients without research authorization were excluded.

Author contributions

RG, CFP, and RRR conceived and designed the study. CFP, PJL, AP, AJV, JCO, RG, ADB, and RRR acquired, analyzed, or interpreted data. RG, CFP, and RRR drafted the manuscript. All authors critically revised the manuscript. CFP, PJL, AP, AJV, JCO, RG, and RRR performed statistical analysis. SJB, JJL, MDB, ADB, and DMB provided administrative, technical, or material support. RO, LLS, SMTS, CGW, SNH, DMB, RG, LLA, RFA, AH, and RRR supervised the project.

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