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ORIGINAL RESEARCH ARTICLE

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Bamlanivimab use in mild-to-moderate COVID-19 disease: A matched cohort design

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Abstract

Study Objective: Our objective was to determine if bamlanivimab (LY-CoV555; BAM), a monoclonal antibody for mild-to-moderate Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-Co-V-2, prevented emergency department (ED) visits, hospitalizations for SARS-CoV-2, or death within 60 days of a positive SARS-CoV-2 viral test.

Design: Patient propensity matching was performed for BAM administration to get two discrete groups of patients; those who received BAM (N = 117) and those who did not (N = 117).

Setting: Outpatients (N = 2107) eligible to receive BAM from November 1 to December 31, 2020, were identified.

Patients: A total of 144 of 2107 patients with mild-to-moderate SARS-CoV-2 received BAM

Intervention: Eligible patients had mild-to-moderate SARS-CoV-2 disease, a positive SARS-CoV-2 test, and risk factor(s) for progression to severe SARS-CoV-2 infection. All patients were reviewed for subsequent ED visits, subsequent hospitalization, and death.

Measurements and Main Results: Patients (N = 234) were matched, 117 in each group. Median (interquartile range) age was 72 (65–80) years. Forty-seven percent of patients were male. Twenty-one patients who received BAM were subsequently seen in the ED compared to 34 untreated patients (18.0% vs. 29.1%; $p = 0.045$). Fourteen BAM-treated patients were subsequently hospitalized post-BAM infusion compared to 27 untreated patients (12.0% vs. 23.1%; $p = 0.025$). Finally, there were no mortalities in the BAM group, however, eleven patients in the untreated group died (0.0% vs. 9.4%; $p < 0.001$). The number needed to treat (NNT) is 11 patients to prevent one mortality event.

Conclusions: BAM infusion for mild-to-moderate SARS-CoV-2 infection in outpatients significantly prevented subsequent ED visits, hospitalizations, and death from SARS-CoV-2.

KEYWORDS
Bamlanivimab, emergency room, hospitalization, mortality, SARS-CoV-2 infection

1 | INTRODUCTION

The United States Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) to permit the administration of the unapproved product, bamlanivimab (LY-CoV555; BAM) for the treatment of mild-to-moderate severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) in adults and pediatric patients with a positive result of a SARS-CoV-2 viral test. Eligible patients must be over 12 years of age, weigh a minimum of 40 kg, and be at high risk for progressing to severe COVID-19 disease and/or hospitalization. Bamlanivimab is a recombinant neutralizing human IgG1K monoclonal antibody that binds to the receptor-binding domain of the spike protein of SARS-CoV-2 and prevents the attachment of spike protein with the human angiotensin-converting enzyme-2 ACE2 receptor.[1] Benefit of treatment with this monoclonal antibody is to prevent hospitalization associated with COVID-19 viral illness; however, this remains unproven. Monoclonal antibodies are most effective when given early in infection.[2–4] The BLAZE-1 study reported SARS-CoV-2 viral load reductions at day 11 post-infusion of three escalating doses of BAM or one dose of the combination of BAM and etesevimab in a phase 2/3 clinical trial.[5] In the BLAZE-1 trial, a significant difference in the secondary endpoint that evaluated reduction in hospitalizations was found to be associated with combination treatment compared with placebo. High risk for progression and/or hospitalization was defined as having a minimum of one criterion from the following: a body mass index (BMI) ≥ 35; chronic kidney disease; diabetes; immunosuppressive illness; receiving immunosuppressive therapy; or age ≥55 years.

Our healthcare system had to surge COVID-19 cases and sought to determine if BAM treatment in patients with mild-to-moderate COVID-19 and risk factors for progression to severe infection impacted whether the patient subsequently required medical care through the Emergency Department (ED), acute hospitalization, or died from COVID-19 infection. We designed a retrospective analysis, which incorporated the review of the first 2 months (November and December 2020) of data from patients who received BAM treatment for outpatient mild-to-moderate SARS-CoV-2. The goal was to determine if this infusion was able to prevent ED utilization, hospitalization, or death from COVID-19 under the EUA.

2 | METHODS

2.1 | Patient selection

All patients had mild-to-moderate SARS-CoV-2 as defined by SARS-CoV-2 signs and symptoms, a positive SARS-CoV-2 test, and were seen as outpatients. Additionally, patients had at least one risk factor for the development of severe COVID-19 infection or hospitalization. Risk factors were defined according to the FDA Fact Sheet for Health Care Providers Emergency Use Authorization (EUA) of Bamlanivimab.[1] A report was generated from the health system electronic medical record of all patients from November 1 to December 31, 2020, who had a positive SARS-CoV-2 PCR test and at least one of the following risk factors: age greater or equal to 65 years, BMI greater than or equal to 35, chronic kidney disease, diabetes, immunosuppressive disease, immunosuppressive treatment, age greater than or equal to 55 years and cardiovascular disease, age greater than or equal to 55 years and hypertension, age greater than or equal to 55 years and chronic respiratory pulmonary disease or other chronic respiratory diseases, or age less than 55 years with sickle cell disease, congenital or acquired heart disease, neurodevelopment disorders, medical-related technological device dependence, asthma, or reactive airway disease. Patients identified in this report were then searched to determine if they received BAM treatment as part of their COVID-19 infection treatment. Exclusion criteria for antibody infusion included hospitalization due to COVID-19; oxygen therapy required due to COVID-19; baseline oxygen flow rate increase due to COVID-19 in those on chronic oxygen therapy due to non-COVID-19-related comorbidity.

2.1.1 | Research ethics

The work described has been carried out in accordance with The Code of Ethics (Declaration of Helsinki) (IRB #2001755). Informed consent was not required from patients given the retrospective nature of the study design.

2.2 | Outcomes of interest

Patients who met eligibility criteria were identified and their electronic medical records (EHR; EPIC) were reviewed to determine if subsequent hospitalization or an ED visit occurred after the date of their antibody infusion specifically for SARS-CoV-2 or within 60 days after the positive SARS-CoV-2 viral test. These data were assimilated for patients who received antibody treatment and for those who did not receive treatment.

2.3 | Propensity matching

Demographic and clinical characteristics of the entire cohort are presented in the Table S1. In the entire cohort, patients who received BAM treatment were older and were more likely to have received immunosuppressive treatment, be older than 55 years and have cardiovascular disease, hypertension, or chronic renal disease, and were also more likely to have acquired or congenital heart disease. Based on these results of the cohort, it was felt that matching BAM and control patients would be appropriate. Patients who received BAM treatment ($n = 144$) were matched to non-treated patients ($n = 1963$) to create two balanced mutually exclusive groups. Propensity scores, defined as the probability of receiving treatment conditional on observed variables of interest, were calculated. Patients with a minimum score of 0.05 with non-missing BMI were

considered eligible for an optimal 1:1 match without replacement.[6–9] The matching algorithm included an exact match of biological sex in conjunction with matching based upon age via Mahalanobis distance for that a pooled covariance matrix was considered.[10] Assessment of post-match balance was conducted by examining standardized differences of reactive airway disease, asthma, technology-dependent, neurodevelopment disability, acquired or congenital heart disease, sickle cell disease, chronic respiratory disease, hypertension, cardiovascular disease, immunosuppressive disease status and treatment, diabetes, chronic kidney disease, calculated risk score, BMI, and age.

2.4 | Statistical analysis

Continuous variables are presented as median and interquartile range (IQR), whereas discrete variables are presented as counts and proportions. Comparisons of patients, contingent upon treatment status, were made with the Mann-Whitney test for continuous variables and the chi-square or Fisher's exact test for discrete variables contingent upon expected frequencies. The subsequent occurrence of a hospitalization or an ED visit for SARS-CoV-2 was modeled with a binary logistic regression model that allowed for the adjustment of immunosuppressive disease treatment. We initially fit models that considered the nesting of patients within each geographic location; however, there were not enough data to obtain convergence. Given the lack of mortality events within the monoclonal antibody infusion group, it was not possible to generate a multivariable model. Instead, a comparison of crude mortality rates is presented, which were calculated alongside exact 95% confidence intervals (CI).

3 | RESULTS

Two thousand, one-hundred and seven eligible patients with positive SARS-CoV-2 test results from November to December 2020 and risk factors for severe disease served as the study population. There was a total of 234 matched patients, 117 who received BAM therapy and 117 control patients who did not. Patient demographics are listed in Table 1. All variables of interest met the criteria of a standardized difference of being less than 0.25 in absolute value except for immunosuppressive disease treatment per Table 2. Further examination showed that the BAM-treated group contained 11 patients receiving immunosuppressive treatment (9.4%), and the control group had two cases of immunosuppressive treatment (1.7%), which was statistically different by Fisher's exact test ($p = 0.019$). Males represented 47% of the study population in both groups.

Regarding subsequent ED visits, 21 patients who received BAM infusion were seen in the ED compared to 34 patients who did not receive BAM (18.0% vs. 29.1%; $p = 0.045$). After adjusting for treatment of immunosuppressive disease, patients who received BAM infusion had a 52.1% reduced odds of an ED visit (95% CI: 8.7% to 74.9%; $p = 0.026$). Fourteen patients had subsequent hospitalizations post-BAM infusion in comparison to 27 patients from the untreated group (12.0% vs. 23.1%; $p = 0.025$). After adjusting for the treatment of immunosuppressive disease, patients who received BAM infusion had a 60.5% decreased odds of hospitalization (95% CI: 16.9% to 81.2%; $p = 0.015$). Finally, there were no mortalities within the BAM infusion group; however, 11 patients within the untreated group died (0.0% vs. 9.4%; $p < 0.001$). The untreated group had a 9.4% (4.8% to 16.2%) mortality rate, whereas the treatment group had a 0.0% (0.0% to 3.1%) mortality rate. The associated number needed to treat (NNT) is 11 patients to prevent one mortality (Table 3).

A total of 27 patients (9 (33%) were male) who received BAM went unmatched. The demographics of these patients demonstrated a median (IQR) age of 46 (40–51) years, and BMI of 41 (34–50), which are substantially different than the overall population that was discussed. Similarly, the overall population included the risk score and hospitalization length. Additionally, the unmatched cohort had a similar comorbid condition percentage as the matched BAM cohort. Eight (29%) of the unmatched patients sought medical attention after the BAM infusion from an ED, and three (11%) were hospitalized. Both outcomes are similar to the overall patient population.

4 | DISCUSSION

Use of monoclonal antibodies for the treatment of mild-to-moderate SARS-CoV-2 has demonstrated efficacy in several clinical trials (BLAZE-1 and -2).[5,11] The FDA subsequently issued an EUA for use of monoclonal antibody therapy to prevent hospitalization secondary to SARS-CoV-2 infection. Based on the experience at our health

TABLE 1 Patient demographics

	Matched patients				
	No BAM treatment		BAM treatment		Standardized difference
	Sample size	Median (IQR)	Sample size	Median (IQR)	
Age (years)	117	72 (65–80)	117	72 (65–80)	0.00
BMI (kg/m^2)	117	29 (27–34)	117	31 (27–37)	<0.25
Risk score	117	5 (3–7)	117	4 (3–7)	−0.13
Hospital length of stay (days)	27	6 (4–19)	14	9 (5–11)	

Abbreviations: BAM, Bamlanivimab; BMI, body mass index; IQR, interquartile range.

TABLE 2 Standardized differences in clinical risk factors for severe SARS-CoV-2 disease

	No BAM treatment		BAM treatment		Standardized difference
	Sample size	Frequency (%)	Sample size	Frequency (%)	
Male	117	55 (47.0)	117	55 (47.0)	0.00
Comorbid conditions					
CKD	117	20 (17.1)	117	21 (18.0)	−0.03
DM	117	21 (18.0)	117	30 (25.6)	−0.18
Immunosuppressive disease	117	2 (1.7)	117	1 (0.9)	0.10
Immunosuppressive treatment	117	2 (1.7)	117	11 (9.4)	−0.32
CV and Age >55 years	117	18 (15.4)	117	22 (18.8)	−0.11
HTN and Age >55 years	117	74 (63.3)	117	81 (69.2)	−0.12
CKD and Age >55 years	117	18 (15.4)	117	12 (10.3)	0.19
Sickle cell disease	117	0 (0.0)	117	0 (0.0)	–
ACQ HD	117	31 (26.5)	117	36 (30.8)	−0.11
Neurodevelopmental disability	117	2 (1.7)	117	1 (0.9)	0.08
Technology-dependent	117	0 (0.0)	117	1 (0.9)	−0.11
Asthma	117	23 (19.7)	117	23 (19.7)	0.00
Reactive Airway Disease	117	3 (2.6)	117	1 (0.9)	0.15

Abbreviations: ACQ HD, acquired or congenital heart disease; BAM, bamlanivimab; CKD, chronic kidney disease; CV, cardiovascular disease; DM, diabetes mellitus; HTN, hypertension.

TABLE 3 Comparison of patient outcomes

	No BAM treatment		BAM treatment		
	Sample size	*N* (%)	Sample size	*N* (%)	*p*-Value
Subsequent Emergency Department Admission	117	34 (29.1)	117	21 (18.0)	0.045
Subsequent Hospitalization	117	27 (23.1)	117	14 (12.0)	0.025
Mortality	117	11 (9.4)	117	0 (0.0)	<0.001

Abbreviation: BAM, Bamlanivimab.

system with surging COVID-19 cases in November to December 2020, there were significant numbers of patients eligible for monoclonal antibody infusion. Our health system devised a plan for approximately 10 infusion centers for monoclonal antibody infusion throughout central-eastern Nebraska and western Iowa. Early in the EUA period, the decision was made to provide BAM infusion to mild-to-moderate SARS-CoV-2 patients meeting criteria that could allow them to progress to severe SARS-CoV-2 and require hospitalization. The goal was to use BAM to prevent SARS-CoV-2 progression and hospitalization. The results of the matched cohort of patients in this study demonstrate that BAM infusion significantly prevented ED visits, hospitalization for SARS-CoV-2, and mortality events secondary to SARS-CoV-2 compared to a control group of patients who did not receive the infusion.

The use of the matched cohort design allows the investigators to optimize the study results as this was not a randomized clinical trial. Using propensity scoring allows us to take a cohort of patients and match them as best as possible to improve the validity of the retrospective nature of the study. Despite this, there are limitations associated with these results. The results from this study provide a real-life assessment of the outcomes that were found from our infusion centers for BAM in our health care system. However, this was not a randomized clinical trial. Further confirmation of these results with a randomized study design is necessary. All patients had evidence of mild-to-moderate SARS-CoV-2 with a positive SARS-CoV-2 viral test and had at least one risk factor for progression to severe SARS-CoV-2 requiring hospitalization. Despite the patients having significant risk factors for progression, some refused the BAM monoclonal antibody infusion. It is unknown if the reason for the refusal was due to lack of knowledge of the mechanism for the monoclonal antibody therapy, or hesitancy for receiving treatment forCOVID-19, as COVID-19 vaccines were in the news, and patients may have been waiting to get the vaccine. Additionally, there were mixed messages as some reports showed that monoclonal antibodies were not working in hospitalized patients.[12] Finally, results of placebo-controlled clinical trials evaluating monoclonal antibody therapy in the treatment of SARS-CoV-2 have yet to be published, possibly

creating hesitancy in clinicians. The goal of the BAM infusion was to prevent hospitalization or ED visits.

Evolving changes in the SARS-CoV-2 spike protein could affect the efficacy of monoclonal antibody therapy.[13] Currently, there has been an evolution in the spike protein with more patients in our area of the United States infected with SARS-CoV-2 (U.K. B.1.1.7 variant). Thus, the combination of BAM and etesevimab or casirivimab and imdevimab will be recommended for patients with mild-to-moderate COVID-19 symptoms and a positive SARS-CoV-2 diagnostic test moving forward. This was not the case in November-December 2020 as SARS-CoV-2 variants were not known to be circulating at that time. Additionally, the FDA EUA states that patients 12 years and older weighing at least 40 kg are eligible to receive the monoclonal antibody infusions from both Lilly and Regeneron. These are important eligibility criteria to remember for younger patients with SARS-CoV-2 infection. Finally, there is emerging efficacy data indicating that the casirivimab and imdevimab antibody cocktail may be able to prevent outbreaks within households, but this evidence has not been peer-reviewed and published yet.[14]

In conclusion, our results demonstrate that BAM infusion significantly prevented ED visits and hospitalizations in SARS-CoV-2 patients with risk factors for progression. Additionally, the NNT of 11 demonstrates that BAM infusion was able to significantly prevent mortality from SARS-CoV-2 infection. These results are similar to or better than other preventive initiatives.[15–19]

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

Collected data and wrote initial draft of manuscript CJD; analyzed data statistically SA; initial idea and edited manuscript DS and LPE; Edited manuscript RV and MT.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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