

# Bamlanivimab Use in a Military Treatment Facility

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## ABSTRACT

### Background:

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of coronavirus disease 2019 (COVID-19), was first identified in 2019 in Wuhan, China, and has rapidly spread across the world. As of April 2021, SARS-CoV-2 has infected more than 140,000,000 and caused more than 3,000,000 deaths globally. In November 2020, the monoclonal antibody bamlanivimab was approved by the FDA for non-hospitalized patients with SARS-CoV-2 (COVID-19) who possessed risk factors for progression to severe COVID-19. This provided a treatment option that may help prevent hospitalization.

### Methods:

Patients who regularly received ambulatory care at a military treatment facility and who were diagnosed with mild-to-moderate COVID-19 and possessed risk factors for progression to severe COVID-19 were treated with a single, intravenous infusion (700 mg) of the virus-neutralizing monoclonal antibody bamlanivimab. The primary outcome was improvement of self-reported symptoms within 24 to 72 hours of receiving the infusion. The secondary outcome was prevention of disease progression requiring emergency department (ED) utilization or hospitalization related to COVID-19 within 30 days of infusion. Bamlanivimab was administered in accordance with the FDA's approval and Defense Health Agency's guidance, including follow-up within 72 hours of administration. Institutional Review Board (IRB) approval was obtained.

### Results:

Of the COVID-19 patients who were given the option of a bamlanivimab infusion, 40 accepted and 6 did not (40/46, 86.9%). Thirty-six of 40 patients in the treatment group were contacted within 72 hours. ED/hospitalization information was available for all 46 patients. In the treatment group, 94.4% (34/36) reported global improvement. Three of 40 (7.5%) patients in the treatment group required inpatient admission, and 2 of 40 patients (5%) required ED evaluation within 30 days of infusion. Therefore, 5 of 40 (12.5%) patients required evaluation shortly after infusion, while 2 of 6 (33.3%) patients who declined treatment required hospital evaluation or admission related to COVID-19 within 30 days of infusion ( $P = .15$ ).

### Conclusions:

Global improvement of symptoms within 24 to 72 hours of infusion was reported by 94.4% of patients receiving bamlanivimab; however, statistical significance could not be determined due to the small sample size and lack of placebo group due to study design. Furthermore, ED visits and hospital admissions were analyzed, but with only six patients in the comparison group, the relative risk was not statistically significant and could not be precisely estimated. In the future, this study can be replicated with both larger control/treatment arms to validate the initial results of this small, retrospective, cohort study.

## INTRODUCTION

Coronavirus disease 2019 (COVID-19) is caused by a highly transmissible virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).<sup>1</sup> A large proportion of patients with COVID-19 experience mild-to-moderate symptoms, with a notable fraction progressing to severe symptoms leading to significant morbidity and mortality.<sup>2,3</sup> Age (>65 years),

pregnancy, immunosuppressive diseases, and a history of lung/cardiac diseases have been associated with higher rates of severe symptoms.<sup>3-5</sup> Until November 2020, there had been no empirical treatments available to patients to prevent progression to severe COVID-19 until the FDA approved the monoclonal antibody bamlanivimab.<sup>6,7</sup> Treatment with monoclonal antibodies such as bamlanivimab may be beneficial to prevent patients at high risk to progress to severe COVID-19.<sup>8,9</sup> By means of the angiotensin-converting enzyme 2 (ACE-2) receptor, SARS-CoV-2 attaches to host cells by the use of a spike protein.<sup>10,11</sup> It has been proposed that monoclonal antibodies have the ability to neutralize the spike protein of SARS-CoV-2 and consequently block attachment to the human ACE-2 receptor and deny host cell entry.<sup>12</sup>

Beneficiaries of a military treatment facility (MTF) who met high-risk criteria were given the option of receiving an infusion of the monoclonal antibody bamlanivimab. We report

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The views expressed are solely those of the authors and do not reflect the official policy or position of the U.S. Army, U.S. Navy, U.S. Air Force, the Department of Defense, or the U.S. Government.

doi:10.1093/milmed/usab188

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a global and symptom improvement for the infused group of patients and compare those treated to the small number of COVID-19 patients who declined infusion on emergency department (ED) visit/hospital admission within 30 days.

**METHODS**

In this retrospective, cohort study at an MTF, patients were given the option to receive an infusion of the virus-neutralizing monoclonal antibody bamlanivimab between December 3, 2020, and January 12, 2021. This MTF provides outpatient and inpatient services to retirees. Patients were required to meet all four of the following inclusion criteria: (1) positive SARS-CoV-2 test result, (2) mild-to-moderate symptoms, (3) duration of symptoms less than 10 days (ideally less than 7 days), and (4) age  $\geq 65$  years or body mass index  $\geq 35$  or age  $\geq 55$  years with one of the following: chronic obstructive pulmonary disease, diabetes mellitus (at least on one medication), chronic kidney disease  $\geq$  Stage III, poorly controlled hypertension, known coronary artery disease or peripheral vascular disease, or immunocompromised or actively receiving immunosuppressive therapy. Patients were infused with a 700-mg dose of bamlanivimab over a 1-hour period in a supervised infusion clinic.

The primary outcome was improvement of self-reported symptoms within 24 to 72 hours of receiving the infusion. The secondary outcome was prevention of disease progression that would require ED utilization or hospitalization related to COVID-19 within 30 days of infusion. Eligible patients who declined bamlanivimab infusion served as the comparison group for the secondary outcome.

During the post-infusion follow-up period (24 to 72 hours), symptoms present before the infusion were confirmed and assessed for improvement or deterioration. The post-infusion follow-up focused on the following symptoms: fever (100.4°F), chills, sinus congestion, cough, dyspnea, fatigue, diarrhea, nausea/vomiting, anosmia, ageusia, myalgia, headache, sore throat, and global improvement in symptoms since receiving bamlanivimab. Additionally, patients were asked if they experienced any side effects from treatment. Patients who declined bamlanivimab infusion were not included in the follow-up protocol due to the lack of a primary event that would be equivalent to the intervention group for the timing of a 24- to 72-hour interval follow-up. A placebo intervention could not be part of the study design.

Continuous variables are summarized with the median and interquartile range. Categorical variables are summarized with counts and percentages. For group comparisons involving continuous variables, the Mann-Whitney U test was used since data seldomly followed a normal distribution. Fisher's Exact Test was used for comparisons involving categorical variables. For each symptom, we report a percent based on those reporting "present before infusion and improving" divided by all those reporting the symptom before infusion. The treatment group was compared to those who declined treatment with respect to ED utilization and hospitalization

**TABLE I.** Patient-Reported Improvement After 24 to 72 Hours of Bamlanivimab Infusion

Symptom	Number of patients who reported symptoms before infusion	Percent of patients who reported improvement of symptoms at 24 to 72 hours compared to those reporting symptoms before infusion
Global improvement	36	94.4
Fever	8	87.5
Sore throat	12	75
Myalgia	15	73.3
Fatigue	30	70.0
Headache	23	69.6
Diarrhea	11	63.6
Nausea/vomiting	11	63.6
Cough	28	53.6
Dyspnea	10	50
Ageusia	10	50
Anosmia	10	50
Chills	10	50
Sinus congestion	18	44

within 30 days. Analyses were conducted using IBM SPSS Statistics 25.0 (IBM, Armonk, NY).

**RESULTS**

Forty-six patients were identified as high-risk candidates who qualified for bamlanivimab infusion. Forty patients accepted treatment, and six patients declined therapy. Thirty-six of 40 treatment patients were contacted within 72 hours post-treatment. The additional four patients that received therapy were lost to follow-up. Table I shows the treatment group's reported improvement of symptoms at 24 to 72 hours compared to those noting the symptom before infusion. Thirty-four of 36 (94.4%) patients reported global improvement. The highest self-reported symptom improvements were for fever (87.5% or 8 of 9 patients), sore throat (75% or 9/12), myalgia (73% or 11/15), and fatigue (70% or 21/30). Other symptom improvements were headache (69.6%); diarrhea (63.6%); nausea/vomiting (63.6%); cough (53.6%); 50% for dyspnea, ageusia, anosmia, and chills; and 44% for sinus congestion. The median time from symptom onset to monoclonal infusion was 4.5 days. The median time from symptom onset to diagnostic testing was 2.5 days. The most common comorbid condition was hypertension (65%) followed by coronary artery disease/peripheral vascular disease (25%), chronic obstructive pulmonary disease/asthma (17.5%), and extreme obesity (17.5%). Table II demonstrates similar demographics between treatment and non-treatment groups with respect to median body mass index, 29.79 and 30.23, respectively. The median age between both groups is 69 years. Although these demographics are similar, the majority of co-variate values such as diabetes, immunocompromised, chronic kidney disease,

**TABLE II.** Demographic and Clinical Characteristics for 46 Patients in Bamlanivimab Infusion Study

Demographic and clinical characteristics	Received infusion (n = 40)	Did not receive infusion (n = 6)
Age—years median	69	69
Age ≥65 years, n (%)	75	50
Gender—male, n (%)	65	50
Body mass index median	29.79	30.23
Body mass index ≥35, n (%)	17.5	16.6
Chronic obstructive pulmonary disease/asthma, n (%)	17.5	16.6
Chronic kidney disease ≥Stage III, n (%)	7.5	0
Coronary artery disease/peripheral vascular disease, n (%)	25	33.3
Immunocompromised, n (%)	2.5	33.3
Hypertension, n (%)	65	50
Diabetes mellitus (HbA1c >7) or on combination therapy, n (%)	10	66.6
Duration from symptoms to PCR—days median	4	n/a
Duration from PCR to infusion—days median	2	n/a

and coronary artery disease could not be matched uniformly between treatment and non-treatment groups, and therefore, confounding bias could not be eliminated.

ED visits/hospital admissions were analyzed between the groups, but with only six patients in the comparison group, the relative risk was not statistically significant and could not be precisely estimated. In the treatment group, 4 of 40 (10%) patients were hospitalized after infusion. Admission diagnoses included generalized weakness with electrolyte derangements, community-acquired pneumonia, and COVID-19. Among the six patients who declined infusion, one was hospitalized and one required ED evaluation (33%;  $P = .35$ ). Expressed differently, the relative risk reduction for an ED visit/hospital admission for those receiving a bamlanivimab infusion was  $0.33 - 0.10 / 0.33 = 0.70$  or 70% (95% CI = -30% to +93%). Thus, the relative risk reduction may not have been affected markedly by these covariates.

No life-threatening adverse events (i.e., anaphylaxis) occurred as a result of the bamlanivimab infusion. One patient experienced post-infusion facial flushing without change in vital signs that resolved without medication. Two patients reported diarrhea as a new symptom during the follow-up window. One patient who was admitted reported perioral numbness and tingling 3 hours after the infusion that self-resolved within 24 hours.

**DISCUSSION**

Although COVID-19 has caused millions of cases and deaths worldwide, there are very few treatments that are effective in blunting disease progression.<sup>8,10</sup> Bamlanivimab is one of the first treatments developed that is proposed to prevent severe

disease in patients at high risk, although limited studies are available to this point. This study was one of only two known projects, as of April 2021, that have been performed monitoring monoclonal antibody use and the COVID-19 virus. This study, in particular, surveyed patient symptoms, while the other published study (the Eli Lilly funded BLAZE-1 trial)<sup>1</sup> identified viral load after bamlanivimab infusion. This study was important to identify whether bamlanivimab and all monoclonal antibody-centered treatments present as effective therapies to improve patient symptoms while also monitoring 30-day hospitalization with these cutting-edge therapies.

Global improvement of symptoms within 24 to 72 hours of infusion was reported by 94.4% of patients receiving bamlanivimab. Prior studies (BLAZE-1 trial)<sup>1</sup> suggest the effect of reducing viral load in early disease can reduce frequency of hospitalization and durable symptom control over time. The patients in this study were identified early during the course of their disease and were provided with treatment very rapidly, as early as 1 day of PCR confirmation. Post-infusion symptom follow-up suggested early and rapid reduction of COVID-19-related symptoms. Unlike other studies, durable response to the infusion was not assessed over time.

Emergency department visits and hospital admissions were analyzed, but with only six patients in the comparison group, the relative risk could not be precisely estimated. The sample size for the two groups, especially in the group who declined therapy, was small, preventing the clinically meaningful relative risk reduction from being determined and statistically significant. Based on the statistical model used, if the sample size was doubled (infusion group = 80 and no infusion group = 14) and the 12.5% and 33.3% rates of ED visit/hospitalization within 30 days remained fixed, then the relative risk reduction for this outcome would have been statistically significant despite the asymmetric sample size.

Qualitative analysis of the admissions in the treatment group provides more granularity and context surrounding their clinical course. One patient was discovered to have concomitant bacterial infection and received guideline-directed therapy. Upon chart review, this patient was not hypoxic and did not require supplemental oxygen, therefore did not meet currently accepted guidelines for initiation of remdesivir and/or dexamethasone as described by the NIH and CDC. Another patient required admission due to generalized weakness, hypokalemia, and hyponatremia approximately 48 hours after infusion. The patient was found to be hypotensive, which was thought to be related to anti-hypertensive medication use and not related to anaphylaxis upon chart review. No indication for epinephrine was documented. The incidence of biphasic/protracted systemic reactions is relatively uncommon and has been mostly described in the context of allergen immunotherapy potentially occurring in patients with low baseline respiratory function and asthma. Biphasic reactions have been reported with monoclonal antibody use in oncology with variable rates. Delayed reactions have been described as mild and present with the same features as an immediate reaction. One patient who declined treatment initially reported

mild symptoms and improvement at the time treatment was offered; however, this patient was admitted for worsening symptoms approximately 14 days after infusion was offered. This particular case suggests progression from mild to severe disease that is congruent with the postulation that increasing viral load is correlated with hospitalization.

No serious adverse events occurred in this study's treatment population. Perioral paresthesia was reported in one patient shortly after infusion and is not currently a known side effect of bamlanivimab. Ultimately, this symptom was self-limiting and resolved within 24 hours. Due to the fact that this patient was also admitted for community-acquired pneumonia, a basic neurologic workup was conducted, which was unremarkable. Of note, two patients reported diarrhea; however, it is unclear if this was a symptom of COVID-19 that had not yet declared itself or a result of the infusion. Diarrhea has been reported in other studies and correlated with progressively higher doses of bamlanivimab. Although there was no placebo group for comparison, a major study found that the safety profile of patients who received the therapy was similar to patients who received placebo. This retrospective study at an MTF provides additional evidence for the efficacy and safety of bamlanivimab for the treatment of patients with mild-to-moderate COVID-19.

This study did have its limitations. It was conducted at a single MTF. Consequently, generalizability to other settings should be done with caution. After the initial use of bamlanivimab at this MTF, additional publications on bamlanivimab have become available. The use of bamlanivimab with etesevimab, but not bamlanivimab monotherapy, has been shown to reduce viral load at 11 days in patients with mild-to-moderate COVID-19.<sup>9</sup> The Infectious Disease Society of America currently suggests the use of bamlanivimab with etesevimab in the ambulatory care setting of mild-to-moderate COVID-19.<sup>13</sup> Although bamlanivimab as monotherapy is no longer suggested as an agent for outpatient therapy for mild-to-moderate COVID-19, the real-world use described in this study demonstrates the tolerability and potential benefits of this therapy.

## CONCLUSIONS

In this small, retrospective cohort study, bamlanivimab infusion has demonstrated that it is a relatively safe treatment option for patients with mild-to-moderate COVID-19 and can be infused in an ambulatory care setting. Patients reported a global symptom improvement within 24 to 72 hours of infusion. This study does not demonstrate a statistically significant reduction in hospital admissions due to the small sample size but would be a potential focus of future investigation

that could inform clinical decision-making and limit disease burden and stress on the current healthcare system.

## ACKNOWLEDGMENT

None declared.

## FUNDING

None declared.

## CONFLICT OF INTEREST STATEMENT

None declared.

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