Real-world Effect of Monoclonal Antibody Treatment in COVID-19 Patients in a Diverse Population in the United States

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Background. Monoclonal antibodies (mAbs) against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are a promising treatment for limiting the progression of coronavirus disease 2019 (COVID-19) and decreasing strain on hospitals. Their use, however, remains limited, particularly in disadvantaged populations.

Methods. Electronic health records were reviewed from SARS-CoV-2 patients at a single medical center in the United States that initiated mAb infusions in January 2021 with the support of the US Department of Health and Human Services’ National Disaster Medical System. Patients who received mAbs were compared with untreated patients from the time period before mAb availability who met eligibility criteria for mAb treatment. We used logistic regression to measure the effect of mAb treatment on the risk of hospitalization or emergency department (ED) visit within 30 days of laboratory-confirmed COVID-19.

Results. Of 598 COVID-19 patients, 270 (45%) received bamlanivimab and 328 (55%) were untreated. Two hundred thirty-one patients (39%) were Hispanic. Among treated patients, 5/270 (1.9%) presented to the ED or required hospitalization within 30 days of a positive SARS-CoV-2 test, compared with 39/328 (12%) untreated patients (P < .001). After adjusting for age, gender, and comorbidities, the risk of ED visit or hospitalization was 82% lower in mAb-treated patients compared with untreated patients (95% CI, 56%–94%).

Conclusions. In this diverse, real-world COVID-19 patient population, mAb treatment significantly decreased the risk of subsequent ED visit or hospitalization. Broader treatment with mAbs, including in disadvantaged patient populations, can decrease the burden on hospitals and should be facilitated in all populations in the United States to ensure health equity.

Keywords. bamlanivimab; COVID-19; emergency response; monoclonal antibody; SARS-CoV-2.

In late 2019, a new respiratory infection was detected in China that alarmed global health experts with its growing incidence and clinical severity [1, 2]. Over the course of a few months, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spread around the world, overwhelming health systems. While a substantial proportion of patients remain asymptomatic [3], coronavirus disease 2019 (COVID-19) can rapidly progress and require hospitalization and intensive care. Severe disease is associated with older age, obesity, and several chronic medical conditions including cardiovascular, kidney, and pulmonary comorbidities [4–7].

As of late January 2021, ~15,000 new COVID-19 hospital admissions were occurring per day in the United States, and hospital bed capacity exceeded 72% [8, 9]. As health care systems continued to approach maximum bed capacity, a critical need for therapeutic interventions to reduce COVID-related hospitalizations emerged. Although therapeutic options for COVID-19 remain limited, monoclonal antibodies (mAbs) that neutralize SARS-CoV-2 are a promising treatment for limiting the progression of disease. Four mAbs are available in the United States through Emergency Use Authorizations (EUAs) by the US Food and Drug Administration (FDA): bamlanivimab monotherapy [10], bamlanivimab in combination with etesevimab [11], and casirivimab in combination with imdevimab [12]. These products are human IgG1 antibodies that neutralize the virus by binding the spike protein of SARS-CoV-2, preventing attachment of the virus to the human cellular receptor angiotensin-converting enzyme 2. A single infusion of bamlanivimab was
recently demonstrated to reduce the risk of hospitalization, emergency department (ED) visits, and death among patients with mild to moderate COVID symptoms in randomized, controlled phase 2/3 trials by >70% [10].

Monoclonal antibodies are underutilized as a treatment for reducing severe disease and could significantly decrease hospitalizations and potentially long-term COVID effects [13]. Utilization can be particularly challenging in racial and ethnic minorities and disadvantaged populations, in whom prevalence of risk factors for COVID-19 progression and death may be higher. A recent review highlights that racial and ethnic minorities are commonly employed in jobs that require in-person presence, increasing exposure to SARS-CoV-2, often face language barriers that limit understanding of public health information, and have poorer access to health care facilities [14]. These factors can delay treatment until patients are in a critical state, which can shorten the therapeutic window for effective mAb receipt or possibly preclude mAb use entirely. Thus, mAb may be particularly underutilized in precisely the populations that would have the greatest benefit, threatening to exacerbate existing health inequities in the United States. Two primary barriers to implementation of mAb infusion therapy at health care facilities are (1) a limited understanding of the necessary resources and processes to mobilize infusion sites and (2) understanding the magnitude of the potential impact of mAb treatment on reducing the severity of disease. We previously addressed the first barrier through a process assessment and improvement analysis [15], demonstrating considerable flexibility in assembling an infusion site and the feasibility of mAb delivery in diverse treatment locations. Here, we aim to determine the extent to which mAb treatment decreases COVID-related hospital admission and ED visits among patients with mild to moderate COVID-19 within 30 days of treatment in the United States.

**METHODS**

We conducted a retrospective cohort study in February 2021 of SARS-CoV-2-positive patients to evaluate the effect of mAb treatment on the risk of a medical visit within 30 days. This study evaluated patients who presented to a single medical center to which the US Department of Health and Human Services’ Assistant Secretary for Preparedness and Response (ASPR) had deployed elements of the National Disaster Medical System (NDMS) to establish an mAb infusion site. This medical center is located in a moderately sized city with a population of ~500,000. The city’s population is 56.4% non-White, with a median household income that is 64% of the US level and a poverty rate of 23.4% [16, 17]. This clinical support activity was conducted as part of the ASPR public health response to the COVID-19 pandemic and at the request of the host institution. Under Department of Health and Human Services (HHS) Office of Health Research Protection guidelines, it was judged to be a nonresearch COVID-19 response [18]. The Johns Hopkins University Applied Physics Laboratory and the medical center concurred with a nonresearch determination.

The target population for this evaluation was patients with positive results of SARS-CoV-2 viral testing who were ≥12 years of age, ≥40 kg in weight, and at high risk for progressing to severe COVID-19 or hospitalization. Clinical data were obtained in February 2021 from electronic health records maintained by the medical system, which includes both a major medical center and several outpatient clinics with integrated health records.

Our retrospective cohort consisted of patients presenting to either outpatient clinics or the medical center who tested positive for SARS-CoV-2 via an antigen or polymerase chain reaction–based test. Patients with positive viral test results recorded in the electronic health record between July 1 and December 20, 2020, were identified as untreated patients. These patients were eligible for inclusion in the analysis if they met the eligibility criteria for mAb treatment (Table 1). Treatment with mAb became available at the medical center on January 7, 2021. SARS-CoV-2 patients who received mAb infusions between January 7 and January 15, 2021, are referred to as treated patients. We selected the test date of December 20, 2020, as the final date of eligibility for untreated patients to ensure no overlap in the treated and untreated patient populations based on the maximum 10-day symptom onset window permitting mAb treatment eligibility and decreased health care–seeking behavior during winter holidays [19]. The decision to seek mAb treatment for COVID-19 was made by the patient and the provider. At presentation for mAb treatment, the date of SARS-CoV-2 test positivity was confirmed through paper records provided by the patient or rapid antigen testing performed on-site, and intake staff collected demographic and clinical information, including eligibility criteria for treatment (Table 1). Any adverse events were recorded on patient forms. While mAb treatments continued after January 15, the end date was established to permit sufficient follow-up at the time of data collection.

Data extracted from existing medical records included age, sex, race, ethnicity, height and weight, and presence of the following preexisting conditions as recorded by clinicians in the health record: blood disorders (eg, sickle cell disease, thalassemia), cancer, diabetes, Down syndrome, chronic lung disease, chronic liver disease, hypertension, immunosuppressive condition, chronic kidney disease, obesity or overweight, and organ transplant. Preexisting conditions were captured from the Chief Complaint of health records within the 6 months before the date of SARS-CoV-2 testing. Laboratory values and clinical exam measurements were not extracted to define preexisting conditions.

Race categories were defined as American Indian/Alaskan Native, Asian, Black, Hawaiian/Pacific Islander, White, and other. Ethnicity was defined as Hispanic or non-Hispanic.
Body mass index (BMI) was calculated as kilograms per meter-squared. In the absence of height and weight, the preexisting conditions of “obesity” and “overweight” were used for BMI categorization. The composite outcome of a medical visit was defined as the first instance of COVID-19-related ED visit or hospitalization after positive SARS-CoV-2 viral test result and was obtained from the electronic health record. A medical visit was COVID-related if 1 or more of the following chief complaints were identified: blood in sputum, chest congestion, chest pain, cough, COVID-19 screening, difficulty breathing, fever, flu-like symptoms, hypoxia, shortness of breath, sore throat, or weakness [20–23]. Dates of COVID-19 symptom onset and positive SARS-CoV-2 antigen test results performed at the infusion center were recorded on paper-based forms upon arrival of patients for mAb treatment, but were not recorded in electronic health records.

Characteristics of patients were compared using Welch $t$ tests for continuous variables and the chi-square test for categorical variables. Age was categorized as ≤65 years or >65 years. Logistic regression was used to evaluate the effect of mAb treatment on medical visits that occurred within 30 days of a positive SARS-CoV-2 viral test by applying a generalized linear model with a logits link function. The occurrence of a medical visit was evaluated as a binary outcome. Variables included in the model were those deemed epidemiologically relevant. Model diagnostics indicated that no data points substantially influenced model estimates, as assessed by Cook’s distance. All data processing and analyses were conducted using R, version 4.0.3 [24].

RESULTS

Medical records were available from 875 SARS-CoV-2-positive patients (Figure 1) confirmed during July 1 through December 20, 2020. Of these, 547 patients did not meet eligibility criteria for mAb treatment (Figure 1). This resulted in the analysis of 598 patients, 270 of whom (45%) were eligible for and received bamlanivimab during a single week in January 2021, comprising the treated group. A total of 328 untreated patients (55%) served as the historical comparator population. These untreated patients represented individuals who would have been eligible for mAb infusion had the treatment been available at the time of their COVID-19-positive viral test results.

Among the 598 patients, no statistically significant differences in sex, race, or ethnicity were identified between the treated and untreated study groups (Table 2). Untreated patients were an average of 3 years younger than the treated patients ($P = .02$), and health records were more likely to report untreated patients as overweight or obese and having a history of hypertension or cardiovascular disease (all $P < .001$).

In the 30 days following a positive SARS-CoV-2 test result, 5 of 270 treated patients (1.9%) presented to the ED or required hospitalization, compared with 39 of the 328 untreated patients (12%; $P < .01$) (Table 2). Untreated patients had a medical visit a median (interquartile range [IQR]) of 4 (2–8) days after a SARS-CoV-2-positive viral test result, while treated patients had a medical visit an average of 8 (4–8) days after mAb treatment ($P = .112$ by Kolmogorov-Smirnov test). No adverse events were reported among mAb-infused patients.

Treatment with mAb was associated with an 82% decrease in the risk of a COVID-19-related medical visit within 30 days of a positive SARS-CoV-2 viral test after adjusting for demographic factors and preexisting conditions (95% CI, 56%–94%) (Table 3). A BMI ≥35 greatly increased the risk of a medical visit in the multivariable analysis (odds ratio, 6.44; 95% CI, 2.48–16.71). Age ≥65 years was also associated with a 2.10-fold

### Table 1. Eligibility Criteria for SARS-CoV-2 Monoclonal Antibody Infusions

| Inclusion Criteria                                                                 |
|-----------------------------------------------------------------------------------|
| Laboratory-confirmed COVID-19 (documented positive COVID-19 viral test result)     |
| Symptom onset within the last 10 d                                                |
| ≥12 y of age and weight ≥40 kg                                                    |
| Plus, at least 1 of the following risk factors:                                  |
| - Body mass index ≥35 kg/m²                                                        |
| - Chronic kidney disease                                                          |
| - Diabetes mellitus                                                               |
| - Immunosuppressive disease                                                       |
| - Currently receiving immunosuppressive treatment                                |
| - ≥65 y of age                                                                    |
| - ≥55 y of age AND:                                                               |
|   *Cardiovascular disease or*                                                      |
|   *Hypertension or*                                                               |
|   *Asthma, reactive airway, or other chronic respiratory disease*                 |
|   *Sickle cell disease or*                                                         |
|   *Congenital or acquired heart disease or*                                        |
|   *Neurodevelopmental disorders (eg, cerebral palsy) or*                          |
|   *A medically related technological dependence (eg, tracheostomy, gastrostomy,|
|   positive pressure ventilation unrelated to COVID-19)* or*                       |
|   *BMI ≥85th percentile for age and gender based on the Centers for Disease       |
|   Control and Prevention’s growth charts [33] or                                 |
|   *Obesity* or *overweight*                                                       |
|   *Diabetes mellitus*                                                             |
|   *Chronic pulmonary obstructive disease/other chronic respiratory disease*       |

Abbreviations: BMI, body mass index; COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
increased risk, but this was not statistically significant (95% CI, 0.97–4.77).

DISCUSSION

This study demonstrated that a single infusion of bamlanivimab within 10 days of COVID-19 symptom onset decreased the risk of COVID-related hospitalization and ED visits among a real-world, diverse patient population in the United States who were at risk of progression to severe disease compared with an untreated population. The association between treatment and improved clinical outcome remained significant after controlling for gender, age, race, ethnicity, and preexisting conditions. A BMI of >35 remained highly associated with disease progression requiring a medical visit, after adjusting for mAb treatment and other co-factors.

Approximately 2% of the treated group were hospitalized or visited the ED after mAb infusion, which was similar to the rate of medical visits in the efficacy assessment of bamlanivimab [10]. In contrast, almost 12% of untreated patients in the current study required a medical visit within 30 days of a positive COVID test. This risk was nearly double the 6.3% of placebo controls who presented to the ED, required hospitalization, or died in the phase 2/3 trial [10], suggesting that the current study’s patient population was older and had a higher risk of progression to severe disease. This difference reinforces the need to evaluate therapeutics in diverse populations and in real-world clinical situations, as patients who are referred for and receive treatments often differ from those who are enrolled in a clinical trial.

Few treatment options have been available during the COVID-19 pandemic for reducing the severity of disease and preventing hospitalization, leading to significant strain on many hospitals [8]. Reducing the proportion of patients who progress to severe disease and require hospitalization by ~80% would be of immense value to medical centers, in which intensive care units contain an average of only 15 staffed beds [25].
The availability of mAbs at no drug cost due to their procurement by the US government places a therapeutic option more easily within reach of many who are at the highest risk of severe disease.

The use of electronic health records is a strength of the current study. Due to the medical center’s electronic record system, we were able to assemble a SARS-CoV-2-positive cohort who would have been eligible for mAb treatment at the time of their diagnosis based on preexisting risk factors, had the therapeutics been available at that time. An additional strength of this study was the diverse patient population in the area, resulting in the inclusion of a large proportion of patients of Hispanic ethnicity (39%). Our results are consistent with prior clinical trial data showing a 70% reduction in medical visits by mAb-infused patients compared with placebo controls [10]. A BMI of ≥35 was a strong independent predictor of an increased risk of medical visits, which was consistent with other COVID-19 studies [7].

A significantly larger proportion of untreated patients had comorbidities that increase the risk of severe COVID-19 outcomes compared with treated patients in the current study, notably a higher proportion with elevated BMI. Although mAb treatment remained significantly associated with a decreased risk of hospitalization or ED visit after adjusting for preexisting conditions (82% reduction; 95% CI, 56%–94%), the baseline differences between the treated and untreated groups suggest a potential difference in accessibility of mAb treatment. For example, patients with fewer comorbidities may have more easily

### Table 2. Baseline Demographic and Medical Characteristics of SARS-CoV-2-Positive Patients

|                      | Untreated (n = 328), No. (%) | mAB Treated (n = 270), No. (%) | Overall (n = 598) | PValue |
|----------------------|-----------------------------|--------------------------------|-------------------|--------|
| **Sex**              |                             |                                |                   | .10    |
| Female               | 211 (64.3)                  | 155 (57.4)                     | 366 (61.2)        |        |
| Male                 | 117 (35.7)                  | 115 (42.6)                     | 232 (38.8)        |        |
| **Age**              |                             |                                |                   | .03    |
| Mean ± SD, y         | 61.0 ± 17.8                 | 63.9 ± 15.9                    | 62.3 ± 17.0       |        |
| Age >65 y            |                             |                                |                   | .33    |
| Yes                  | 168 (51.2)                  | 150 (55.6)                     | 318 (53.2)        |        |
| No                   | 160 (48.8)                  | 120 (44.4)                     | 280 (46.8)        |        |
| **Race**             |                             |                                |                   | .66    |
| American Indian, Alaskan Native | 5 (1.5) | 6 (2.2) | 11 (1.8) |        |
| Asian                | 5 (1.5)                     | 4 (1.5)                        | 9 (1.5)           |        |
| Black                | 14 (4.3)                    | 5 (1.9)                        | 19 (3.2)          |        |
| Hawaiian, Pacific Islander | 1 (0.3) | 1 (0.4) | 2 (0.3) |        |
| Other                | 11 (3.4)                    | 6 (2.2)                        | 17 (2.8)          |        |
| White                | 278 (84.8)                  | 214 (79.3)                     | 492 (82.3)        |        |
| Missing              | 14 (4.3)                    | 34 (12.6)                      | 48 (8.0)          |        |
| **Ethnicity**        |                             |                                |                   | .58    |
| Hispanic             | 129 (39.3)                  | 102 (37.8)                     | 231 (38.6)        |        |
| Non-Hispanic         | 188 (57.3)                  | 133 (49.3)                     | 321 (53.7)        |        |
| Missing              | 11 (3.4)                    | 35 (12.0)                      | 46 (7.7)          |        |
| **BMI**              |                             |                                |                   | <.01   |
| ≥30                  | 52 (15.9)                   | 24 (8.9)                       | 76 (12.7)         |        |
| ≥35                  | 35 (10.7)                   | 11 (4.1)                       | 46 (7.7)          |        |
| **Hypertension**     |                             |                                |                   | <.01   |
| Yes                  | 176 (53.7)                  | 55 (20.4)                      | 231 (38.6)        |        |
| No                   | 152 (46.3)                  | 215 (79.6)                     | 367 (61.4)        |        |
| **Chronic kidney disease** |               |                                |                   | .22    |
| Yes                  | 19 (5.8)                    | 9 (3.3)                        | 28 (4.7)          |        |
| No                   | 309 (94.2)                  | 261 (96.7)                     | 570 (95.3)        |        |
| **Cardiovascular disease** |            |                                |                   | <.01   |
| Yes                  | 71 (21.6)                   | 20 (7.4)                       | 91 (15.2)         |        |
| No                   | 257 (78.4)                  | 250 (92.6)                     | 507 (84.8)        |        |
| **COVID-related ED visit or admission within 30 d** | |                   |                   | <.01   |
| Yes                  | 39 (11.9)                   | 5 (1.9)                        | 44 (7.4)          |        |
| No                   | 289 (88.1)                  | 265 (98.1)                     | 554 (92.6)        |        |

Abbreviations: BMI, body mass index; COVID-19, coronavirus disease 2019; ER, emergency room; mAb, monoclonal antibody; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
been able to avail themselves of treatment. The continued US government efforts to increase access to mAbs are intended to ensure that COVID-19 therapeutics are equally available to all patients—an important national health equity consideration.

To receive mAb infusions and prevent the progression of disease, patients must seek out treatment within 10 days of a positive SARS-CoV-2 antigen test result. This can be burdensome and stresses the importance of widespread availability of testing. Evidence also suggests that patients with more significant or severe comorbidities are likely to have more complete health records [26, 27]. This effect may have overrepresented those or severe comorbidities are likely to have more complete health records [26, 27]. This effect may have overrepresented certain and severe disease are prioritized for vaccination in most US states, therapeutic options such as mAb infusions remain a necessity for those who remain unvaccinated due to contraindications or vaccine hesitancy [28, 29]. Although viral variants are being discovered that are poorly neutralized by several mAbs in laboratory studies [30, 31], suggesting reduced effectiveness in patient populations, relatively minor adjustments to the currently available mAb products can counter these changes. Additionally, the FDA has issued guidance encouraging the use of existing formulations, platforms, and clinical protocols to facilitate expedited review and rapid introduction of these modified mAb products to the general public [32].

In summary, we demonstrated that mAb treatment with bamlanivimab was associated with an ~80% reduction in the risk of medical visits among a diverse COVID-19 patient population under real-world conditions. Increasing the availability and utilization of novel COVID-19 therapeutics may improve patient outcomes, reduce the burden on the health system, and contribute to increased health equity in the United States.

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