

Outcomes of Monoclonal Antibody Use in Patients with COVID-19

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Table of contents

Abstract	3
Introduction	4
Methods	5
Patient population	5
Outcomes	5
Variable definitions	5
Statistical analysis	6
Results	8
Characteristics of the mAb patients in the primary cohort	8
Primary and secondary outcomes	9
Discussion	11
Strengths	11
Limitations	12
Conclusion	13
References	14

Abstract

Background. Since 2021, monoclonal antibody (mAb) therapy has effectively treated patients with mild-to-moderate COVID-19 infections at risk of more severe infections. Clinical researchers have studied mAb effectiveness in reducing hospitalization and mortality. This study further examines the effectiveness of available mAb therapies in reducing rehospitalization and mortality over 19 months in the greater Seattle area.

Methods. We conducted an IRB-approved retrospective chart review of nonhospitalized adult patients who presented to emergency departments (ED) in the greater Seattle area from March 2021-October 2022 with mild-to-moderate COVID-19 infections. We compared mAbs treated patients to non-treated eligible patients with 28-day rehospitalization and all-cause hospital mortality as primary outcomes. Secondary outcomes were rates of inpatient admission, intensive care, and mechanical ventilation. Propensity score matching and logistic regression models were used to control for demographic and comorbidities.

Results. 21,139 patients were included. MAb treatment was associated with reduced significantly odds of 28-day rehospitalization (adjusted odds ratio [aOR] 0.66, (95% CI 0.49-0.87), $P = 0.004$), mortality (adjusted odds ratio [aOR] 0.32, (95% CI 0.19-0.51), $P < 0.001$), and inpatient admissions (adjusted odds ratio [aOR] 0.43, (95% CI 0.31-0.61), $P < 0.001$).

Conclusions. In a single hospital system, From March 2021 through October 2022, mAbs treatments were associated with reduced rehospitalization, mortality, and inpatient admission in patients with mild-to-moderate COVID-19 infections in western Washington. Our study contributes real world evidence to the medical literature on the efficacy of monoclonal antibodies as a treatment for outpatients with mild-to-moderate COVID-19 at risk of developing severe infection.

Key Words comorbidities, COVID-19, mild-to-moderate, monoclonal antibody therapy, mortality, rehospitalization

Introduction

Since early 2021, monoclonal antibody (mAb) therapy has emerged as an efficacious intervention for patients with mild-to-moderate COVID-19 infections, particularly those at high risk of progressing to more severe infections. With favorable results from clinical trials, the U.S. Food and Drug Administration (FDA) issued Emergency Use Authorizations for a series of mAb treatments: casirivimab-imdevimab (REGEN-COV) in November 2020 [1,2], bamlanivimab plus etesevimab (BAM+ETE) in February 2021 [3,4], sotrovimab (SOT) in May 2021 [5,6], then bebtelovimab (BEB) in February 2022 [7,8]. As these therapeutic agents became readily available, clinicians and researchers embarked on comprehensive investigations into their impact on hospitalization rates and mortality outcomes. In spring 2021, bamlanivimab was associated with reduced rehospitalizations and, in most cases, mortality within 28 days [9–12]. Later, in the fall of 2021, sotrovimab use also seemed to decrease odds of hospitalization and mortality [13,14]. Later studies of bebtelovimab use, however, found mixed results [15,16].

More recent studies have examined the effect of all available mAb agents, along with COVID vaccinations, on patient outcomes over a longer period of the pandemic. These studies have also found decreased odds of rehospitalization and mortality in treated patients across phases of the pandemic [17,18].

This study delves deeper into the effectiveness of accessible mAb therapies and their synergistic interactions with COVID-19 vaccinations in mitigating rehospitalization and mortality over a span of 19 months, within the encompassing landscape of greater Seattle in western Washington.

Methods

Patient population

We conducted a propensity-matched, retrospective, observational study using data from our electronic medical record system (EHR; Epic). This study was approved by the institutional review board of Providence-St. Joseph Health Care, a large multistate healthcare organization. Individual patient consent was not required. The setting for this study was Providence Swedish Health Services, a regional healthcare network in the Puget Sound area of western Washington which includes approximately 1,570 licensed beds. The network includes seven EDs that were host to 221,000 ED visits in 2022.

We identified a study population of adult patients who were eligible for monoclonal antibody therapy. Our inclusion criteria were adult outpatients who presented to an ED from March 25, 2021 (the date of the first mAb administration) through October 31, 2022, with mild-to-moderate SARS-CoV-2 infections and at least one of the following active comorbidities: arrhythmia, cancer, cardiovascular dysfunction, diabetes, immunosuppression, obesity, renal dysfunction, a respiratory disorder, and/or tobacco use. We excluded patients who lacked all of the aforementioned comorbidities, who received oxygen therapy on their first ED visit, and who were admitted to the hospital on their first ED visit. Baseline demographic data we collected included age, sex, and race. We also collected acuity levels and dates of COVID-19 vaccinations.

Outcomes

Our two primary outcomes were 28-day rehospitalization and all-cause hospital mortality. Secondary outcomes were any days as a hospital inpatient, in intensive care, and/or on mechanical ventilation following discharge from their first ED visit.

Variable definitions

We defined our first primary outcome of 28-day rehospitalization as admission to an ED or an inpatient hospital admission for a COVID-19-related reason within 28 days of discharge from the first ED visit. We operationalized this outcome as a dichotomy in which 1 indicated

readmission to an ED or hospital within 28 days and 0 all others. Our second primary outcome of mortality we defined as all-cause hospital mortality, and this we measured as a dichotomy in which 1 indicated all-cause hospital mortality in the time between discharge from the ED visit and the end of the study period, and 0 all others. We defined a COVID-19-related reason as either (1) a positive SARS-CoV-2 lab test undertaken within the hospital encounter, (2) a SARS-CoV-2 infection documented in the ED infectious risk screening, and/or (3) a COVID-19-related ED encounter diagnosis using ICD10 codes (U00, U09, U49, U50, U85, J12.82, M35.81, Z20.822). To account for historical change in the pandemic, we calculated the time in months from the date of the first mAb approval (November 21, 2020) to the date of the hospital encounter (whether an ED visit or inpatient admission). Because our secondary outcomes were skewed, we measured these as dichotomies in which 1 indicated any inpatient days, ICU days, and/or mechanical ventilation days, and 0 all others.

Our covariates of interest included sex, race, age, comorbidities, mAb treatment status, acuity level, and number of vaccinations at the first ED visit. We coded sex as a dichotomy in which a value of 1 indicated male and 0 female, and race as a dichotomy in which 1 = nonwhite and 0 = white. We dichotomized age into patients below or at least 65 years of age at the time of the hospital encounter. For comorbidities we used ICD10 codes on the patient problem list. We coded each comorbidity as a dichotomy in which 1 indicated active presence within the study period and 0 nonpresence. We identified mAb-treated patients from documented administrations of mAb infusions on the first ED visit. Treatments included bamlanivimab, casirivimab + imdevimab, bamlanivimab + etesevimab, sotrovimab, and bebtelovimab. Acuity level we coded into the following 4-point ordinal scale of increasing urgency: 1 = Non-urgent, 2 = Less urgent, 3 = Urgent, 4 = Emergent or Immediate. Finally, we measured vaccination status as the cumulative count of documented COVID-19 vaccination dates received by the hospital encounter.

Statistical analysis

We first reported baseline characteristics and clinical indicators for the treated and untreated patients both before and after propensity score matching. We reported as descriptive statistics means and standard deviations for continuous variables and frequencies and percentages for categorical variables.

We estimated propensity scores for receipt of mAb therapy using the 1:1 nearest neighbor method without replacement with logistic regression. We matched on the factors shown in the descriptive analyses to be statistically significant differences between the treated and untreated patients in the full unmatched sample. These factors included age, race, immunosuppression, renal disorder, respiratory disorder, tobacco use, months into availability of mAb treatment, acuity level, and number of vaccinations. To estimate the treatment effect and its standard error, we fit logistic regression models for our outcomes on mAb treatment and any covariates

remaining unbalanced after propensity score matching. We conducted all statistical analyses in RStudio [19]. For propensity score matching we used the MatchIt package [20].

Results

Between March 2021 and October 2022, a total of 21,139 patients met our inclusion criteria and were included the study. Upon propensity matching, 1,349 patients were included in the primary matched cohort (1,349 mAb-treated; 1,349 untreated). The propensity score matching diminished the imbalance in most of the key covariates, including age, race, immunosuppression, renal disorder, respiratory disorder, tobacco use, months into availability of mAb treatment, acuity level, and number of vaccinations. However, the propensity matched sample did differ significantly in months into mAb availability and number of COVID-19 vaccinations. Measures of association are available in Table 1.

Characteristics of the mAb patients in the primary cohort

In the propensity-matched cohort, mAb-treated patients reflected characteristics consistent with patients at a high risk for progression to severe COVID-19 (Table 1). Among patients who received mAb therapy ($n = 1,349$), 805 (60%) were aged 65 years or older, 387 (29%) were nonwhite, 136 (10%) were immunosuppressed, 275 (20%) suffered from renal disorders, and 452 (34%) suffered from respiratory disorders.

Table 1. Patient Characteristics and Covariate Balance Before and After Propensity Matching

Characteristic	Before propensity matching, N = 1,349
Male	636 (47%)
Nonwhite	387 (29%)
Age 65+	805 (60%)
Arrhythmia	305 (23%)
Cancer	186 (14%)
Cardiovascular disease	777 (58%)
Diabetes	250 (19%)
Immunosuppressed	136 (10%)

Characteristic	Before proper Treated, N =
Obese	522 (39%)
Renal disease	275 (20%)
Respiratory disease	452 (34%)
Tobacco user	47 (3.5%)
Months since mAb approval	15 (5)
Acuity level	
1	5 (0.4%)
2	173 (13%)
3	923 (68%)
4	248 (18%)
COVID vaccinations	
0	1,298 (96%)
1	14 (1.0%)
2	4 (0.3%)
3	9 (0.7%)
4	24 (1.8%)

¹ n (%); Mean (SD)

² Pearson's Chi-squared test; Wilcoxon rank sum test

Primary and secondary outcomes

The crude rates of rehospitalization, mortality, and inpatient outcomes are shown in Table 2. During the study period, the incidence of 28-day hospitalization in our primary matched cohort was 9.4% (n = 127/1,349) for untreated patients compared to 6.3% (n = 85/1,349) among mAb-treated patients. The mortality rate for untreated patients was 5.3% (n = 71/1,349) compared to 1.7% (n = 23/1,349) for mAb-treated patients. The rate of inpatient admission for untreated patients was 8.6% (n = 116/1,349) compared to 3.8% (n = 51/1,349) for mAb-treated patients. Rates of ICU and mechanical ventilation did not differ significantly by treatment group.

Table 2. Primary and Secondary Outcomes for Primary Matched Cohort

Characteristic	Treated, N = 1,349 ¹	Untreated, N = 1,349 ¹	p ²
Primary outcomes			
28-Day Readmission	85 (6.3%)	127 (9.4%)	0.003
Mortality	23 (1.7%)	71 (5.3%)	<0.001

Characteristic	Treated, N = 1,349 ¹	Untreated, N = 1,349 ¹	p ²
Secondary outcomes			
Any days as hospital inpatient	51 (3.8%)	116 (8.6%)	<0.001
Any days in ICU	10 (0.7%)	20 (1.5%)	0.066
Any days on ventilator	4 (0.3%)	4 (0.3%)	>0.9
¹ n (%)			
² Pearson's Chi-squared test			

The adjusted analyses are presented in Table 3. Treatment with mAb was associated with reduced odds of 28-day rehospitalization (adjusted odds ratio [aOR] 0.66, [95% confidence interval (CI)] 0.49-0.87), $P = 0.004$. Mortality rates also differed significantly between the two groups. Treatment with mAb was associated with reduced odds of mortality (adjusted odds ratio [aOR] 0.32, [95% confidence interval (CI)] 0.19-0.51), $P < 0.001$. Treatment was also associated with reduced odds of inpatient admissions (adjusted odds ratio [aOR] 0.43, [95% confidence interval (CI)] 0.31-0.61), $P < 0.001$.¹

Table 3. Adjusted Odds Ratios

Characteristic	28-Day Reho	
	OR ¹	95% C
Received mAb	0.66	0.49, 0.87
Months since mAb approval	0.97	0.94, 1.00
COVID vaccinations	1.16	0.90, 1.49

¹ OR = Odds Ratio, CI = Confidence Interval

¹In these adjusted analyses, months since mAb approval of the first ED visit remained a statistically significant covariate after controlling for mAb treatment and number of COVID vaccinations. Months since mAb approval was associated with significantly but slightly reduced odds of rehospitalization (adjusted odds ratio [aOR] 0.97, [95% confidence interval (CI)] 0.94-1.00), $P = 0.038$ and inpatient admissions (adjusted odds ratio [aOR] 0.93, [95% confidence interval (CI)] 0.90-0.96), $P < 0.001$.

Discussion

This study evaluated the effect of mAb therapy for outpatient use with mild-to-moderate COVID-19 on 28-day rehospitalization, all-cause hospital mortality, and inpatient admissions over a 19-month period in a major metropolitan area in western Washington. In a sample of propensity-matched treated and untreated patients, mAb treatment was associated with significantly reduced odds of 28-day rehospitalization, all-cause hospital mortality, and inpatient admissions. These findings are consistent with the literature on mAbs in real-world settings and contribute further real-world evidence of the effectiveness of mAbs in treating outpatients with mild-to-moderate COVID-19 infections.

While not the primary focus of this paper, it is illuminating to look at the initial differences between treated and non-treated patients with an eye to understanding physicians' decision making in these cases. Conspicuously, patients who were immunosuppressed, were roughly over four times more likely to receive monoclonal treatment. Additionally, treated patients were likely to be older, have cancer and cardiovascular disease more frequently, and had fewer vaccinations. So clearly physicians were targeting the most vulnerable ED patients for monoclonal antibody treatment.

Another thought-provoking aspect of this paper is our focus on patients with mild to moderate COVID-19 symptoms. While these patients had reported to an ED for treatment, they were not hospitalized. We can therefore assume that the treating physicians believed their patients had milder instances of COVID-19 infections. This would suggest that our results might underestimate monoclonal treatment benefits with more severe COVID-19 infections. Although plausible, we are unable to examine this possibility with this data set.

Strengths

This study has several strengths by virtue of occurring within a single hospital system. All of the data are collected in a limited geographic area, thereby limiting regional differences, potential differences in strain exposure, differences in ED guidelines or hospital procedures, and differences in ED access to monoclonal treatment over the course of the pandemic. Additionally, propensity matching succeeded in rendering an untreated sample that was in many respects virtually identical to the treated sample.

Limitations

This study is limited in several ways. First, given the retrospective nature of this study, which relied entirely on pre-existing information documented in the electronic medical record, all eligibility for monoclonal antibodies were based on the provider who evaluated the patient and were there for not double checked for accuracy. Patients who may have qualified for a monoclonal antibody were not offered treatment based on the provider's discretion.

Conclusion

From March 2021 through October 2022, monoclonal antibodies emerged as a pivotal factor in significantly reducing the incidence of rehospitalization, mortality, and inpatient admission amongst patients with mild-to-moderate COVID-19 infections in western Washington. Our study contributes real-world evidence to the medical literature, reaffirming the efficacy of monoclonal antibodies as a therapeutic option for outpatients with mild-to-moderate COVID-19 who are at an increased risk of developing severe infection. In light of the evolving landscape of the COVID-19 pandemic, marked by changing variants, the efficacy of individual mAb agents should continue to be vigilantly evaluated.

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