

Monoclonal Antibody Treatment of Breakthrough COVID-19 in Fully Vaccinated Individuals with High-Risk Comorbidities

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40-word summary

Breakthrough COVID-19 may occur among vaccinated individuals with a high number of medical comorbidities, especially during the SARS-CoV-2 Delta surge. Anti-spike monoclonal antibody treatment was associated with significantly lower rates of hospitalization, particularly among high-risk persons.

Abstract

Breakthrough COVID-19 may occur in fully vaccinated persons. In this cohort of 1395 persons (mean age, 54.3 years; 60% female; median body mass index, 30.7) who developed breakthrough COVID-19, there were 107 (7.7%) who required hospitalization by day 28. Hospitalization was significantly associated with the number of medical comorbidities. Anti-spike monoclonal antibody treatment was significantly associated with a lower risk of hospitalization (Odds Ratio: 0.227; 95% confidence interval, 0.128 - 0.403; $p < 0.001$). The number needed to treat (NNT) to prevent one hospitalization was 225 among the lowest-risk patient group compared to NNT of 4 among those with highest numbers of medical comorbidity.

Keywords: breakthrough covid-19, casirivimab-imdevimab, vaccination, covid-19, SARS-CoV-2, outcome, hospitalization

Footnotes

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Ethical approval: This study was approved by the Mayo Clinic Institutional Review Board.

Conflict of Interest Statement:

Dr. Razonable is principal investigator of research funded by Regeneron, Roche, Gilead (all funds provided to his institution), and is a member of Data Safety Monitoring Board of Novartis, on projects not directly related to this submission. Dr. Razonable received research funds from the Mayo Clinic for studies on monoclonal antibodies for COVID-19.

All other no conflict to report.

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Introduction

COVID-19 vaccination is the primary strategy to reduce severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) outbreaks and its great burden to healthcare systems¹. Clinical trial and real-world experience suggest high efficacy of SARS-CoV-2 vaccine for the prevention of COVID-19^{1,2,3}. Despite the effectiveness of COVID-19 vaccines, breakthrough infections have been reported⁴. Among healthcare workers with breakthrough COVID-19, the majority of infections were mild, although 19% had persistent symptoms⁴. With the surge in SARS-CoV-2 B.1.617.2 (Delta) variant, there have been increasing reports of breakthrough infections among vaccinated persons.

Real-world clinical data are needed to characterize breakthrough COVID-19 in fully vaccinated persons and assess their risk of hospitalization. Moreover, there is no data as to whether vaccinated individuals with breakthrough COVID-19 would benefit from passive immunotherapy with casirivimab-imdevimab or bamlanivimab-etesevimab. In this study, we assessed the clinical outcomes of 1395 fully vaccinated adult patients with breakthrough COVID-19. We specifically investigated the rates of severe disease, as measured by oxygen requirement and need for hospitalization, and we compared these outcomes between patients who received or did not receive treatment with anti-spike monoclonal antibody.

Methods

Patient Population and Study Design

After approval by the Mayo Clinic Institutional Review Board, this retrospective study enrolled fully vaccinated patients with breakthrough COVID-19 who were screened for eligibility for treatment with bamlanivimab (Eli Lilly, Indianapolis, IN), bamlanivimab-etesevimab (Eli Lilly, Indianapolis, IN) or casirivimab-imdevimab (Regeneron, New York) as single infusion from January to August 16, 2021. All patients developed PCR-confirmed breakthrough COVID-19 at least 2 weeks

after the second of two doses of SARS-CoV-2 mRNA vaccine (Pfizer-BioNTech or Moderna) or the single dose of Ad26.COV2.S (Johnson and Johnson) vaccine.

All patients were identified after being screened by the Mayo Clinic Monoclonal Antibody Treatment Program in Mayo Clinic sites in the Midwest, as previously described.⁵ Patients were contacted by telephone to assess clinical symptoms and by online portal to indicate their eligibility for monoclonal antibody treatment. High risk patients were also enrolled in a virtual remote monitoring program. All patients had at least 28 days of follow up after the COVID-19 diagnosis. Those who were incidentally diagnosed with COVID-19 upon hospital admission for a non-COVID 19 indication were excluded from analysis. Only the patients who provided authorization for the use of their medical records for research purposes were included. The conduct of this study was in compliance with the aims of Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)⁶.

Clinical Variables

The demographic and clinical characteristics of all patients, including COVID-19 vaccination status and date of vaccination, were collected by a review of their Electronic Health Records. Medical comorbidities and other characteristics that portend high-risk for progression to severe COVID-19 were recorded. The degree of medical comorbidity was assessed using Monoclonal Antibody Screening Score (MASS), a clinical criteria for risk of severe COVID-19 outcomes that has been previously described^{7,8}. MASS assigned points to characteristics and comorbidity that made a person eligible for monoclonal antibody, according to the initial Food and Drug Administration (FDA) Emergency Use Authorization (EUA) guidance issued in November 2020⁹. In May 2021, the US FDA expanded the use of monoclonal antibodies to include lower-risk persons such as those with body mass index of ≥ 25 kg/m². For the purposes of this study, MASS was used as a measure of medical comorbidity burden, as previously described^{7,8}.

Clinical Outcomes

The primary outcome for this study was the rate of all-cause hospitalization by day 28 after the diagnosis of breakthrough COVID-19. ICU admission and the need for oxygen supplementation was recorded as an indicator of severe disease. All 1395 patients had completed at least 28 days of follow up by the end of this study on September 15, 2021.

Statistical Analysis

Data are presented in aggregate using descriptive statistics. The differences in the outcomes between two subgroups of patients, defined based on receipt or non-receipt of monoclonal antibodies, were compared using descriptive statistics. To calculate the proportion of patients who experienced 28-day hospitalization or use of oxygen supplementation, each patient who experienced one of the two outcomes was assigned to the numerator with the total population as the denominator. Simple proportions were calculated by receipt of monoclonal antibody therapy and stratified by MASS score. Differences in these proportions were assessed using Chi Square test for independence for categorical variables or a t-test for continuous variables after ensuring testing parameters were met. Fisher Exact test was used if testing assumptions were not achieved. Crude odds ratios (OR) with 95% confidence intervals (CIs), absolute risk reduction and number needed to treat were calculated to compare associations of patient characteristics with outcomes; $P < 0.05$ was deemed statistically significant. The association between monoclonal antibody therapy and hospitalization within 28 days was assessed with logistic regression with adjustment for MASS. Data was analyzed using Microsoft Excel (Microsoft Excel for Office 365, Version 16.0.13127.21766, Microsoft Corporation, Redmond, WA) and BlueSky Statistics (Commercial Server Edition, Version 7.40).

Results

The total population consisted of 1395 fully vaccinated patients (mean age, 54.3 years; 39.6% male) with breakthrough COVID-19 and were screened for monoclonal antibody therapy, under US FDA EUA guidance. The majority of breakthrough SARS-CoV-2 infections (n=1002; 71.8%) occurred during a 6-week period from July 1 to August 16, 2021, when the Delta variant was predominant in our region (Supplemental Figure). The most common medical comorbidities were hypertension (34.5%), cardiovascular disease (13.8%), chronic pulmonary disease (13.6%), and chronic kidney disease (10.2%) (Table 1). A total of 170 (12.2%) patients were immunocompromised, including 149 patients (10.7%) with solid cancer and hematologic malignancies and 35 (2.5%) transplant recipients. Most patients (69.8%) received the Pfizer-BioNTech SARS-CoV-2 mRNA vaccine.

Breakthrough COVID-19 occurred at median of 124 days (mean, 120 days) after full completion of the vaccination series. At 28 days after breakthrough COVID-19 diagnosis, 107 patients (7.7%) had progressed to require hospitalization. The rate of hospitalization was significantly higher among patients with higher medical comorbidity score (**Table 2** and **Supplementary Table**).

Table 2 stratifies the population into those who received (n=527; 37.8%) versus those who did not receive (n=868; 62.2%) treatment with anti-spike monoclonal antibody. Among those who received treatment, the majority were treated with casirivimab-imdevimab, including all patients diagnosed after May 7, 2021. Patients received the monoclonal antibody treatment at a median of 5 days (interquartile range, 3-6 days) from symptom onset and 2 days (interquartile range, 1-3 days) from testing. Overall, the rate of hospitalization was 2.65% among patients treated with monoclonal antibody compared to 10.7% among those who did not receive therapy (Odds Ratio [OR]: 0.227; 95% confidence [CI] interval, 0.128 - 0.403; p<0.001). Controlling for MASS, monoclonal antibody therapy was associated with a lower rate of hospitalization (OR: 0.14; 95% CI, 0.079-0.265; p<0.0001). The

number needed to treat (NNT) to prevent one hospitalization correlated with the degree of medical comorbidity. NNT was 255 among vaccinated persons without high-risk medical comorbidity while NNT was between 3 and 8 among patients with multiple high-risk medical conditions (**Table 3**, pooled NNT of 4 for patient groups with MASS \geq 4).

Treatment of hospitalized patients with breakthrough COVID-19 followed institutional protocol that included remdesivir and dexamethasone for severe COVID-19. Sixty-one patients (4.4%) developed hypoxia and required oxygen supplementation and dexamethasone. Anti-spike monoclonal antibody treatment was significantly associated with lower rates of hypoxia when compared to those who did not receive monoclonal antibody (0.95% versus 6.45%; OR, 0.139; 95% CI, 0.055 – 0.349; $p < 0.001$). The majority ($n=56$; 91.8%) of patients who required oxygen supplementation did not receive monoclonal antibody treatment. Five (0.36%) patients required admission to the intensive care unit (ICU), none of whom were treated with monoclonal antibody. No death was reported among 1395 vaccinated patients with breakthrough COVID-19.

Discussion

This study provides several observations that are relevant in the current era of the SARS-CoV-2 pandemic that is dominated by the Delta variant causing breakthrough COVID-19. . First, this study observed that, among vaccinated patients with breakthrough COVID-19, 8% developed clinical progression to require hospitalization, including some needing intensive unit care and oxygen supplementation. The vast majority of breakthrough COVID-19 occurred during a period when the policy for face mask is no longer mandatory for all persons. This finding emphasizes the need for other public health strategies (e.g., use of face mask and avoidance of large gatherings) for all individuals, even among vaccinated individuals, during periods characterized by high community SARS-CoV-2 Delta transmission.

Second, this study demonstrates that the risk of hospitalization among breakthrough COVID-19 cases varies according to the degree of medical comorbidity, as measured by MASS. Because of the clinical correlation of the MASS and rates of severe outcomes, one may propose to use this scoring system to guide allocation of scarce resources, such as when there is limited drug supply or infusion capacity. Some of the multi-comorbidity patients in this study included those with cancer and immune compromised patients who may have suboptimal response to COVID-19 vaccine.

Third, this study provides clinical evidence of the benefit of augmented passive immunotherapy among fully vaccinated patients with breakthrough COVID-19. This benefit is especially evident among those with a high number of medical comorbidities, who may have had suboptimal response to COVID-19 vaccine. Supplementing these patients with monoclonal antibody immunotherapy may have mitigated their risk of clinical disease progression¹⁰. Similar to our prior study, monoclonal antibody treatment of breakthrough COVID-19 resulted in a lower risk of hospitalization, and a reduced need for oxygen supplementation among hospitalized patients^{11,12}. It is therefore important to encourage the use of these experimental therapies, and to address the various reasons why patients declined the offer for monoclonal antibody therapy, including sociodemographic factors that influence their decision to consent for these therapies.⁸ Since the vast majority of our cohort developed breakthrough COVID-19 during the Delta surge, our finding also provides the clinical correlate to experimental data that suggested that casirivimab-imdevimab retains efficacy against SARS-CoV-2 B.1.617.2^{13,14}.

This was a retrospective study with the inherent limitations to this study design. For example, we would not have captured treated patients who may have been hospitalized at outside institutions. However, we believe that this is not a considerable number since our program enrolls high-risk patients to a remote monitoring program, thereby ensuring continued contact with these patients until symptom resolution⁵. Our population was predominantly Caucasian, and our findings may not be generalizable to other patient populations. Most patients received treatment with

casirivimab-imdevimab, limiting generalizability to other monoclonal antibodies such as bamlanivimab-etesevimab and sotrovimab. The study observations should also be interpreted in the context that it was performed in patients screened and treated in a single healthcare system. The study included patients with breakthrough COVID-19 after two doses of an mRNA vaccine (or less commonly, a single dose of of Ad26.COV2.S vaccine), and it will be important to assess the outcomes of those individuals who have received a third or a booster dose. These limitations are counterbalanced by having a relatively large cohort of breakthrough COVID-19 cases identified in our healthcare system, with many identified during the period of the Delta surge. This large patient cohort allowed for robust statistical analysis of the potential efficacy of treatment with monoclonal antibody therapy.

Conclusion

Fully vaccinated persons, particularly those with multiple medical comorbidities, may develop breakthrough COVID-19, especially during the surge of a more communicable SARS-CoV-2 Delta variant. Some patients progressed to severe COVID-19 that required hospitalization, including the need of ICU care and oxygen supplementation. The severity of breakthrough COVID-19 significantly correlated with a high number of medical comorbidities. Reassuringly, no death was reported among our vaccinated cohort. Early treatment with anti-spike monoclonal antibody was associated with a significantly lower rate of severe COVID-19 that would require hospitalization.

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Table 1. Demographic and Clinical Characteristics of 1395 Vaccinated Persons with Breakthrough Coronavirus Disease-2019, Mayo Clinic in the Midwest, January 1 – August 16, 2021

Characteristics	Number of patients (percentage), unless otherwise specified
Age, in years, mean \pm standard deviation	54.3 \pm 18.5
Male sex	553 (39.64%)
Body mass index, mean \pm standard deviation	30.7 \pm 8.8
Cancer	149 (10.68%)
Cardiac disease	192 (13.76%)
Chronic kidney disease	142 (10.18%)
Diabetes mellitus	208 (14.91%)
Hypertension	481 (34.48%)
Pulmonary disease	190 (13.62%)
Covid-19 vaccine type	
Ad26.COVS vaccine (Johnson and Johnson)	133 (9.53%)
BNT162b2 vaccine (Pfizer-BioNTech)	974 (69.82%)
mRNA-1273 vaccine (Moderna)	288 (20.65%)
Time between full vaccination date and breakthrough COVID-19, in days; mean \pm standard deviation	120 \pm 53.7
Monoclonal antibody treatment	
Bamlanivimab or bamlanivimab-etesevimab	43 (3.08%)
Casirivimab-imdevimab	484 (34.70%)
No treatment	868 (62.22%)

Table 2. Differences in Rates of Hospitalization among 1395 Vaccinated Persons with Breakthrough Coronavirus Disease-2019 According to Treatment with Anti-spike Monoclonal Antibody

MASS*	Monoclonal antibody treatment		No treatment		Relative Risk	Odds Ratio (95% CI)	Absolute Risk Reduction	NNT
	Number (hospitalized)	Rate	Number (hospitalized)	Rate				
0≈	117 (2)	0.017	428 (9)	0.021	0.813	0.809 (0.173-3.800)	0.004	255
1	83 (0)	0	86 (2)	0.023	0	0.202 (0.010-4.280)	0.023	43
2	49 (1)	0.020	60 (4)	0.067	0.306	0.292 (0.032-2.700)	0.046	22
3	92 (3)	0.032	57 (7)	0.123	0.266	0.241 (0.060-0.973)	0.090	12
4	39 (0)	0	53 (8)	0.151	0	0.068 (0.125-0.028)	0.151	7
≥4 (pooled)	186 (8)	0.043	237 (71)	0.300	0.143	0.105 (0.049-0.225)	0.257	4
5	41 (2)	0.048	72 (21)	0.292	0.167	0.125 (0.243-0.040)	0.243	5
6	37 (2)	0.054	21 (4)	0.190	0.284	0.243 (0.152-0.031)	0.136	8
7	26 (2)	0.076	34 (12)	0.353	0.218	0.153 (0.058-0.128)	0.276	4
≥8 (pooled)	43 (2)	0.046	57 (26)	0.456	0.102	0.058 (0.013-0.264)	0.409	3

*MASS assigned a score to each of the FDA EUA eligibility criteria (November 2020), as follows: age ≥65 (2 points), BMI ≥35 (1 point), diabetes mellitus (2 points), chronic kidney disease (3 points), cardiovascular disease in a patient ≥55 years (2 points), chronic respiratory disease in a patient ≥55 years (2 points), hypertension in a patient ≥55 years (1 point), and immunocompromised status (3 points).

≈MASS score 0 includes COVID-19 patients who were made eligible for anti-spike monoclonal antibody therapy after the FDA expanded the criteria in May 2021 (e.g., those with BMI ≥25 but less than 35, those with hypertension and age <55 years, those with chronic lung disease and age <55 years, among many other new clinical criteria that were not originally included in November 2020).