

Outcomes of Monoclonal Antibody Infusion Treatment During Delta (B.1.617.2) and Omicron (B.1.1.529) COVID-19 Variant Surges among Vaccinated and Unvaccinated Patients

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ABSTRACT

BACKGROUND: Coronavirus infection of 2019 (COVID-19) is associated with significant morbidity and mortality. Vaccines supplement public health and social measures in preventing severe illness and mortality from COVID-19; however, vaccination rates remain inadequate in many regions. It is important to continuously explore the effective treatment due to the insufficient vaccination rate and increasing number of patients infected with virus. The emergence of new variants has led to multiple surges throughout the world requiring changes to treatment protocols.

METHOD: We conducted a single-center observational study on all adult patients who received monoclonal antibody (mAb) infusion as a treatment for COVID-19 infection. Based on the predominant variant, patients were either offered Casirivimab (600mg)/imdevimab (600mg) or Sotrovimab (500mg). Forty-six patients were given mAbs; 24 were vaccinated, and the remaining unvaccinated.

RESULT: The mean age was 56 years, and the majority (63.04%) of the patients were female. Clinical symptoms of COVID-19 improved within 3 days of infusion in the majority of the patients (70%). None of the patients who received mAb showed progression of disease or required hospitalization at 30 days follow-up. There were no deaths at 30 days follow-up. Monoclonal antibodies are highly effective in reducing hospitalizations and mortality when given within 7 days of symptoms onset in patients with high-risk factors for progression to severe COVID-19 infection. The mean number of days after the onset at which the mAbs were administered to the patient was 4.

CONCLUSION: Monoclonal antibodies should be considered in both vaccinated and unvaccinated patients with COVID-19 infection if newer antiviral agents are contraindicated. Our study highlights the effectiveness of monoclonal antibody infusions when given early in the course of COVID-19 infection regardless of vaccination status

KEYWORDS: Monoclonal antibodies, breakthrough infection, COVID-19, risk factors, vaccination

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Background

In March 2020, the World Health Organization (WHO) declared the coronavirus disease of 2019 (COVID-19) outbreak a pandemic. By April 19, 2022, the CDC reported 986545 SARS Cov2 related deaths in the United States.¹ To date, WHO has identified 5 variants of concern; Alpha (B.1.1.7) (December 2020), Beta (B.1.351) (December 2020), Gamma (P.1) (January 2021), Delta (B.1.617.2) (October 2020), and Omicron (B.1.1.529) (November 2021).² In a study involving 592 hospitals in the United States, inpatient mortality was 20.3%.³ A meta-analysis of 69 studies concluded that almost half of COVID-19 patients on invasive mechanical ventilation died.⁴ The introduction of highly effective vaccines just 11 months after the start of the pandemic was a significant milestone. As per CDC, unvaccinated individuals are 6.1 times more likely to test positive for COVID-19 and are 11.3 times more likely to die from COVID-19 as compared those who were fully vaccinated.⁵

Public health and social measure are the mainstay of protection against COVID-19. Vaccination supplement its effect and gives protection against severe illness and deaths. The emergence of new variants has led to multiple surges including breakthrough infections throughout the world. A study done in Connecticut, US found 35% of hospitalized patients and 22% of critically ill patients were fully vaccinated.⁶ Omicron (B.1.1.529) variant appears to evade immunity provided by vaccination with 12 to 44-fold higher efficiency than the Delta (B.1.617.2) variant.⁷ Nirmatrelvir with Ritonavir (Paxlovid), Molnupiravir (Lagevrio), and Remdesivir (Veklury) have been shown to be effective in managing COVID-19. Monoclonal antibodies infusions were approved under emergency use authorization (EUA) for selected patients with early symptomatic COVID-19 infection and risk factors for progression to severe disease. The first monoclonal antibody approved was casirivimab (EUA: November 2020), followed by; casirivimab-imdevimab (EUA: November 2020), bamlanivimab-etesevimab (February 2021),



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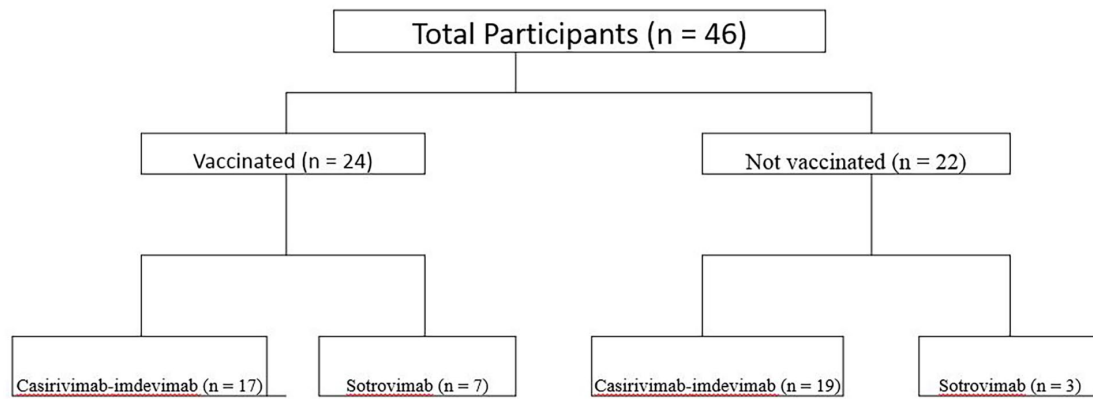


Figure 1. Study design.

and sotrovimab (May 2021). Casirivimab-imdevimab and bamlanivimab-etesevimab were also authorized for post-exposure prophylaxis under EUA for individuals with close contact or at high risk of exposure who have not been fully vaccinated or who are expected to have an inadequate response to vaccination.^{8,9} In January 2022, FDA withdrew the EUA for Casirivimab-imdevimab and bamlanivimab-etesevimab because of markedly reduced activity against the omicron (B.1.1.529) variant.

Clinical trials using monoclonal antibodies have shown promising results in treating patients with mild to moderate COVID-19 who are at high risk for progression to severe COVID-19.¹⁰ It is important to assess efficacy of monoclonal antibodies against SARS Cov2 in clinical practice due to emergence of variants. The objective of our study was to assess the effectiveness of monoclonal antibody infusion in vaccinated and unvaccinated patients during the periods of Delta (B.1.617.2) and Omicron (B.1.1.529) COVID-19 surges.

Methods

We conducted a single-center observational study from June 2021 to January 2022. Adult patients who attended our COVID-19 testing sites and patients who tested positive at our primary care clinics were included in the study. Patients who qualified for monoclonal antibody infusions as per emergency use authorization (EUA) issued by U.S. Food and Drug Administration (FDA) were offered treatment.¹¹ Patients more than 18 years of age who had mild to moderate COVID-19 symptoms of less than or equal to 7 days of duration and who were at a high risk of progression to severe COVID-19 disease were included in the study. Patients who were hypoxic, had symptoms for more than 7 days, and those hospitalized due to COVID-19 were excluded from the study. Risk and benefits were explained as stipulated in EUA to all the patients who met the inclusion criteria. During the study period, casirivimab (600 mg)/imdevimab (600 mg) and Sotrovimab (500 mg) were approved by the FDA in treating COVID-19. All patients who received monoclonal antibody infusions were monitored for 90 minutes for any adverse reaction. The study was approved by the Institutional Review Board (IRB) at BronxCare Health

System IRB # 01 14 21 16. There were 750 patients who tested positive for COVID-19, out of which 120 were offered monoclonal antibody infusions based on inclusion criteria. Forty-six patients received monoclonal antibody infusions while the remaining refused. The main reasons of refusal was that patient believed that mAbs were not effective in treating COVID-19, that monoclonal antibodies will not work as they have already received COVID-19 vaccination and that the monoclonal antibodies could lead to long term side effects. Patients were divided into 2 groups for analysis; Group A included vaccinated patients, while Group B included unvaccinated patients as depicted in Figure 1.

Demographic, comorbidities, clinical symptoms, vaccination status, initial laboratory findings, and clinical outcomes were collected for all patients. All patients were followed up for up to 30 days after monoclonal antibody infusions to assess for effectiveness, side effects, hospitalization, and mortality. Pearson's chi-square test was used to find an association between vaccination status with age over 65, comorbidities, smoking history, history of illicit substance abuse, clinical symptoms, and outcome. An Independent t-test was performed to find the association between vaccination status and age, risk factors, duration of signs and symptoms prior to monoclonal infusion, white blood cell count, neutrophil, lymphocyte, eosinophil, D dimer, Lactate dehydrogenase (LDH), C reactive protein (CRP), and ferritin. A *P*-value of less than .05 was considered significant.

Results

Forty-six patients were included in the study, of which 24 were vaccinated, and 22 were unvaccinated. The mean age of the patients was 55.8 years, and the majority (63.04%) of the participants were female. There was no significant difference between the vaccinated and unvaccinated group in the mean number of risk factors 3.46 ± 2.64 versus 3.64 ± 2.21 ($P = .806$). There was no significant differences in comorbidities, clinical symptoms, and outcomes between the 2 groups ($P > .05$). D Dimer was significantly higher in the unvaccinated group as compared to the vaccinated group ($P = .033$). Patient

Table 1. Patient demographic characteristics, comorbidities, initial symptoms, initial laboratory finding, and outcome.

PARAMETER	VACCINATED (N=24)	UNVACCINATED (N=22)	P-VALUE
Age			
Age	56.37 ± 15.38	55.77 ± 18.32	.904
Age over 65	7 (29.2%)	8 (36.4%)	.603
Gender			
Male	8 (33.3%)	9 (40.9%)	.59
Female	16 (66.7%)	13(59.1%)	
Comorbidities			
Hypertension	21 (87.5%)	22 (100%)	.086
Diabetes	16 (66.7%)	19 (86.4%)	.118
Chronic kidney disease	3 (12.5%)	7 (31.8%)	.113
Chronic cardiac disease	8 (33.3%)	6 (27.3%)	.655
Chronic pulmonary disease	8 (33.3%)	5 (22.7%)	.425
Immunocompromised	4 (16.7%)	3 (13.6%)	.775
Chronic liver disease	0 (0%)	2 (9.1%)	.131
Chronic neurologic disease	4 (16.7%)	2 (9.1%)	.446
Risk factors	3.46 ± 2.64	3.64 ± 2.21	.806
Social history			
Smoking history	2 (8.3%)	6 (27.3%)	.09
History of illicit substance use	2 (8.3%)	1 (4.5%)	.603
Clinical symptoms			
Anosmia	6 (25%)	5 (22.7%)	.857
Cough	16 (66.7%)	17 (77.3%)	.424
Shortness of breath	1 (4.2%)	5 (22.7%)	.062
Ageusia	5 (20.8%)	5 (22.7%)	.876
Diarrhea	6 (25%)	6 (27.3%)	.861
Fatigue	7 (29.2%)	8 (36.4%)	.603
Fever	9 (37.5%)	11 (50.0%)	.393
Headache	12 (50.0%)	9 (40.9%)	.536
Myalgia	10 (41.7%)	13 (59.1%)	.238
Nasal congestion	11 (45.8%)	7 (31.8%)	.331
Sore throat	4 (16.7%)	4 (18.2%)	.892
Duration of sign and symptoms	3.54 ± 1.53	4.25 ± 1.60	.145
Initial laboratory parameter			
White blood cell count— $\times 10^{-3}/\text{mm}^3$	6.14 ± 2.65	5.11 ± 1.34	.108
Neutrophil count— $\text{k}/\mu\text{l}$	3.61 ± 2.28	2.67 ± 1.09	.09

(Continued)

Table 1. (Continued)

PARAMETER	VACCINATED (N=24)	UNVACCINATED (N=22)	P-VALUE
Lymphocytes—k/ μ l	1.71 \pm 0.66	1.59 \pm 0.60	.518
Eosinophils—k/ μ l	0.24 \pm 0.56	0.15 \pm 0.40	.55
D-Dimer—ng/ml	189.96 \pm 85.15	304.87 \pm 240.45	.033
Lactate dehydrogenase—unit/L	258.88 \pm 186.94	301.10 \pm 254.98	.523
C reactive protein—unit/L	11.91 \pm 10.49	15.25 \pm 27.36	.582
Ferritin	185.86 \pm 187.23	241.28 \pm 190.94	.326
Outcomes			
Improvement of symptoms within 48 h after infusion	18 (75.0%)	22 (100%)	.403
Improvement of symptoms at day 14 after infusion	24 (100%)	22 (100%)	
30 d all cause hospitalization	0 (0%)	0 (0%)	
What monoclonal antibody did the patient received			
Casirivimab/Imdevimab	17 (70.8%)	19 (86.4%)	.202
Sotrovimab	7(29.2%)	3 (13.6%)	

demographic characteristics, vaccination status, comorbidities, initial symptoms, initial laboratory findings, and outcomes are included in Table 1.

Majority of the patients had at least 2 risk factors. Number of risk factors in the participants depicted in Figure 2.

Majority of the patients improved within 3 days of receiving monoclonal antibody infusion. None of the patients who received monoclonal antibody infusion were hospitalized within 30 days of receiving the monoclonal antibody infusion. Out of the 24 vaccinated patients, 7 had received Ad26.COVS COVID-19 vaccine, 11 had received mRNA-1273 COVID-19 vaccine, and 6 had received BNT162b2 mRNA COVID-19 vaccine. The mean number of days since last vaccination in the vaccinated group was 102 days. The mean number of days since last vaccination for the 6 vaccinated patient that did not improve within 48 hours was 130 days. Out of the 6; 2 had received Ad26.COVS COVID-19 vaccine and 3 had received mRNA-1273 COVID-19 vaccine and 1 had received BNT162b2 mRNA COVID-19 vaccine. Five out of the 6 were more than 65 years of age and all of them had more than 2 risk factors.

In our study, 10 patients received monoclonal antibody infusion during omicron (B.1.1.529) surge, and 36 patients received monoclonal antibody infusion during delta (B.1.617.2) surge. We gave only Sotrovimab to the patient who were admitted during the omicron surge as EUA had withdrawn approval for Casirivimab-imedevimab during that time period.

Discussion

Monoclonal antibodies are produced from the B cells of animals that have been injected with a specific viral protein. The

host receptor for SARS Cov2 cell entry is the angiotensin-converting enzyme 2 (ACE2) receptor. SARS Cov2 binds to ACE2 through the receptor-binding domain of its spike protein.⁸ Casirivimab and imdevimab are recombinant human (IgG1 κ and IgG1 λ , respectively) monoclonal antibodies to the spike protein of SARS Cov2. Casirivimab and imdevimab bind to the nonoverlapping epitopes of the spike protein receptor-binding domain, blocking attachment to the human ACE2 receptor.¹² Bamlanivimab and etesevimab are both recombinant neutralizing human IgG1k monoclonal antibodies to the spike protein of SARS Cov2. They bind to different but overlapping receptors, thus blocking the spike protein attachment to the human ACE2 receptor.¹³ Sotrovimab is also a recombinant human IgG1k monoclonal antibody that binds to a conserved epitope on the spike protein of SARS Cov2. This prevents viral entry into human cells.¹⁴

A study conducted by the CDC showed that the risk of severe COVID-19 disease is significantly higher among the vaccinated patients who have certain risk factors, including age \geq 65 years, immunosuppressed, chronic pulmonary disease, chronic liver disease, chronic kidney disease, chronic neurological disease, diabetes mellitus, and chronic cardiac disease. 78% of the patients who died had at least 4 risk factors.¹⁵ In our study, both the vaccinated and unvaccinated patients with multiple risk factors showed remarkable improvement with monoclonal antibodies and none of them had disease progression.

In 1 multicenter trial, the infusion of casirivimab and imdevimab was associated with a 71.3% reduction in

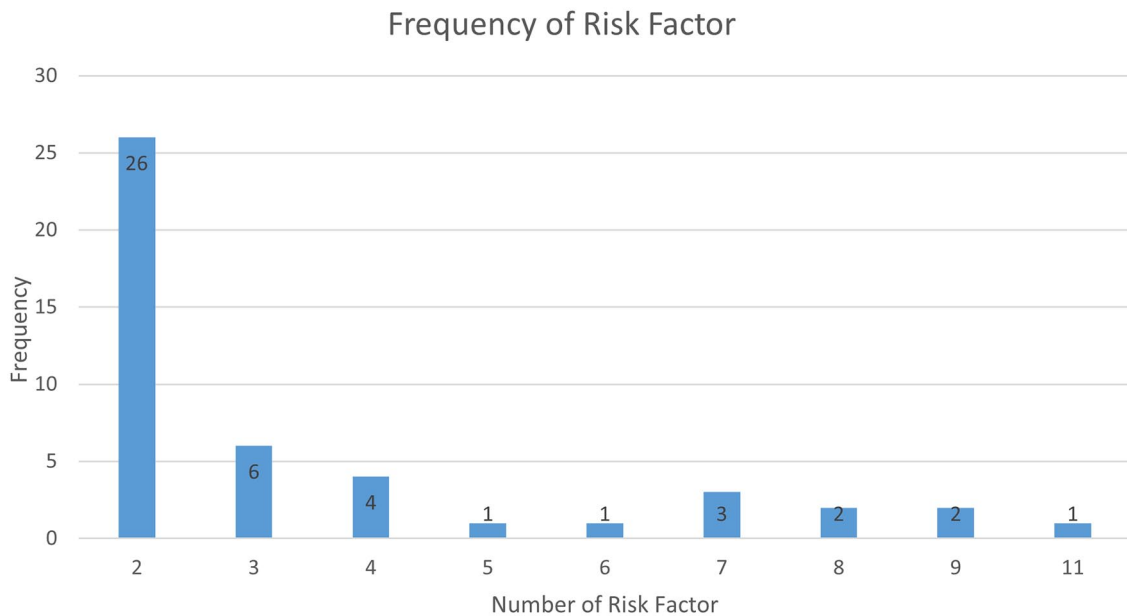


Figure 2. Number of risk factors in patients.

COVID-19—related hospitalization or death from any cause. The median time to resolution of symptoms was 4 days shorter in the group which received casirivimab and imdevimab as compared to the placebo group.¹⁶ The 2400 mg of casirivimab and imdevimab received emergency use authorization in November 2020 to treat mild to moderate COVID-19 in high-risk patients.¹¹ Later, studies showed that 1200 mg dose had the same efficacy as 2400 mg. The 1200 mg received an emergency use authorization in June 2021.¹⁶ In our study 1200 mg was given. Sotrovimab infusion is associated with an 85% relative risk reduction of hospitalization from any cause and death ($P=.002$).¹⁷ Although omicron (B.1.1.529) was reported to cause higher number of breakthrough infections, sotrovimab remained highly effective in preventing disease progression.

None of the patient in our study were hospitalized within 30 days after infection. In our experience, monoclonal antibodies given early are highly effective against both delta (B.1.617.2) and omicron (B.1.1.529) COVID-19 variant regardless of vaccine status and number of risk factors. In March 2022, FDA limited the use of sotrovimab in many regions in the United States due to the emergence of BA.2 Omicron sub-variant.¹⁸ Efficacy of monoclonal antibody infusions need to be monitored due to the emergence of COVID-19 variants. Newer antiviral agents may be more suitable and easier to administer and monoclonal antibody infusions should be restricted to patients who may have contraindications to receive antiviral agents (nirmatrelvir/ritonavir, molnupiravir, and remdesivir).

One of the major limitations of our study was the high refusal rate in our community for monoclonal antibodies. Based on the result we have tried to increase awareness among patients following in our system regarding the effectiveness of monoclonal antibodies in preventing progression of COVID 19 infection. Further

studies can be done to compare the effectiveness of monoclonal antibodies in different variant of COVID-19. Patients who have received monoclonal antibodies should be followed up to assess for any long-term side effect of monoclonal antibodies.

Conclusion

Monoclonal antibodies should be considered in both vaccinated and unvaccinated patients with COVID-19 infection if newer antiviral agents are contraindicated. Our study highlights the effectiveness of monoclonal antibody infusions when given early in the course of COVID-19 infection regardless of vaccination status. Monoclonal antibodies effectively reduce hospitalizations and deaths in patients with high-risk factors for progression to severe COVID-19.

Author Contributions

All the authors were involved in developing the study protocol, collecting the data, analyzing the data, manuscript preparation and approving the final version of this manuscript.

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