A Real-World Assessment of Unvaccinated And Vaccinated Patients With Coronavirus Disease 2019 (COVID-19) Treated With Monoclonal Antibodies During The Delta Wave

Yi Guo (✉ yiguo@montefiore.org)

Montefiore Medical Center

Kelsie Cowman

Montefiore Medical Center

Mei Chang

Montefiore Medical Center

Hongkai Bao

Montefiore Medical Center

Austin Golia

Montefiore Medical Center

Terrence Mcsweeney

Montefiore Medical Center

Linda Bard

Montefiore Medical Center

Roxanne Simpson

Montefiore Medical Center

Erin Andrews

Montefiore Health System

Liise-anne Pirofski

Montefiore Medical Center

Priya Nori

Montefiore Medical Center

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Abstract

Background: Monoclonal antibodies (mAb) prevent COVID-19 progression during early disease presentation. We aimed to compare the mAb treatment outcomes among vaccinated and unvaccinated patients during Delta wave and assess the feasibility of implementing stricter eligibility criteria given mAb scarcity in New York City.

Methods: We conducted a retrospective observational study of casirivimab/imdevimab recipients with mild-to-moderate COVID-19 infection in an emergency department or outpatient infusion center (July 1 – August 20, 2021). The outcome was all-cause hospital admission within 30 days post-treatment between vaccinated vs. unvaccinated patients during Delta surge in the Bronx, NY.

Results: A total of 250 patients received casirivimab/imdevimab (162 unvaccinated vs. 88 vaccinated). The median age was 39 years for unvaccinated patients, and 52 years for vaccinated patients ($p<0.0001$). The median number of EUA criteria met was 1 for unvaccinated and 2 for vaccinated patients ($p<0.0001$). Overall, 6% (15/250) of patients were admitted within 30 days post-treatment. Eleven unvaccinated patients (7%) were admitted (all-cause) within 30-days compared to 4 (5%) of vaccinated patients ($p=0.48$).

Conclusions: All-cause 30-day admission was not statistically different between vaccinated and unvaccinated patients. With limited federal allocation of therapies, programs must prioritize patients at highest risk of hospitalization and death regardless of vaccination status.

Background

Multiple studies demonstrate the efficacy of monoclonal antibodies (mAb) in preventing progression of COVID-19 when administered to high-risk patients early in disease presentation.¹⁻⁶ A study by Cooper and colleagues evaluated nearly 3000 patients with coronavirus disease 2019 (COVID-19) who received mAb therapies in Houston, TX.⁷ Compared to a propensity-matched control cohort, mAb-treated patients had significantly lower rates of hospitalization at 14- and 28-days and decreased mortality at 28-days post-infusion.⁷ However, the impact of circulating SARS-CoV-2 variants was not addressed. A study conducted at our medical center in the Bronx, NY revealed a concerning increase in bamlanivimab treatment failures between January and April 2021, likely due to an increase in the locally circulating variant B.1.526, which was resistant to bamlanivimab monotherapy.⁸ To date, there is a paucity of data addressing regional heterogeneity, outcomes during the Delta surge, or vaccination status of mAb-treated COVID-19 patients. The SARS-CoV-2 variant B.1.617.2 was identified in 70–98% of sequenced isolates across multiple New York City zip codes until July 2021.⁹ Despite the high efficacy of mRNA vaccines against severe disease and hospitalization, an increasing number of breakthrough SARS-CoV-2 infections due to the Delta variant were reported^{10,11}, potentially due to waning antibody levels.¹² The Bronx has had lower vaccine uptake among New York City boroughs. Its residents remain particularly vulnerable to SARS-CoV-2 infection¹³ and access to COVID-19 mAb therapies is of great importance here.

In December 2020, our antimicrobial stewardship team (AST) established a COVID-19 infusion program to treat high-risk patients in the Bronx as per Food and Drug Administration (FDA) emergency use authorization (EUA) criteria.⁸ In May 2021, the FDA expanded treatment criteria by lowering the body mass index (BMI) threshold from 35 kg/m² to 25 kg/m² and including additional comorbidities.^{14, 15} Importantly, patients with history of COVID-19 vaccination are not excluded. In September 2021, the US Health and Human Services Administration modified the mAb allocation process whereby states with fewer COVID-19 infections would receive fewer doses than states with high SARS-CoV-2 transmission.¹⁶ The new federal strategy impacted workflows of programs serving communities with high SARS-CoV-2 transmission and lower vaccine uptake.

The primary objective of this study was to evaluate mAb treatment outcomes among vaccinated and unvaccinated patients during the Delta surge in the Bronx, NY. The secondary objective was to assess the feasibility of implementing stricter mAb eligibility criteria given the impending resource scarcity in New York City.

Methods

We conducted a retrospective observational study of patients with mild-to-moderate COVID-19 meeting expanded EUA criteria received casirivimab/imdevimab in an emergency department (ED) or outpatient infusion center at Montefiore Medical Center (MMC) between July 1 – August 20, 2021.¹⁴⁻¹⁵ Our primary outcome was all-cause hospital admission 30 days post-treatment. COVID-19-related admissions were defined as known symptoms or sequelae (e.g., worsening respiratory status or thromboembolic complications), as determined by the study team.⁸ Patients were considered fully vaccinated two weeks following receipt of 2 doses of BNT162b2 or mRNA-1273, or 1 dose of Ad26.COV2.S.

Immunocompromise was defined as having HIV, liver cirrhosis, sickle cell anemia, asplenia, malignancy, solid organ transplant, bone marrow transplant, active chemotherapy treatment within the past 30 days, chronic use of steroids, tacrolimus, mycophenolate, or biologics.⁸ Institutional prioritization schema utilized September 2021 onward is shown in table 1.

Table 1: Institutional Prioritization Schema for Monoclonal Antibody Therapy during the Delta Wave

	Preferred option	Alternative option
Unvaccinated/partially vaccinated AND symptomatic ≤ 7 days*	Immediate treatment (Emergency Department or same day in infusion center)	Next day scheduling at infusion center
Fully vaccinated > 4 or more months ago OR suspected poor response to vaccine, AND symptomatic ≤ 7 days*	Immediate treatment (Emergency Department or same day in infusion center)	Next day referral at infusion center
Unvaccinated/partially vaccinated AND asymptomatic	Wait and watch, reassess for treatment in 48h if symptom progression	
Fully vaccinated AND asymptomatic	Hold off on treatment	
Fully vaccinated AND mildly symptomatic ≤ 7 days*	Wait and watch, reassess for treatment in 48h if symptom progression	
Post-exposure prophylaxis (PEP) (recent significant exposure in high-risk unvaccinated patient OR severely immunocompromised patient without recent booster or no documented response by serologic testing)	If sufficient doses available for PEP, treat in ED or other non-COVID location as soon as possible; requires same-day negative SARS-CoV-2 PCR)	

*Patients with immune compromise, suspected poor response to vaccines, and potential prolonged viral shedding can be treated up to 10 days from symptom onset per Emergency Use Authorization criteria; use SARS-CoV-2 PCR cycle threshold (Ct) value (if available) to help guide clinical judgement; ONLY use Ct value in clinical context

Patients admitted due to COVID-19 progression on the same day as mAb treatment were excluded.⁸ Bivariate analyses were conducted using χ^2 , Fisher's exact test, or t test, as appropriate. Multivariable analysis was conducted using logistic regression. All statistical tests were 2-tailed and $P < 0.05$ were considered significant. Analyses were conducted using SAS, version 9.4 software (SAS Institute, Cary, NC). The Albert Einstein College of Medicine institutional review board approved the study with waiver of informed consent (IRB# 2020-12525)

Results

Between July 1 – August 20, 2021, 250 COVID-19 patients received casirivimab/imdevimab; 162 (65%) were unvaccinated and 88 (35%) were vaccinated at time of treatment. The median age was 39 years for unvaccinated patients, and 52 years for vaccinated patients ($p < 0.0001$). Overall, 101 (40%) of patients were Hispanic, 89 (36%) non-Hispanic Black, and 31 (12%) non-Hispanic white. Median BMI was not significantly different between the unvaccinated (30) and vaccinated (30) groups ($p = 0.87$). Vaccinated patients had shorter duration of COVID-19 symptoms prior to treatment (median 3 vs. 4 days, $p = 0.02$). The most common risk factor was BMI $> 25 \text{ kg/m}^2$, observed in 115 (71%) unvaccinated and 67 (76%)

vaccinated patients ($p=0.66$). The median number of EUA criteria met was 1 for unvaccinated and 2 for vaccinated patients ($p<0.0001$), table 2. Cycle threshold (Ct) values were available for 104 (64%) of unvaccinated and 36 (37%) of vaccinated patients, with no significant differences between groups, table 2.

Table 2: Characteristics of SARS-CoV-2-Positive Patients Treated with Monoclonal Antibodies by Vaccine Status Prior to Treatment

	Non-vaccinated n (%) n=162	Vaccinated n (%) n=88	P-value
Age, median (IQR)	39 (29-47)	52 (41-63)	<0.0001
Sex			0.65
Male	73 (45)	37 (42)	
Female	89 (55)	51 (58)	
Race/Ethnicity			0.0002
Hispanic	68 (42)	33 (38)	
Non-Hispanic Black	69 (43)	20 (23)	
Non-Hispanic White	11 (7)	20 (23)	
Asian	0 (0)	1 (1)	
Other	6 (4)	5 (6)	
Unavailable	8 (5)	9 (10)	
BMI	30 (25-35)	30 (26-35)	0.87
High-risk co-morbidities per EUA*			
BMI >=25	115 (71)	67 (76)	0.66
Pregnancy	7 (4)	0 (0)	0.054
Chronic lung disease	33 (20)	18 (20)	0.99
Chronic kidney disease	1 (1)	5 (6)	0.0045
Diabetes mellitus	22 (14)	25 (28)	0.004
Immunocompromised conditions**	12 (7)	13 (15)	0.06
Medical-related technological dependence	1 (1)	2 (2)	0.25
Neurodevelopmental disorders	5 (3)	0 (0)	0.17
Cardiovascular disease or hypertension	28 (17)	36 (41)	<0.0001
Number of EUA criteria met	1 (1-2)	2 (1-3)	<0.0001
Symptom Duration Prior to Treatment			
Days, median (IQR)	4 (3-6)	3 (2-5)	0.02
Asymptomatic, n (%)	0	0	

Exact days unavailable, n (%)	0	1 (1)	
Cycle threshold (Ct) values	n=104	n=36	0.06
<25	70 (67)	25 (69)	
Between 25 – 35	30 (29)	6 (17)	
>35	4 (4)	5 (14)	
Hospitalization			
All-cause 30-day admission	11 (7)	4 (5)	0.48
COVID-19-related 30-day admission	7 (4)	1 (1)	0.27
Days between vaccination and treatment, median (IQR)			
Admitted (all-cause 30-day admission)	—	154 (118-166)	
Not admitted	—	160 (133 – 190)	

*EUA: emergency use authorization

**Immunocompromised conditions: HIV, cirrhosis of the liver, sickle cell anemia, asplenia, malignancy, solid organ transplant, bone marrow transplant, patient received chemotherapy, chronic steroids, tacrolimus, mycophenolate, biologics, etc.

Overall, 6% (15/250) of patients were admitted to MMC within 30 days of mAb treatment. Eleven unvaccinated patients (7%) were admitted (all-cause) within 30-days compared to 4 (5%) of vaccinated patients (p=0.48). One (1%) vaccinated patient had a COVID-19-related admission compared to 7 (4%) unvaccinated patients (p= 0.27). When adjusting for age and number of EUA risk factors, vaccine status was still not significantly associated with either all-cause (OR:0.55, CI 0.14-1.83, p=0.30) or COVID-related 30- day admission (OR:0.19, CI 0.01-1.71, p=0.13). Median duration between vaccination and mAb treatment was 160.5 days; 153.5 days for admitted and 160.5 days for non-admitted patients.

Discussion

Although low absolute admission numbers, mAb recipients had a similar all-cause 30-day admission rate regardless of vaccination status supporting FDA *in-vitro* data indicating retained activity of casirivimab/imdevimab against B.1.617.2.¹⁴ Among the 250 treated patients, the majority were unvaccinated, which reflects local statistics in the Bronx during this timeframe.¹³ One vaccinated and 7 unvaccinated patients were admitted for worsening COVID-19.

Overall admissions in this cohort were lower and median age was younger compared to patients treated at our medical center in early 2021⁸, likely due to expanded EUA criteria allowing treatment of younger patients with fewer comorbidities. A low rate of admissions among vaccinated individuals suggests that

prioritization of unvaccinated or higher risk vaccinated individuals (e.g., age >65 with more comorbidities, potentially poor vaccine response, or extended interval since last vaccination) is supported, given recent modifications to the federal mAb allocation process.¹⁶

Our findings indicate that vaccinated, treated patients were more likely to be older and have more underlying risk factors for development of severe COVID-19. Despite this, vaccinated patients had a low rate of both all-cause (5%) and COVID-related (1%) admission within 30-days, which is likely due to the well documented effectiveness of vaccines in protecting against severe disease, hospitalization, and death.¹⁷⁻²² Data from hospitals across the country indicate that most patients admitted with COVID-19 were unvaccinated during the study timeframe.²³⁻²⁵ A study of fully vaccinated mAb-treated patients reported that the number needed to treat (NNT) to prevent one hospitalization was 225 among the lowest-risk patients compared to a NNT of 4 among the highest risk patients.²⁶ Our results also suggest that a “watch and wait” approach is appropriate for fully vaccinated patients with fewer comorbidities versus an immediate test and treat approach for the highest risk patients.

Median duration between vaccination and mAb treatment was high in both admitted and non-admitted patients at 154 and 161 days, respectively, suggesting that waning vaccination-induced antibody levels may have contributed to “breakthrough” infections in our cohort.

Overall, 30-day admission for mAb untreated, SARS-CoV-2 positive patients at MMC (regardless of vaccine status) was low at 4% (22/538) between July-August 2021, perhaps due to a high background rate of prior infection (seroprevalence of 24.3%) along with steadily increasing uptake of vaccination.²⁷ The overall admission rate of mAb-treated patients was similarly low at 6%. Lieberman-Cribbin and colleagues reported that the Bronx residents are more likely to have increased SARS-CoV-2 seropositivity suggestive of past infection.²⁷

Acharya and colleagues demonstrated that there is no significant difference in viral load between vaccinated and unvaccinated patients infected with the SARS-CoV-2 Delta variant.²⁸ We also did not observe any significant difference in available Ct values between vaccinated and unvaccinated patients, although few vaccinated patients had documented Ct values since most were tested outside of our system. A limitation of our study is that the sample size was only 250 patients with full 30-day follow up, and other mAb-treatment outcomes such as reduction in symptom severity or duration, or spread to secondary contacts, were not evaluated. Additionally, the observational, non-randomized, design limited the ability to draw further conclusions about vaccinated vs. unvaccinated mAb-treatment outcomes. The current unprecedented Omicron surge has intensified the resource scarcity of mAbs and the need to prioritize patients at highest risk of hospitalization and death. Institutional prioritization criteria utilized during the Delta wave (table 1) were tightened significantly December 2021 onward.

Conclusion

Since initial authorization of SARS-CoV-2 mAb therapies, multiple factors have impacted the effectiveness of mAbs, including local access to care and SARS-CoV-2 variants. Limited federal allocation of mAbs compels infusion programs to prioritize patients at highest risk of death from COVID-19, particularly during the current Omicron surge. We suspect that the role of mAb therapies in COVID-19 treatment and prevention armamentarium will continue to evolve as other outpatient therapies become available.

Declarations

Ethics approval and consent to participate

The study was approved by Albert Einstein College of Medicine institutional review board approved with waiver of informed consent since analyses were based on retrospective data collection via electronic health record (IRB# 2020-12525). All methods were performed in accordance with the relevant guidelines and regulations as stated in the Declarations of Helsinki.

Consent for publication

Not applicable

Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available due to patient privacy and confidentiality but are available from the corresponding author on reasonable request.

Competing interests

PN receives speaker fees from Regeneron and Medscape. All other authors declare that they have no competing interests.

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Authors' contributions

YG, KC, MC, HB, AG, TM, LB, RS, LP, PN contributed to study design, data review, and manuscript preparations. YG, MC, HB, AG, TM also completed data collection. KC and EA performed software data acquisition and interpretation of data. KC completed the formal statistical analysis. YG, KC, PN drafted manuscript. All authors reviewed and edited manuscript. All authors have read and approved the final manuscript.

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