Implementation and outcomes of monoclonal antibody infusion for COVID-19 in an inner-city safety net hospital: A South-Bronx experience

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Abstract: Background: Monoclonal antibody therapy (MAT) is recommended in mild to moderate Coronavirus disease 2019 (COVID-19) patients who are at risk of progressing to severe disease. Due to limited data on its outcomes and the logistic challenges in administering the drug, MAT has not been widely used in the United States (US) despite of emergency use authorization (EUA) approval by the Food and Drug Administration (FDA).

Aim: We aim to study the outcomes of MAT in patients predominantly from ethnic minority groups and the challenges we experienced in implementing the infusion therapy protocol in an inner-city safety-net-hospital in the South Bronx.

Methods and results: We conducted a retrospective observational study of 49 patients who were offered MAT as per EUA protocol of FDA. Patient who met the criteria for MAT and received therapy were included in treatment group ($n = 38$) and the remaining ($n = 11$) who declined treatment were included in the control group. A majority of patients (76%) in the study group reported symptomatic improvement, the day after infusion. There was statistically significant reduction in COVID-19 related hospitalizations (7.8 vs 54.5%, $P = < 0.001$) mortality (0 vs 18.1%, P value $= 0.008$) in the treatment group.

Conclusion: MAT reduced both hospitalization and mortality in this predominantly Hispanic patient population with mild to moderate COVID-19 with high risk factors for disease progression.

Keywords: Casirivimab-imdevimab ■ Bamlanivimab-etesevimab ■ Bamlanivimab ■ Mild-moderate COVID-19 ■ Mortality

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INTRODUCTION

COVID-19 began in Wuhan, China in December 2019 and as of May 6th, 2021 it has infected 32,356,034 people in the US alone.[1] A disproportionately higher rate of infections, hospitalizations, and deaths are reported among the minority population in the US. As compared to Caucasians, African Americans have 1.1 times higher rates of infections, 2.8 times higher rates of hospitalization and 1.9 times higher death rates. Hispanics have 2 times higher rates of infection, 3 times higher rates of hospitalization and 2.3 times higher death rates as compared to Caucasians.[2] As per US census 2019, the Bronx borough has a Hispanic population of 56.4%.[3] Located in the South Bronx, our hospital serves a community with predominantly minority population. As of May 6th, 2021, the rate of COVID-19 cases in the Bronx borough is 10,377 per 100,000 people,[4] one of the highest in the US.

Patients with mild COVID-19 illness are usually managed at home with supportive care.[5] In November 2020, FDA issued an EUA for the use of Bamlanivimab (BAM), a MAT for mild to moderate COVID-19. EUA has been recently revoked for Bamlanivimab monotherapy due to the emergence of resistant strains.[6] FDA currently approved EUA for use of combination treatment with Casirivimab-Imdevimab (CAS-IMD), and Bamlanivimab-Etesevimab (BAM-ETE).[7,8]

Clinical trials of MAT in mild to moderate COVID-19 showed promising outcomes in preventing progression to severe disease in patients with risk factors. Published literature on MAT showed a decrease in viral load and better clinical outcomes including emergency room visits and hospitalization in the treatment group as compared to the control group.[9,10] However African American and

Hispanic patients were underrepresented in these clinical trials. In our retrospective observational study, we report the outcomes of MAT in mild to moderate COVID-19 in predominantly Hispanic patients of the South Bronx.

MATERIAL AND METHODS

We conducted a retrospective observational study from November 27th, 2020 to March 17th, 2021 at BronxCare Health System. The study was approved by the Institutional Review Board (IRB) at BronxCare Health System IRB # 01 14 21 16.

Adult patients ($\geq$ 18 years of age) diagnosed with mild to moderate COVID-19 based on National Institute of Health (NIH) guidelines who were offered the MAT, were included in the study. The diagnosis of COVID-19 was confirmed using the real-time reverse transcriptase polymerase chain reaction (RT-PCR) of Severe Acute Respiratory Syndrome Coronarvirus-2 (SARS-CoV-2) in nasopharyngeal swabs of study population. The inclusion and exclusion criteria were based on EUA guidelines issued by FDA.[6-8] Patients with symptoms of less than 10 days duration and presence of one or more high risk conditions for progression to severe disease qualified for the infusion. Criteria for high-risk of disease progression include (1). Body mass index (BMI) $\geq$ 35 kg/m^2, (2). Chronic kidney disease, (3). Diabetes, (4). Immunosuppressive disease, (5). Current immunosuppressive treatment, or (6). $\geq$ 65 years of age. High risk groups also included patients $\geq$ 55 years of age with cardiovascular disease or hypertension or chronic obstructive pulmonary disease/other chronic respiratory disease.

Patients received BAM (700 mg) or CAS-IMD (1200–1200 mg) based on the availability and were administered in a dedicated infusion unit. All patients were monitored for an hour after infusion for any adverse reactions.

Patients who required admission for COVID-19, patients with severe disease, patients requiring oxygen, or increasing oxygen requirements in patients who were on long term oxygen therapy for non-COVID-19 causes were excluded from the study.

Patients with mild-moderate COVID-19 disease with risk factors who were offered to us for MAT infusion but declined therapy, served as control group (Table 2).

Data pertaining to demographics, comorbidities, laboratory parameters and medications were abstracted from electronic medical records. All patients were followed up to 30 days via tele or clinic visits.

Statistical analysis: Continuous variables were expressed as mean $\pm$ standard deviation. Categorical variables were expressed as proportions. Mann Whitney U test was applied using the computer-generated program SPSS, version 27. Normality was checked using kurtosis coefficients and P-value of less than 0.05 was considered to be statistically significant.

RESULTS AND DISCUSSION

Results

A total of 49 patients were included in the study, of which 38 (treatment group) received MAT and 11 declined MAT (control group). In the treatment group 16 received the BAM monotherapy and 22 received the CAS-IMD therapy. We compared BAM monotherapy with CAS-IMD therapy. The median age group for BAM and CAS-IMD receiving groups were 70 years and 65 years, respectively (P value = 0.49) and both groups had female predominance (56.3 vs 59.1%; P value = 0.89). A majority of the patients were Hispanics (60.5%) followed by African Americans (23.7%), Whites (10.5%) and Asians (5.3%). Both the groups had an average BMI of 30.8 kg/m^2 (P value = 0.53). Hypertension and diabetes were the most common risk factors in both the groups (78.9%, P value = 0.74 and 44.7% Pvalue = 0.94, respectively). There was a wide range of symptom presentation with a median duration of 5 days from symptom onset ($P = 0.42$). Six patients (15.8%) were noted to have antibodies to SARS-CoV-2 nucleocapsid antigen on presentation. There were no significant differences between the two monoclonal antibody infusions (Table 1).

Patients with mild-moderate COVID-19 disease and risk factors who were referred to us for MAb infusion but declined the therapy, served as control group. Data for control group was restricted to hospitalizations and deaths. Eleven patients were included as control group (Table 2). There was a statistically significant reduction in COVID-19 related hospitalization rates (7.8 vs 54.5%, P = < 0.001) and in mortality (0 vs 18.1%, Pvalue = 0.008) in the treatment group.

Discussion

MAT has been approved for mild to moderate COVID-19 in patients at high risk for progression to severe disease. One of the earliest published data available on the use of MAT in mild to moderate COVID-19 was the interim results of BLAZE-1 trial, where use of LY-CoV555 reduced the viral load on day 11 after infusion in patients with mild to moderate COVID-19.[11] Weinreich et al. used a combination of monoclonal antibodies REGN-CoV2 which reduced viral load by day 7 after infusion in patients with mild to moderate COVID-19.[10] Gottelib showed that a combination of BAM-ETE had significant decrease in viral loads as compared to BAM monotherapy. The study

Table 1. Characteristics of 38 Patients with COVID-19 treated with monoclonal antibodies*.

	Total (N = 38)	Bamlanivimab 700 mg(N = 16)	Casirivimab 1200 mg and Imdevimab 1200 mg(N = 22)	P value
Median age (IQR) - years	65 (55 – 65)	70 (58 – 79)	65 (55 – 65)	0.49
Male sex — no. (%)	16 (42.1)	7 (43.7)	9 (40.9)	0.89
Race or ethnic group — no. (%)[†]				0.145
White	4 (10.5)	1 (6.3)	3 (13.6)	
Black	9 (23.7)	3 (18.7)	6 (27.2)	
Hispanic	23 (60.5)	12 (75.0)	11 (0.5)	
Asian	2 (5.3)	0 (0)	2 (0.9)	
Body Mass Index (IQR) - kg/m2	30.8 (26.2 – 33.1)	32.6 (27.1 – 32.6)	30.1 (26.1 – 35.0)	0.53
Risk factor — no. (%)				
Hypertension	30 (78.9)	12 (75.0)	18 (81.8)	0.74
Diabetes mellitus	17 (44.7)	7 (43.7)	10 (45.4)	0.94
Chronic kidney disease	5 (13.2)	2 (12.5)	3 (13.6)	0.96
Cardiovascular disease	10 (26.3)	2 (12.5)	8 (36.4)	0.22
Chronic respiratory disease	13 (34.2)	4 (25.0)	9 (40.9)	0.42
Immunosuppressive disease or currently receiving immunosuppressive treatment	6 (15.8)	2 (12.5)	4 (18.2)	0.67
Signs and symptoms around the time of neutralizing monoclonal antibody infusion — no. (%)				
Anosmia	12(31.5)	4(25)	6 (27.3)	0.92
Cough	27 (71)	10 (62.5)	16 (72.7)	0.61
Shortness of breath	2 (5.2)	0 (0)	2 (9.09)	0.65
Ageusia	10 (26.3)	6 (37.5)	4 (18.18)	0.33
Diarrhea	4 (10.5)	1 (6.25)	3 (13.6)	0.71
Fatigue	16 (42.1)	9 (56.2)	7 (31.8)	0.21
Fever	22 (57.9)	10 (62.5)	12 (54.5)	0.69
Headache	10 (26.3)	3 (18.7)	7 (31.8)	0.62
Myalgia	25 (65.8)	10 (62.5)	15 (68.2)	0.78
Nasal Congestion	7 (18.4)	1 (6.25)	6 (27.2)	0.28
Sore throat	8 (21.1)	2 (12.5)	6 (27.2)	0.45
Duration of signs and symptoms prior to neutralizing monoclonal antibody infusion (IQR) — days	5 (4 – 7)	5 (3 – 7)	6 (4 – 7)	0.42
Median laboratory values (IQR)				
White-cell count — × 10−3/mm3	5.1 (4.0 – 6.2)	4.8 (3.8 – 6.1)	5.4 (4.3 – 6.3)	0.34
Neutrophil count — k/μl	2.9 (2.0 – 3.7)	3.0 (2.0 – 4.3)	2.9 (2.0 – 3.4)	0.83
Lymphocytes — k/μl	1.6 (1.1 – 1.9)	1.5 (1.0 – 1.7)	1.6 (1.3 – 1.9)	0.34

Table 1 (*continued*)

	Total (N = 38)	Bamlanivimab 700 mg(N = 16)	Casirivimab 1200 mg and Imdevimab 1200 mg(N = 22)	P value
Eosinophils – k/μl	0.45 (0-0.1)	0.5 (0-0.1)	0.41 (0-0.1)	0.61
d-Dimer — ng/ml	160 (150 – 313)	160 (150-307)	166 (150 – 359)	0.83
Lactate dehydrogenase — unit/L	258 (206 – 330)	238 (190 – 296)	270 (222 – 371)	0.19
C reactive protein — unit/L	6.2 (5.0 – 13.4)	5.0 (5.0 – 12.2)	6.7 (5.0 – 13.4)	0.40
Ferritin	177 (99 – 447)	122 (62 – 361)	292 (153 – 477)	0.09
Anti-SARS-CoV-2 IgG/IgM — no. (%)	6 (15.8)	2 (12.5)	4 (18.2)	0.99
Outcomes — no. (%)				
Improvement of symptoms at day 1 after infusion	29 (76.3)	10 (62.5)	19 (86.4)	0.42
Improvement of symptoms at day 14 after infusion	33 (86.84)	12 (85.71)	21 (95.45)	0.69
30 day all cause hospitalization	4 (10.5)	2 (12.5)	2 (9.1)	0.47
Hospitalization due to COVID-19 within 30 days	3 (7.8)	2 (12.5)	1(4.5)	0.69

*Percentages may not total 100 because of rounding. COVID-19 denotes coronavirus disease 2019, and IQR interquartile range.

†Race and ethnic group were reported by the patient.Two patients from the BAM group and one patient from CAS-IMD group required hospitalization for COVID-19 disease. However, all three patients were eventually discharged. A majority of patients (76%) reported symptomatic improvement in 24 h after infusion.

Table 2.. Hospitalization and mortality rates.

Variable	Treatment group(n = 38)	Control group(n = 11)	P value
Hospitalization due to any cause	4 (10.5%)	6 (54.5%)	0.002
Hospitalization due to COVID-19 related cause	3 (7.8%)	6 (54.5%)	< 0.001
30-day mortality	0	2 (18.1%)	0.008

also reported higher percentage of putative treatment resistant strains when BAM was used as monotherapy. This lead the FDA to revoke EUA for BAM monotherapy.[6,9] Multiple trials on MAT use in COVID-19 are underway.[12]

Although these studies showed promising outcomes, very limited number of patients in the US who were eligible received MAT. Our study aim was to examine the efficacy and feasibility of MAT in an inner-city safety-net-hospital with limited resources. In our inner-city safety-net-hospital with limited resources creating infusion units with adequate isolation from other patients is particularly challenging. Given the high rate of risk factors for adverse outcomes in our population we recognized a clear need for MAT. We created a comprehensive and successful mon-

oclonal antibody infusion program. Education of primary care physicians and fast track emergency room physicians was the first task. Identifying a space isolated from other non COVID-19 patients was the next and difficult task as traditional infusion centers had many immunocompromised patients being simultaneously treated. A dedicated infusion team was created which could be activated once patient was identified and made available around the clock. This infusion team has been made available round to clock to help in care transition and management of identified patients. Infusions were administered in rooms equipped with negative pressure and cardiopulmonary monitoring which were made available during late evenings on most days and all weekends. Patients were brought to these in-

fusion rooms using a separate entrance with minimal exposure to others. All patients were followed up using televisits.

In our study we used both BAM and CAS-IMD infusion based on availability. There was no statistically significant difference in baseline characteristics between the two groups. A total of 38 patients received infusions and a majority of patients (76.3%) reported early improvement of symptoms which was similar to other clinical trials.[13] There were no adverse reactions reported in the study group. There were no deaths in the treatment group during the 30-day study period post infusion (0 vs 18%: Pvalue $= 0.08$). Our study showed a significant mortality benefit as opposed to other studies which showed only a decrease in viral load. We believe early administration of MAT in majority of our patients (median duration: 5 days) may have influenced this favorable outcome. More prospective randomized studies are needed to determine the benefits of MAT in minority Hispanic population.

We also found that MAT administration significantly reduced COVID-19 hospitalizations (7.8 vs 54.5%, Pvalue < 0.001) and hospitalization due to any cause (10.5 vs 54.5%, Pvalue $= 0.002$) in the treatment group when compared to control group. Among the 4 patients in the treatment group who were hospitalized, three were hospitalized due to progression to severe COVID-19 and one was admitted for abdominal pain secondary to partial gastric outlet obstruction diagnosed a month prior to SARS-CoV-2 infection. He was discharged after resolution of symptoms. Three of the 38 patients (7.8%) admitted for COVID-19 management presented later after symptoms onset (8–9 days). This may suggest that delay in MAT administration after symptom onset may affect its efficacy. However, all patients were discharged with resolution of symptoms. Our study findings are consistent with other studies in reduction of hospitalization rates.[10,11]

Our study has certain limitations. Though our study population was small, we met the target for comparable number needed to treat to show benefit (NNT to prevent hospitalization $= 16.7$)[8] aligned with findings of other studies. We used BAM when EUA was initially issued. However, in view of recent revocation of BAM due to emergence of BAM resistant strains, our study results can not be extrapolated to use BAM as monotherapy. We now administer BAM- ETE and CAS-IMD.

CONCLUSION

MAT appears to be significantly effective in reducing COVID 19 related hospitalizations and mortality in our predominantly Hispanic patients with a high burden of risk factors for adverse outcomes and disease progression. The

logistical challenges are difficult, but they can be overcome by a dedicated team of medical personnel. Early administration of MAT is paramount to achieving favorable outcomes. Given the mortality benefit seen in our population we encourage hospitals and community health centers to establish infusion centers to provide MAT for COVID-19 patients.

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