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Background

Higher rates of COVID-19 related hospitalization and death are reported in patients with underlying health conditions and advanced age as compared to the general population. While polyclonal immunity generated by vaccines has demonstrated protection against severe disease, vaccine response takes time and may be inadequate in some high-risk populations.[1] Treatment with anti-SARS-CoV-2 neutralizing monoclonal antibodies affords prompt, passive humoral immunity and has been shown in randomized, controlled trials to reduce rates of hospitalization and death from COVID-19 in high-risk ambulatory patients treated early in the course of infection.[2,3] The U.S. Food and Drug Administration (FDA) has issued Emergency Use Authorization for four monoclonal antibody products requiring intravenous administration including bamlanivimab monotherapy (since retracted), casirivimab/imdevimab, bamlanivimab/etesevimab (since retracted) and sotrovimab for the treatment of early, mild-moderate COVID-19 in high-risk outpatients as well as inpatients not hospitalized for COVID-19. How to effectively identify qualifying patients, arrange for infusion and administer therapy, however, poses challenges to the widespread, equitable utilization of these potentially lifesaving therapies.

Methods

In this observational feasibility study conducted at three affiliated healthcare centers in the Philadelphia region between Nov 15, 2020 and April 30, 2021, patients meeting high-risk EUA criteria were identified through primary care or specialist provider referral or self-referral. Secure text accounts and a call center were utilized for referrals as well as electronic medical record (EMR) based communication. Outreach to harder-hit ZIP codes included identifying primary care teams and testing sites to facilitate referrals.

Treatment workflow included Advanced Practice Providers who contacted patients to confirm eligibility, obtain consent given the products' investigational nature, and schedule infusion appointments. Patients provided their own transportation to infusion sites. In cases where private transportation was unavailable, patients were directed to use public transportation in accordance with Centers for Disease Control (CDC) guidance including masking and social distancing in transit. Dedicated rooms were available at three outpatient infusion centers with nursing and pharmacy staff trained in SARS-CoV-2 infection control measures, rapid response and drug preparation.

The primary study outcome was treatment of as many possible qualifying patients with SARS-CoV-2 monoclonal antibody therapy. Secondary outcomes included infusion related complications, COVID-19 related hospitalization or death within thirty days, and time to symptom resolution. Information on Community Need Index and Social Vulnerability Index based on patient ZIP codes was also collected. The study was reviewed and approved by our Institutional Review Board.

Results

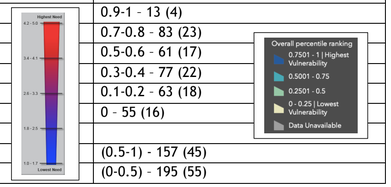
Patient characteristics (Table 1): 367 patients were treated with neutralizing monoclonal antibodies during the study period. The mean patient age was 63 years (SD 13.47 years). A total of 201 patients (55%) were male, 276 patients (75%) were white, 54 patients (15%) were African American, 10 patients (2.7%) were Asian and 9 patients (2.4%) identified as Latino or Hispanic. All patients had a first positive direct SARS-Cov-2 test within 10 days of infusion and met EUA high-risk criteria with 232 patients (63%) having more than one risk factor. Thirty-two patients (9%) had received at least one dose of SARS-CoV-2 vaccination with 19 patients presenting 10 or more days from first vaccination. Of 352 patients with available zipcodes (Table 2), 135 patients (38%) had a Community Need Index >3.5 and 157 patients (45%) had a Social Vulnerability Index >0.5.

Table 1: Patient Characteristics

Characteristic	Total N=367
Age – yr	
>75	74 (20)
65-74	98 (27)
55-64	108 (29)
<55	87 (24)
Male sex – no. (%)	201 (55)
Race – no. (%)	
White	276 (75)
Black	54 (15)
Asian	10 (2.7)
Latino/Hispanic	9 (2.4)
Other	7 (1.9)
Unknown	11 (3)
Risk factor for hospitalization – no. (%)	
Age >65y	164 (45)
Age >55y + Hypertension	115 (31)
Immunosuppression	91 (25)
Body-mass index >35	83 (23)
Diabetes mellitus	78 (21)
Age>55y + COPD	67 (18)
Age >55y + CAD	50 (14)
Chronic Kidney Disease	24 (6.5)
>1 Risk factor	232 (63)
Vaccinated for SARS CoV-2 – no. (%)	N=32 (9)
1 dose of vaccine	30 (94)
mRNA	28 (88)
Adenoviral vector vaccine	2 (6)
COVID-19 10 days from first dose	19(59)
2 doses of mRNA vaccine	2 (7)

Table 2: Community Need Index and Social Vulnerability Index based on Zipcode

Community Need Index, N=352, no. - %	Social Vulnerability Index, N=352, no. - %
5 - 15 (4)	0.9-1 - 13 (4)
4 - 75 (21)	0.7-0.8 - 83 (23)
3 - 91 (26)	0.5-0.6 - 61 (17)
2 - 142 (40)	0.3-0.4 - 77 (22)
1 - 29 (8)	0.1-0.2 - 63 (18)
	0 - 55 (16)
(5-3.5) - 135 (38)	(0.5-1) - 157 (45)
(3.5-1) - 217 (62)	(0-0.5) - 195 (55)



(cni.dignityhealth.org, atsdr.cdc.gov, n.d.)

Table 3: COVID-19 Course

COVID-19 course	Total N=367
Monoclonal Antibody received	
bamlanivimab	190 (52)
casirivimb/Imdevimab	93 (25)
bamlanivimab/etesevimab	84 (23)
Infusion reaction – no. (%)	
Acute[1]	3 (0.8)
Leading to infusion cessation[2]	2 (0.5)
Delayed[3]	1 (0.2)
Time to full symptom resolution after infusion as reported by patient – no (%)	N=236
1-2 d	92 (39)
3-5 d	80 (34)
6-11 d	34 (14)
14+ d	30 (13)
Hospitalized for COVID-19 after infusion	
Total – no. (%)	20 (5)
Within 24h of infusion	11 (3)
Within 7d of infusion	8 (2)
Within 30d of infusion	1 (0.2)
COVID-19 related death	1 (0.2)
Symptom onset to infusion, median, d	7, SD (2.82)
COVID-19 course	Total N=367
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Infusion reaction – no. (%)	
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Delayed[3]	1 (0.2)
Time to full symptom resolution after infusion as reported by patient – no (%)	N=236

[1]A disorder characterized by an adverse reaction to infusion to the pharmacological substance occurring immediately, with the infusion.
[2]A disorder characterized by an acute inflammatory reaction causing a hypersensitivity immune response necessitating infusion cessation.
[3]A disorder characterized by an adverse reaction to infusion to the pharmacological substance occurring within hours of the infusion.
(Limsuwan T, Demoly P. Acute Symptoms of Drug Hypersensitivity. Med Clin N Am 2010 Jul;94(4):691-710).

Results

Bamlanivimab monotherapy was administered to 190 patients (52%), while 93 patients (25%) received casirivimab/imdevimab and 84 patients (23%) received bamlanivimab/etesevimab (Table 3). Four patients experienced an infusion reaction including two necessitating infusion cessations, one with anaphylaxis. Of 236 patients reporting time to symptom resolution, 172 patients (73%) were symptom free within 5 days of infusion. Twenty patients (5%) treated were hospitalized for COVID-19 within thirty days of infusion including one patient death from COVID-19. Patients requiring hospitalization had a median time from symptom onset to infusion of seven days (SD 2.82) and eleven patients (55%) were admitted within twenty-four hours of infusion. Five hospitalized patients (25%) were receiving therapy for active malignancy.

Conclusions

Our study demonstrates that treatment with anti-SARS-CoV-2 neutralizing monoclonal antibodies is feasible in a high resource urban health care setting. Infusion was well tolerated by the majority of patients and there were no known infusion center SARS-CoV-2 exposures.

Twenty treated patients (5%) were hospitalized for COVID-19 including one patient death during the study period. Randomized clinical trials of anti-SARS-CoV-2 monoclonal antibodies have reported lower rates of hospitalizations in treated patients than we found in our patients.[2,3] This may reflect the expanded time frame for infusion through EUA therapy (10 days) as compared to clinical trials with patients missing the optimal window for benefit, and/or increased comorbidities in real world patients. Monoclonal antibody efficacy may be diminished in SARS-CoV-2 viral mutations involving spike protein substitutions which are now in global circulation although data are lacking on the clinical relevance of mutations. Casirivimab/imdevimab has been shown to maintain variant coverage, while Sotrovimab, the most recent antibody to receive authorization, has expanded coverage of viral variants.[4]

Given the potential for benefit in high-risk patients, especially those who are unvaccinated or at risk for poor vaccine response, and feasibility with a coordination of resources as our study demonstrates, anti-SARS-CoV-2 monoclonal antibody therapy in early COVID-19 and efforts towards equitable utilization should remain a focus for researchers and clinicians. Expanding therapy to include emergency department and/or observation admission administration as well as sub-cutaneous dosing may increase accessibility.

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