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Bamlanivimab for Mild to Moderate COVID-19 in Kidney Transplant Recipients

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Kidney transplant recipients (KTRs) are at an increased risk of hospitalization, complications, and mortality from COVID-19 compared with the general population.[1–5] Among KTRs with COVID-19 in the United States, studies have shown hospitalization rates ranging from 32% to 100%,[1,3–6] intensive care unit (ICU) admission rates from 20% to 61%,[2,4] and overall mortality of 13% to 39%.[1,2,4–6] A high incidence of acute kidney injury was noted, ranging from 30% to 89%,[2,4–6] while renal replacement therapy was required in 13% to 21% of patients.[1,7] Given the natural history of COVID-19 pneumonia, most of these complications occurred ≥1 week after the diagnosis of COVID-19.

Given the high impact of COVID-19 infection on KTRs, early COVID-19–directed therapies are critical. Bamlanivimab (LY-CoV555) was given Emergency Use Authorization (EUA) by the US Food and Drug Administration on November 9, 2020.[8] It is a neutralizing IgG1 monoclonal antibody that binds to the receptor-binding domain of the spike protein of SARS-CoV-2, inhibiting attachment to human angiotensin-converting enzyme 2 receptor. This EUA was given for treatment of mild to moderate COVID-19 in patients ≥12 years of age weighing >40 kg who are positive with a direct viral testing for SARS-CoV-2 and have high risk for progressing to severe COVID-19 and/or hospitalization.[8]

KTRs with COVID-19 are considered high risk because of immunosuppressive medication use.[9] Studies on the use of bamlanivimab among KTRs are limited. To provide more insight on the use of bamlanivimab in KTRs we report our experience with 24 KTRs.

RESULTS

Demographics

Demographic information is shown in Table 1.

Symptom Course, Testing, and Time to Infusion

The average time from symptom onset to SARS CoV-2 polymerase chain reaction (PCR) results was 2.08 ± 1.2 days. The most common symptoms were fatigue, fever, and cough. Three of 24 patients were tested before a scheduled procedure or because of positive contacts for SARS CoV-2. They were asymptomatic at the time of SARS CoV-2 PCR testing but subsequently developed symptoms. The mean time from diagnosis to bamlanivimab infusion was 2.67 ± 2.5 days. More than half (62.5%) of KTRs received the infusion locally from their primary care or emergency department physician; 37.5% received it at our transplant center's designated COVID-19 infusion center. Most of the patients reported a resolution of symptoms within 31.4 ± 15.9 hours after the infusion. None of the patients reported difficulty in arrangement of bamlanivimab infusion. Three patients reported side effects during or after the infusion, including nausea, headache, worsening of body aches for 1 day, and rash on the fingers. No anaphylactic reactions were reported. This is summarized in Table 1.

Immunosuppression and Outcomes

Fourteen of 24 patients (54.2%) were taking tacrolimus and mycophenolic acid on a prednisone-free regimen before COVID-19 infection. Thirteen of 24 had no change to their immunosuppressive regimen after COVID-19 diagnosis, while 7 of 24 had their dose of mycophenolic acid decreased by ≥50%. Four of 24 (16.7%) patients required hospitalization, all of whom required supplemental oxygen and 2 of whom required ICU care. One patient required mechanical ventilation and dialysis therapy for acute kidney injury and died. Among those who required ICU admission, 1 patient

Table 1. Demographics, transplant history timeline of symptoms, testing, resolution, and adverse events

Demographics, timelines, and adverse events	Value or %, N = 24
Age, yr, median (range)	53.1 (36.3–76.6)
Gender, n (%)	
Male	15 (62.5)
Female	9 (37.5)
Race, n (%)	
Caucasian	19 (79.2)
African American	4 (16.6)
Hispanic	1 (4.2)
Kidney transplant, n (%)	
Living donor	10 (41.7)
Deceased donor	14 (58.3)
Combined transplants, n	
Kidney and pancreas	3
Heart and kidney	1
Liver and kidney	1
Comorbidities, n (%)	
Hypertension	19 (79.2)
Hyperlipidemia	11 (45.8)
Diabetes mellitus (types I and II)	7 (29.2)
Asthma	3 (12.5)
Hypothyroidism	4 (16.7)
Coronary artery disease	3 (12.5)
Median time from transplant to COVID-19, days (range)	1610 (19–11,884)
Baseline creatinine before COVID-19, mg/dl ± SD	1.43 ± 0.46
Median ± SD time from symptom onset to COVID-19 testing, days (median [range])	2.08 ± 1.2 (2 [0–4])
Median ± SD time from SARS CoV-2 PCR test result to infusion,[a] days	2.67 ± 2.5 (1.5 [0–9])
Median ± SD time from onset of symptoms to infusion,[a] days	4.75 ± 2.3 (4 [2–8])
Major symptoms, n (%)	
Fatigue	15 (62.5)
Fever	12 (50)
Cough	9 (37.5)
Anosmia/dysgeusia	4 (16.7)
Chills	4 (16.7)
Headache	4 (16.7)
Shortness of breath	4 (16.7)
Sore throat/sinus congestion	3 (12.5)
Pre–COVID-19 immunosuppressive regimen	
Tacrolimus/mycophenolic acid	13 (54.2)
Tacrolimus/mycophenolic acid/prednisone	4 (16.7)
Tacrolimus/sirolimus	3 (12.5)
Tacrolimus/sirolimus/mycophenolic acid	1 (4.2)
Mycophenolic/prednisone	1 (4.2)
Other	2 (8.3)
Post–COVID-19 immunosuppressive regimen	
No change to regimen	13 (54.2)
Decrease mycophenolic acid by ≥50%	7 (29.2)
Hold mycophenolic acid	4 (16.7)
Adverse events from infusion, n (%)	
Nausea	2 (8.3)
Headache	2 (8.3)
Rash on fingers that resolved within 2–3 days	1 (4.2)
No side effects noted, %	87.5
Median ± SD time to resolution of symptoms reported (among those who reported improvement), hours (median [range])	31.4 ± 15.9 (24 [12–72]), n = 14
No improvement, n (%)	6 (26.1)
Other symptoms improved but fever for 30 days, n (%)	1 (4.2)
Fatigue for 30 days, n (%)	1 (4.2)
Fever 14 days, n (%)	1 (4.2)
Unable to recall, n (%)	1 (4.2)

(Continued on following page)

Table 1. (Continued)

[a]Bamlanivimab infusion
PCR, polymerase chain reaction; SD, standard deviation.

each was diagnosed with COVID-associated pulmonary aspergillosis and disseminated histoplasmosis later in the course and were treated with antifungal therapies. All admitted patients received dexamethasone for 10 days per our COVID-19 infection treatment protocol and 2 of 4 received remdesivir. Patients in the ICU received additional dexamethasone based on the Dexamethasone Treatment for the Acute Respiratory Distress Syndrome trial regimen.[S1] These data are shown in Table 2.

DISCUSSION

Clinical data on bamlanivimab use in KTRs are currently limited. We hereby report its use, safety, effect on timeline of symptoms, and outcomes in a real-world setting. Most of our patients avoided hospitalization, ICU admission, and did not report any sequalae of COVID-19 in the follow-up period. Dhand *et al.*[S2] reported outcomes in 6 KTRs with none requiring hospitalization. In their report, the average time from onset of symptoms to infusion was 3.3 days.[S2] In our

Table 2. Follow-up and outcomes

Follow-up or outcome	Value or %, N = 24
Mean ± SD follow-up after bamlanivimab, days (median [range])	66.7 ± 20.7 (70 [23–113])
Hospitalization, n (%)	4 (16.7)
Need for supplemental oxygen[a]	4/4 admitted patients
Median ± SD time from infusion[b] to admission, days (median [range])	13.5 ± 9.5 (11 [5–27])
Site of infusion,[b] %	
Transplant infusion center	37.5
Local clinic/hospital	62.5
Intensive care unit admission, n (%)	2 (8.3)
Additional diagnosis in patients admitted to the intensive care unit, n	
Aspergillosis	1
Histoplasmosis	1
Additional COVID-19 treatments, n (%)	
Dexamethasone	4 (12.5)
Remdesivir	2 (8.3)
Mechanical ventilation, n (%)	1 (4.2)
Acute kidney injury, n (%)	3 (12.5)
Need for dialysis, n (%)	1 (4.2)
Death, n (%)	1 (4.2)

[a]At the time of admission to the hospital.
[b]Bamlanivimab infusion.

study, the mean time from onset of symptoms to infusion was 4.75 days; however, mean SARS CoV-2 PCR testing and return time was 2 days, which accounted for nearly half the time. Distance from the transplant center, availability, and arrangement of bamlanivimab were other factors in this regard. In our series, 4 patients required hospitalization over a mean follow-up time of 66 days, with an average time to hospitalization of 13.5 days after receiving bamlanivimab infusion. Respiratory failure with hypoxemia related to COVID-19 infection was the cause of hospitalization in 3 cases, while it was a contributory cause in the other. Work-up for clinical evidence of other etiologies for hypoxemia, such as heart failure, pulmonary embolism, and acute respiratory distress syndrome, was negative at the time of hospitalization in all 4 patients, and none had underlying lung disease. All hospitalized patients received 10 days of dexamethasone therapy. Among these, 2 required ICU admission and received additional dexamethasone based on the Dexamethasone Treatment for the Acute Respiratory Distress Syndrome trial[S1] and 1 of the 2 required mechanical ventilation. Interim analysis from the BLAZE-1 clinical trial showed a day 29 hospitalization rate of 1.6% for those treated with bamlanivimab compared with 6.3% in the placebo group.[9] Our rates of hospitalization are higher than the preliminary studies in nontransplant settings; however, it could be related to the longer follow-up time in our study and the smaller number of patients. Final data from the BLAZE-1 trial became available after our study timeframe and reported bamlanivimab alone versus bamlanivimab plus etesevimab (combination therapy) compared with placebo. These data[S3] showed that combination therapy was successful in reducing day 11 viral load compared with bamlanivimab alone. While it failed to show a significant difference in the primary outcome, rates of hospitalization among patients who received a 700-mg dose of bamlanivimab or combination therapy was 1% and 0.9%, respectively, compared with 5.8% in the placebo group, although it was significant only in the combination therapy group. Mean total symptom scores were also comparable between bamlanivimab monotherapy and the combination group.[S3] Because of emerging SARS CoV-2 variants with resistance, the EUA for bamlanivimab use alone has been withdrawn[S4]; however, combination monoclonal antibody therapies including bamlanivimab plus etesevimab and casirivimab plus imdevimab[S5] still retain their EUA for use as previously authorized for bamlinivimab alone.

Bamlanivimab was well tolerated with no significant major adverse effects or allergic reactions in our cohort, which is similar to previously reported cases[S2] and the BLAZE-1 trial.[9,S3] Nausea (3.9%) was most common symptom in the BLAZE-1 trial, followed by diarrhea (3.2%). Infusion reactions occurred in 2.3% of the patients and included rash and pruritis.[9] Similar trends were seen in our study, with 4.2% having a rash, 8.3% reporting nausea, and no reports of diarrhea. None of the side effects required discontinuation of the infusion.

The mortality rate in our series of KTRs (4.2%) was lower compared with those KTRs who had COVID-19 but did not receive bamlanivimab infusion (9.4%) over the same timeframe. Confounding factors in ICU admission included additional diagnosis of disseminated histoplasmosis in 1 patient and COVID-19–related pulmonary aspergillosis in another who died. Additional factors contributing to patient death included multiorgan dysfunction from sepsis caused by ventilator-associated pneumonia from Klebsiella and Stenotrophomonas, pneumothorax, acute respiratory distress syndrome, and acute stroke late in the course leading to decision a transition to comfort measures by the family. The patient with disseminated histoplasmosis received a kidney transplant 2 years before their COVID-19 infection, while the patient with COVID-19–related pulmonary aspergillosis had a kidney transplant 10 years earlier. There was no history of these diagnoses in each case. In addition to these 2 patients, 1 patient was treated for community-acquired pneumonia at 4 weeks from COVID-19 infection based on radiologic findings. This highlights the fact that among KTRs who require hospitalization, other infectious etiologies such as fungal pneumonia should be worked up and excluded.

There are several limitations to our study. We relied on patients to establish a timeline of reported symptoms and their resolution after receiving bamlanivimab, which can lead to recall bias. Second, the total number of patients in our series was small to estimate hospitalization rates. Third, there was no control group, although it may not be ethically justified to withhold this therapy in such high-risk individuals. Fourth, given the study timeframe, testing for variants of SARS CoV-2 and viral loads were not possible. Finally, the effects of other COVID-19 treatments may have confounded our results.

Important lessons for transplant programs in a quickly changing COVID-19 pandemic situation include effective communication with and tracking of KTRs with COVID-19 infection. The emergence of resistant variants to bamlanivimab may have reduced its clinical benefit, as seen during the BLAZE-1 trial study period; however, it provides insight into potential use of similar agents alone or in combination in the future and the coordination it requires in a real-world setting.

In conclusion, bamlanivimab showed a safe profile among immunosuppressed KTRs with mild to moderate COVID-19 symptoms. A majority of our KTRs avoided hospitalization and did not develop sequelae of COVID-19 in the follow-up period. It is important for transplant centers and KTRs alike to ensure quick symptom reporting and testing turn-around times for SARS CoV-2 PCR, with effective communication between KTRs and transplant programs to determine the window of opportunity. Additional data from larger studies will help clarify the role of bamlanivimab among KTRs with COVID-19.

DISCLOSURE

All the authors declared no competing interests.

SUPPLEMENTARY MATERIAL

Supplementary File (Word)

Supplementary Methods.

Supplementary References.

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