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EDITORIAL

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Organ transplant patients, COVID-19, and neutralizing monoclonal antibodies: The glass is half full

Organ transplant recipients are among the most vulnerable populations for severe infections with SARS-CoV-2 both because of the effects of immunosuppression and the high burden of other high-risk co-morbid medical conditions.[1] The severity and devastating impact of COVID-19 on transplant patients is evidenced by high rates of hospitalization and mechanical ventilation and high mortality. These poor outcomes coupled with the suboptimal immunogenicity of SARS-CoV-2 vaccines in the transplant population underscore the urgency for effective therapies for COVID-19.[2]

To date, the only recommended therapeutic agents for COVID-19 in the ambulatory setting are neutralizing monoclonal antibodies directed to SARS-CoV-2 spike protein.[3–6] Four monoclonal antibody preparations have been made available through emergency use authorization by the Food and Drug Administration (FDA) for the treatment of mild to moderate COVID-19 in persons at high risk for progression to severe COVID-19, including solid organ transplant (SOT) recipients; the approved agents include bamlanivimab (revoked April 16, 2021),[3,8] casirivimab–imdevimab,[4] bamlanivimab–etesevimab,[5] and sotrovimab.[6] The emergency use authorizations were based on early clinical trials data demonstrating reductions in SARS-CoV-2 viral load,[3–5,9,10] hospitalizations, emergency department (ED) and/or medically attended visits,[3–6,9–12] and deaths[5] in persons who receive therapy early in the course of clinical symptoms compared to placebo. However, transplant recipients were not among the early trial participants. Thus, although transplant patients with mild to moderate COVID-19 are eligible for neutralizing monoclonal antibody therapies, data regarding their safety and efficacy are lacking.

In this issue of *Transplant Infectious Disease*, Kutzler et al. present the outcomes and tolerability of bamlanivimab for mild to moderate COVID-19 in SOT recipients.[13] Eighteen adult SOT recipients (15 kidney recipients, two liver recipients, and one heart recipient) were included in this retrospective, observational cohort. The average age was 52 years, and 72% of the patients were male and predominately Caucasian (67%). Other comorbidities included an average BMI of 32 kg/mm^3, hypertension (8.39%), and diabetes (44%). The majority had symptomatic SARS-CoV-2 infection, with fatigue and cough being the most common symptom. Bamlanivimab was given 5 ± 2 days from a positive test for SARS-CoV-2. Four (22%) patients required either hospitalization or emergency room visit within 32 days of treatment. Three (16.7%) of the patients required hospitalization, two with worsening shortness of breath at days 9 and 32 postinfusion and one patient with acute kidney injury at day 7 postinfusion. No patients required additional COVID-19 treatments. The bamlanivimab infusion was well tolerated and no infusion reactions were noted. There were no deaths reported in this patient cohort.

The experience by Kutzler et al. adds to the literature documenting the clinical experience with anti-SARS-CoV-2 monoclonal antibodies in SOT recipients (Table 1). Dhand et al. describe the outcome of 10 SOT recipients given bamlanivimab. In this small cohort, there were no ED visits or hospitalizations.[14] A second study by Jan et al. details the clinical response to bamlanivimab in 24 kidney transplant recipients. In this cohort, 16.7% of recipients required hospitalization, with two intensive care unit (ICU) admissions and one death.[15] The largest series of anti-SARS-CoV-2 monoclonal antibody use in SOT recipients, presented by Yetmar et al, describes the use of bamlanivimab or casirivimab–imdevimab in 73 SOT recipients. In this cohort, 15.1% (11/73) of patients required an ED visit, with nine of these patients requiring admission and one requiring ICU admission.[16] There were no deaths in this cohort. Overall, the outcome of the Kutzler cohort is similar to that described in these other reports of monoclonal antibody use for the management of SARS-CoV-2 in SOT recipients.

Newly emerged SARS-CoV-2 variants such as B.351 (Beta), B.1.617 (Delta), P.1 (Gamma), and P.2 (Zeta) represent a high proportion of circulating virus and have reduced susceptibility to the neutralizing monoclonal antibodies due to the presence of one or more amino acid substitutions in the receptor binding domain of the spike protein.[17] Bamlanivimab is inactive and bamlanivimab–etesevimab is less active against all of these variants due to the presence of the E484K substitution.[18–20] The variants, B.1.617 and P.1, carry two substitutions, E484Q/K and L452R, that lead to the loss of neutralizing activity of bamlanivimab–etesevimab and reduced activity of casirivimab.[18,19] Because of theoretical concerns for treatment failure, the FDA emergency use authorization for bamlanivimab has been revoked, and bamlanivimab–etesevimab is no longer recommended.[7,8] However, casirivimab and imdevimab bind at nonoverlapping regions of the receptor binding domain, and casirivimab–imdevimab retains activity against these variants.[18–20] Sotrovimab, designed to bind at a more conserved region of the receptor binding domain, also remains active against all circulating SARS-CoV-2 variants.[6]

The concern for emerging treatment resistant variants is even higher in organ recipients with COVID-19. With higher levels of virus in respiratory secretions and more prolonged viral shedding than the general population,[21] it is feasible that resistant variants could emerge with monoclonal antibody treatments. This scenario has been described in a patient with acute myelogenous leukemia

TABLE 1 Comparison of retrospective observational cohorts of the use of anti-SARS-CoV2 monoclonal antibody in solid organ transplant recipients

Study	Participants	Transplant type	Time to mAB therapy	ED or hospitalization	Deaths	Adverse effects
Kutzler et al.[13]	18	15 KT 2 LT 1 HrtT	5 (3–7) from test	4/18 (22.2%) • 3 hospitalizations • 1 ED visit	None	No infusion reactions Postinfusion • 1 HA, fatigue
Dhand et al.[14]	10	6 KT 2 LT 1 LK 1 HrtT	3.3 (1–10) from symptoms	None	None	No infusion reactions Postinfusion • 1 pruritis
Jan et al.[15]	24	24 KT	4.75 (2.45–7.05) from symptoms	4/24 (16/7%) • 2 ICU	1	No infusion reactions Postinfusion • 2 HA • 2 Nausea • 1 Rash
Yetmar et al.[16]	73	41 KT 4 KP 13 LT 11 HrtT 1 HrtL 2 Lung 1 Panc	4 (3–7) from symptoms 75.3% bamlanivimab 24.7% casirivimab–imdevimab	11/73 (15.1%) • 9 hospitalized • 1 ICU	None	No infusion reactions Postinfusion • 4 fever • 2 vomiting • 1 nausea • 1 rigors • 1 rash • 1 worsening sinus congestion

Abbreviations: ED, emergency department; HA, headache; HrtT, heart transplant; HrtL, heart liver transplant; KT, kidney transplant; LK, liver transplant; LT, liver transplant; mAB, monoclonal antibody; Panc, pancreas transplant; SARS-CoV2, severe acute respiratory syndrome coronavirus-2.

who received bamlanivimab and from whom a viral variant with the E484K substitution was subsequently detected.[22] It is unknown if the higher observed hospitalization rate in bamlanivimab-treated transplant recipients compared to reported hospitalization rates in the monoclonal antibody clinical trials reflects treatment failure because of a resistant infecting variant, emergence of resistance variants after receipt of the monoclonal antibody, or simply because the transplant patients are a "higher acuity population[13]" with low thresholds for hospitalization when infection is present. Future studies addressing the virology and viral dynamics of SARS-CoV-2 in the transplant population are essential for a better understanding of treatment response and outcomes in this population. Furthermore, it is crucial to investigate whether SARS-CoV-2 resistance variants will emerge more frequently with single antibody therapies such as sotrovimab versus monoclonal antibody combination therapies; this is critically important in the transplant population and other immunocompromised patients with higher burden of viral disease.

Pre- and postexposure prophylaxis is potentially the best application of COVID-19 neutralizing monoclonal antibodies in the transplant population, and postexposure prophylaxis with casirivimab–imdevimab is now available through FDA EUA.[4] In a Phase 3 trial, a single infusion of bamlanivimab was administered to skilled nursing facility residents and staff after a confirmed case of COVID-19 in a facility; residents who received bamlanivimab had a lower incidence of COVID-19 than those treated with placebo (8.4% vs. 15.2%, odds ratio = 0.43 [95% CI, 0.28–0.68], $p < .001$).[23] In another Phase 3 randomized trial, household contacts of a person with confirmed COVID-19 who received a subcutaneous injection of casirivimab–imdevimab had 81.4% ($p < .001$) and 66.4% ($p < .001$) reduction in risk for symptomatic and overall SARS-CoV-2 infection.[24] These studies also demonstrated lower viral loads and duration of viral shedding in monoclonal antibody-treated persons who went on to develop SARS-CoV-2 infection. Sotrovimab (ADZ7442), with its modified antibody structure, has a prolonged half-life and may be well suited for prophylactic use; clinical trials for pre- and postexposure prophylaxis are in progress (NCT04625972, NCT04625725). Similarly, pre- and postexposure trials with ADG20, a neutralizing antibody that targets a highly conserved region of spike protein, are in progress (NCT04859517). None of these trials has specifically targeted transplant recipients, and so future clinical trials should include SOT and other vulnerable populations with demonstrated poor response to COVID-19 vaccination.

The major drawback of the Kutzler cohort and other SOT cohorts has been the lack of a comparator group. Apart from the small experience by Dhand et al., each of these cohorts has an ED visit or hospitalization rate of 15.1%–22%,[13–16] but it is unknown how this compares to hospitalization rates for SOT recipients not treated with monoclonal antibodies. Contemporary cohorts of COVID-19 in SOT recipients have rates of hospitalization much higher than that reported in these small monoclonal antibody cohorts. All of these studies have demonstrated the safety of these therapies in SOT recipients, with no episodes of anaphylaxis or immediate transfusion reactions. Larger studies with active control groups and enrolling SOT recipients need to be undertaken to determine the true efficacy and benefit of these monoclonal antibodies in this patient population.

CONFLICT OF INTERESTS

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