Early in the coronavirus disease 2019 (COVID-19) pandemic in the United States, kidney transplant recipients (KTRs) with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection were reported to experience rapid clinical deterioration, resulting in high rates of hospitalization, severe illness, and death. One case series from New York City, for example, found a hospitalization rate of 78% and an overall mortality rate of 28% in KTRs (1). A subsequent larger study of 485 transplant recipients, of whom 318 (66%) were kidney recipients, repainted this grim picture, with close to 80% of those diagnosed with COVID-19 requiring hospitalization and 21% dying within 28 days of hospital admission (2). These data, collected before COVID-19 vaccines were available, highlighted the critical need for an intervention in mildly symptomatic SARS-CoV-2 infection to prevent disease progression in high-risk individuals, such as KTRs.

Until recently, the only intervention shown to reduce hospitalization and death in nonhospitalized patients with early COVID-19 infection had been anti-SARS-CoV-2 mAb therapy (MAT) (3–6). MAT products target epitopes on the receptor binding domain (RBD) of the SARS-CoV-2 spike protein and block binding to the host receptor, angiotensin-converting enzyme 2 (ACE2). The Food and Drug Administration has issued emergency use authorizations for four MAT products: bamlanivimab alone as a single intravenous dose of 700 mg (20 patients) or casirivimab plus imdevimab as a single intravenous dose of 2400 mg (seven patients). Thirteen KTRs who did not receive MAT but provided blood samples that could be tested for the presence and functionality of anti-SARS-CoV-2 antibodies were selected as controls. In all patients, antimetabolite immune suppression was held at the time of COVID-19 diagnosis. Outcomes, including hospitalization, AKI, graft loss, patient survival, and quantitative and qualitative antibody responses, were compared between the MAT group and controls. The investigators tested for the presence of IgG and IgM antibodies to the SARS-CoV-2 RBD in all subjects at baseline (before antibody infusion if given) and at later intervals using a standard ELISA. In subjects with a positive IgG, the ability of the IgG antibody to block the interaction between the SARS-CoV-2 RBD and the ACE2 receptor was measured in a competition assay. This method was previously shown by the investigators to correlate with neutralization of SARS-CoV-2 pseudovirus (12).

Compared with the MAT group, the control group experienced a two-fold higher rate of hospitalization overall (31% versus 15%) and a nearly three-fold higher rate of COVID-19–related hospitalizations (31% versus 11%). One patient in the MAT group (4%) and two in the control group (15%) required intensive care unit care. Both groups had baseline similar kidney function and experienced similar frequencies of AKI during their COVID-19 illness. Serum creatinine levels recovered to baseline in both groups. There were no instances of rejection, allograft loss, or death. Two mild infusion reactions occurred in KTRs receiving bamlanivimab.

Unfortunately, outcomes for transplant recipients included in clinical trials of MAT have not been separately analyzed. Thus, it has been unclear whether the benefits of MAT could be generalized to the transplant population. In this issue of Kidney360, Wang et al. (11) address this gap. They report the results of a single-center, retrospective analysis of clinical outcomes and anti-SARS-CoV-2 antibody responses in 40 unvaccinated KTRs diagnosed with mild to moderate COVID-19 between July 2020 and February 2021. Patients were diagnosed with COVID-19 using RT-PCR for SARS-CoV-2 on nasopharyngeal samples. Twenty-seven KTRs with COVID-19 received MAT: bamlanivimab alone as a single intravenous dose of 700 mg (20 patients) or casirivimab plus imdevimab as a single intravenous dose of 2400 mg (seven patients). Thirteen KTRs who did not receive MAT but provided blood samples that could be tested for the presence and functionality of anti-SARS-CoV-2 antibodies were selected as controls. In all patients, antimetabolite immune suppression was held at the time of COVID-19 diagnosis. Outcomes, including hospitalization, AKI, graft loss, patient survival, and quantitative and qualitative antibody responses, were compared between the MAT group and controls. The investigators tested for the presence of IgG and IgM antibodies to the SARS-CoV-2 RBD in all subjects at baseline (before antibody infusion if given) and at later intervals using a standard ELISA. In subjects with a positive IgG, the ability of the IgG antibody to block the interaction between the SARS-CoV-2 RBD and the ACE2 receptor was measured in a competition assay. This method was previously shown by the investigators to correlate with neutralization of SARS-CoV-2 pseudovirus (12).

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Twenty-three of 24 KTRs in the MAT group who underwent serologic assessment lacked anti-SARS-CoV-2 IgG antibodies at baseline (measured a median of 3 days after COVID-19 diagnosis). All 23 patients
with follow-up serologic assessment developed IgG antibodies with very high levels of blocking activity (22 with >90% inhibition and one with >80% inhibition). Among the 13 KTRs who did not receive MAT, seven were IgG seropositive on initial assessment (measured a median of 13 days after COVID-19 diagnosis); a single control patient had high levels of antibody blocking activity (≈90%). Of the six patients who were IgG seronegative on initial testing, one remained seronegative on follow-up assessment. In the five patients who seroconverted, antibody blocking activity did not exceed 20%.

This study has several important limitations, including small sample size, single-center experience, and retrospective study design utilizing nonparallel (partially asynchronous) cohorts. Because of the lack of randomization, the two groups were not well matched at baseline. Approximately 30% of the MAT group had received organ transplantation within a year of study participation (and attendant antithymocyte globulin or alemtuzumab) compared with 8% of the non-MAT group. The MAT group also contained a higher percentage of men (56% versus 30%), patients with diabetes (30% versus 15%), and older patients (median age of 52 versus 44 years), and the MAT group had more risk factors for severe disease compared with the non-MAT group. These imbalances would be expected to result in higher rates of hospitalization in the MAT group. On the other hand, the non-MAT group had a larger proportion of Hispanics (77% versus 33%), an ethnic group with higher risk of severe COVID-19 (13). Five in the control group had symptoms for >10 days and thus, did not meet emergency use authorization criteria for MAT. It is possible that these patients with extended symptoms were more likely to progress to severe disease and that this predilection, rather than the benefit of MAT, contributed to higher hospitalization rates in controls. Finally, the study investigators did not capture nonhumoral aspects of the immune response to SARS-CoV-2, which may play a role in disease severity (14).

Despite these limitations, the results are similar to those of another retrospective study carried out during roughly the same phase of the pandemic. Sarrell et al. (15) analyzed outcomes (hospitalization within 30 days, rejection, graft loss, and death) in 93 transplant recipient (50 KTRs) with mild or moderate COVID-19 who received bamlanivimab (71) or casirivimab-imdevimab (22) and 72 MAT-eligible controls. After adjusting for age, the investigators found a nonsignificantly lower risk of hospitalization in patients who received MAT (9%) compared with controls (15%). Interestingly, all eight patients in the MAT group who required hospitalized received bamlanivimab. The authors speculated that these individuals may have been infected with resistant strains of SARS-CoV-2. Two patients (one heart transplant recipient and one lung transplant recipient) in the MAT cohort experienced mild rejection with 30 days of infusion. No graft losses and no deaths occurred in the MAT group compared with two deaths among controls. Infusion reactions were rare and mostly mild (one patient experienced anaphylaxis).

In a third study, Del Bello et al. (16) analyzed outcomes in 16 patients with transplants (12 KTRs) who received MAT compared with 32 historical controls diagnosed with COVID-19 prior to MAT availability. Per French protocols, all patients were hospitalized for antibody infusion. During a median of 39 days of follow-up, none of the MAT-treated patients required high levels of oxygen compared with 47% in the control group. No infusion reactions were noted. Three deaths occurred, all in the control cohort.

A number of uncontrolled, observational studies of MAT in KTRs have also been published, claiming safety or benefit (17-19).

The study by Wang et al. (11) adds to the evidence that MAT is safe and may prevent COVID-19-related hospitalizations in KTRs. Uniquely, the authors demonstrate that MAT confers high levels of SARS-CoV-2 neutralizing activity that persists up to 3 months. Given the durability of this protection, another use of MAT specific to patients with transplants might be to provide immune prophylaxis during the first 1–3 months following transplant, when vaccines are least likely to be effective. There is no doubt that mRNA-based vaccines have greatly reduced morbidity and mortality due to COVID-19 in the general public and in patients with transplants (20-22). Nonetheless, breakthrough infections and the ongoing emergence of new COVID-19 variants suggest that MAT will remain relevant in the next phases of this pandemic.

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Author Contributions
E.A. Misch conceptualized the study, was responsible for formal analysis, wrote the original draft, and reviewed and edited the manuscript.

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