Understanding the Risks of Immunosuppression Reduction for Active COVID-19 Infection

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Kidney transplant recipients (KTRs) are at higher risk of mortality and morbidity from COVID-19 infection compared with the general population. 1 Some of this elevated risk comes from non-modifiable factors common to KTRs, such as diabetes, hypertension, and chronic kidney disease. However, transplant immunosuppression is a theoretically modifiable risk factor. Though better studied in the setting of COVID-19 vaccination rather than active COVID-19 infection, immunosuppressed patients are less likely to mount a T-cell response measured via ELISPOT assay and less likely to mount a robust, durable antibody response. 2 This is particularly true for patients on mycophenolate or belatacept. There is some evidence to support the intuitive idea that reduction in immunosuppression helps transplant recipients develop a more robust anti–COVID-19 immune response. In at least 1 study, transplant recipients who underwent immunosuppression reduction in the setting of active infection had the ability to generate interferon-γ–secreting CD3+ T cells against SARS-CoV-2 peptides and generate anti–S protein and anti–N protein IgG, presumably markers of cellular and humoral immunity against COVID-19, respectively. 3 Alternatively, underimmunosuppression, whether through patient noncompliance or physician directed, is associated with rejection and the development of de novo donor-specific anti–human leukocyte antigen antibodies (dnDSAs). 4

Balancing the risk of immunosuppression reduction with the potential benefits is quite challenging and carried out on a case-by-case basis depending on the severity of COVID-19 infection. A common approach among clinicians is to stop antiproliferative agents in moderate COVID-19 infection and discontinue or reduce the dose of calcineurin inhibitors in more severe cases. 5 In a systematic review involving 420 adult KTRs, reduction or discontinuation of immunosuppression was observed in 58% of the patients and antimetabolites and calcineurin inhibitors were discontinued in 91% and 58% of KTRs, respectively. 6 Undoubtedly, in light of a number of recent publications, our knowledge regarding graft outcomes, rejections, and mortality in KTRs following COVID-19 infection has taken a huge leap. However, the question concerning the effect of immunosuppression modulation on the development of human leukocyte antigen antibodies after SARS-CoV-2 (COVID-19) infection is still unanswered. Vásquez-Jiménez et al. 7 did a follow-up of 4 weeks in 20 KTRs after COVID-19 infection and performed anti–human leukocyte antigen antibody testing to screen for dnDSA and kidney graft biopsy. The analysis showed the development of dnDSA in 11 patients (class I in 2 patients, class II in 6 patients, and both classes I and II in 3 patients). Of these 11 patients, 27.2% had antibody-mediated rejection, 36.4% mixed antibody-mediated rejection and T-cell mediated rejection, and 36.4% chronic antibody-mediated rejection. However, the possibility of the presence of dnDSA before the COVID-19 diagnosis could not be ruled out and a lack of serial renal biopsies rendered it difficult to draw any cause-effect relationship. Another analysis by Pampols et al. 8 including 47 KTRs with 3 months of follow-up after COVID-19 infections failed to demonstrate any appearance of dnDSA or rejection episodes despite reduction in immunosuppressive medications for a median time of 17 days.

In this context, Masset et al. 9 provided a retrospective cohort analysis of 179 KTRs following COVID-19
infection from 2 French institutions. The authors assessed the occurrence of dnDSA in addition to allograft rejection and graft loss following COVID-19. Of note, almost half of the patients (49.2%) were hospitalized and interruption of antimitabolites was done in 47% (82% in hospitalized and 15% in nonhospitalized patients). The median time of resumption of the antimitabolites was 23 days and 7 days in hospitalized and nonhospitalized patients, respectively. Furthermore, calcineurin inhibitors were interrupted in 12% of the KTRs.

Before COVID-19 infection, screening for dnDSA had been done at a median of 212 days (range 2–701 days). Post–COVID-19 dnDSA screening was performed at a median of 45 days (range 4–412 days). The authors demonstrated that the incidence of dnDSA after COVID-19 infection was 4% overall and 8% in hospitalized patients. Allograft rejection was detected in 3 patients (1.7%), but there was no immunologic-related graft loss. The occurrence of post–COVID-19 dnDSA was associated with younger age, the onset of infection within the first year after transplantation, and a history of pre-existing DSA (different from the dnDSA) before transplantation. Surprisingly, there was no impact of raised inflammatory markers, such as interleukin-6 and C-reactive protein levels, total lymphocyte count, the severity of COVID-19, and the use of antiviral therapies.

The results of the study support the findings of TANGO cohort analysis in which no survival benefit of immunosuppression interruption in KTRs with COVID-19 infection was observed. Although the study did not reveal any higher incidence of post–COVID-19 dnDSA appearance despite the substantial reduction of immunosuppression suggesting that COVID-19 itself may not be a major immunologic trigger, some issues remain to be addressed. The absence of systematic protocol biopsies during ongoing COVID-19 infection at the time of immunosuppression interruption might have underestimated the alloimmune response and subclinical rejections. Because the screening of dnDSA after COVID-19 infection was done at variable intervals of time, the status of immediate post–COVID-19 dnDSA changes that may have been transient remains unknown. It is difficult to know about the ongoing immunologic response in asymptomatic patients with COVID-19. In addition, any inference of the results is challenged by the retrospective nature of the published studies.

In summary, Masset et al. provide an interesting analysis indicating that risks of the development of post–COVID-19 DSA, allograft rejection, and graft loss are low and are mainly restricted to high-risk immunologic patients and those with severe disease requiring hospitalization and/or elimination of calcineurin inhibitor. Hence, a transient interruption or modulation of immunosuppression in COVID-19–infected KTRs for a short period of time seems safe and can be applied according to the COVID-19 severity. However, long-term prospective studies with a large cohort group are warranted.

DISCLOSURE
All the authors declared no competing interests.

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