COVID-19 and Calcineurin Inhibitors: Should They Get Left Out in the Storm?

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JASN 31: 1145–1146, 2020. doi: https://doi.org/10.1681/ASN.2020030348

Establishing the equipoise between infection and rejection in any individual transplant recipient has always been the aim when prescribing immunosuppression. Today the world is facing a global pandemic which has never been seen in the era of transplantation and immunotherapy. As of April 7, coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been confirmed in >1.25 million people worldwide with a mortality rate of 5.7%. The presence of comorbid conditions is associated with higher risk of death, which is concerning because significant comorbidity is common in recipients of transplants.[1] The additional risk posed by immunosuppression in these patients cannot be estimated due to lack of data. Logically, transplant clinicians are needing to extrapolate from evidence obtained from treating other life-threatening infections in recipients of transplants, which involves reducing or stopping immunosuppression. At the time of writing, published data are available in 11 transplant patients infected with SARS-CoV-2 (eight adult and three pediatric patients).[2–6] Calcineurin inhibitors (CNIs) are the cornerstone of transplant maintenance immunosuppressive regimens, and all patients were receiving CNIs at the time of diagnosis. In keeping with what is known in the general population, all pediatric outcomes were favorable. In the adult cases, seven of the eight case reports describe management that included withdrawal of both CNIs and antiproliferative agents; in these cases, outcomes were variable (three patients survived, three remain in critical care, and two deaths).[2–4,6] Several guidelines have since been developed that recommend withdrawal of CNIs in transplant patients with severe SARS-CoV-2 infection.[7,8]

Two features of CNIs, one experimental and the other clinical, warrant attention because they may have important repercussions not only for patients who have received a transplant but also in the management of SARS-CoV-2 infection in general.

Firstly, it is known that a number of viruses use active immunophilin pathways during their life cycle, and that CNIs may inhibit viral replication *in vitro*.[9,10] Cyclosporine, for example, has been shown to inhibit the replication of several coronaviruses *in vitro* at noncytotoxic concentrations and independently of its immunosuppressive effect.[10,11] In addition, the inhibitory effect of cyclosporine on hepatitis C virus replication *in vitro* is well documented.[12] However, the observed longer time to hepatitis C virus recurrence after liver transplantation in patients treated with cyclosporine compared with tacrolimus suggests a discordance *in vivo* between the different CNIs.[12] Focusing explicitly on SARS-CoV infection, a genome-wide analysis of protein-protein interactions between SARS-CoV and human host proteins identified both cyclophilin family members and FK506 (tacrolimus)-binding proteins as interaction partners for SARS-CoV proteins.[9] In addition, both FK506 treatment and knock down of FK506-binding proteins 1A and 1B inhibited SARS-CoV replication *in vitro*.[13] This suggests that both commonly prescribed CNIs, cyclosporine and tacrolimus, have inhibitory potential in SARS-CoV. Although we do not advocate the use of these drugs for their potential antiviral properties based solely on these experimental observations in related viruses, these findings may support their continued use as the preferred maintenance immunosuppressant in transplant recipients with SARS-CoV-2 infection. In addition, given that withdrawal of CNIs may result in increased corticosteroid usage in this population, it is also prudent to consider that there appears to be no therapeutic benefit from corticosteroid therapy in SARS-CoV and there may well be deleterious effects, acknowledging there are differences in the replacement dosage used in transplantation.[14,15]

Secondly, emerging evidence suggests acute respiratory distress syndrome is the leading cause of death after infection with SARS-CoV-2, and severe disease may be associated with a hyperinflammatory state

Published online ahead of print. Publication date available at www.jasn.org.

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or cytokine-release syndrome (CRS).[1,16] Parallels have been drawn with both hemophagocytic lymphohistiocytosis (HLH) and capillary leak syndrome after chimeric antigen receptor T-cell therapy, which is also associated with excessive proinflammatory cytokine release.[17,18] Although the SARS-CoV-2 CRS appears distinct from both, there is certainly overlap between the predominant cytokines involved in HLH pathogenesis—such as IL-1β, IL-6, IL-18, and IFN-γ—and that seen in patients with COVID-19.[19]

As such, clinical interventional trials of tocilizumab (a mAb against IL-6) in patients who are infected is already underway.[16] This may have important consequences for patients who have received a transplant, because hyperinflammatory syndromes require immunotherapy rather than immunosuppression withdrawal, with treatment options including anakinra (an IL-1 receptor antagonist), tocilizumab, intravenous Ig, and steroids.[16,20] Cyclosporine has also been used to successfully treat HLH and inhibits NF of activated T cells–mediated IL-2 gene transcription, reducing cell proliferation and the concomitant production of other cytokines, although it remains to be seen if CNIs at the therapeutic range would be capable of inhibiting the SARS-CoV-2 CRS.[20] This does, however, suggest that CNIs may not be harmful in the hyperinflammatory phase of SARS-CoV-2 infection, which may also justify their continued usage in recipients of transplants.

Together, these observations demonstrate that now, as always, we must work to understand underlying pathogenic mechanisms, to test these hypotheses, and to build a robust clinical evidence base for the treatment of this devastating viral infection. This process should be expeditious rather than rushed, otherwise we risk abandoning safe treatments with proven benefits for optimum transplant care. Moreover, although there is no firm evidence that patients with renal transplants are at higher risk from complications after SARS-CoV-2 infection than the general population, it is worth bearing in mind that it is the established risk factors (*e.g.*, age, cardiometabolic comorbidity) that is most likely to determine their outcome after diagnosis with SARS-CoV-2.[1]

DISCLOSURES

Dr. Willicombe has received funding support from Chiesi Pharmaceuticals. All remaining authors have nothing to disclose.

FUNDING

None.

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