Organ Transplantation in the Era of the COVID-19 Global Pandemic

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Since December 2019, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)-associated coronavirus disease-2019 (COVID-19) has spread widely, becoming a global pandemic, with over 31 million cases reported worldwide as of September 2020, and a crude mortality rate of 3% [1]. In Israel, over 209,000 COVID-19 cases have been diagnosed as of September 2020 [2]. Solid organ transplant (SOT) recipients appear to be at a particularly high risk for contracting COVID-19, with reported incidence rates as high as 5% [3].

In an article published in the *Israel Medical Association Journal* (*IMAJ*), Tzukert and colleagues [4] described the first two kidney transplant recipients diagnosed with COVID-19 in Israel. Both patients had their transplants years before COVID-19 infection and were stable on standard immunosuppressive regimens. The first patient had mild COVID-19 and recovered uneventfully with no specific therapy other than temporary discontinuation of mycophenolate mofetil (MMF). The second patient had moderate COVID-19, for which he was treated with azithromycin. No immunosuppressive drug was withheld, and he also recovered uneventfully.

Previous reports have shown that the prognosis of transplant patients with COVID-19 is worse than that of non-transplant patients, with mortality rates in the range of 14–32%. Mortality rates are especially high in kidney transplant recipients [5-7].

Since SOT recipients are at high risk for severe COVID-19, protecting this population is of particular importance. A critical method of protection is prevention of exposure to SARS-CoV-2, and indeed, major national transplant societies have published guidelines emphasizing the need to advise SOT recipients on the importance of maintaining social distancing, wearing face masks, and adhering to strict hand hygiene routines. An essential part of this practice is minimizing healthcare visits, including utilizing telemedicine services, minimizing routine blood testing, and using home spirometry for the monitoring of lung transplant recipients [8].

There is limited data on the proper management of SOT recipients with COVID-19, and thus evidence-based guidelines are lacking. An important dilemma is whether immunosuppression should be adjusted to balance the risk of COVID-19 progression with the risk of allograft rejection. In most patient series reported, reduction of immunosuppression was the mainstay of management. Antimetabolites and mammalian target of rapamycin (mTOR) inhibitors were discontinued in the majority of patients and calcineurin inhibitors (CNIs) were withheld in fewer patients. Glucocorticoids were infrequently stopped or reduced. Notably, no episodes of acute rejection due to changes in immunosuppression were reported [3,5,6,9-11]. Based on these data and a number of national consensus statements [12-14], a logical approach would be to withhold antimetabolites in mild-moderate COVID-19 and to consider withholding all immunosuppression except steroids (antimetabolites, CNIs, mTOR inhibitors) in severe-critical COVID-19 patients.

In a recent study, the use of dexamethasone resulted in lower mortality in COVID-19 in patients requiring oxygen or ventilatory support [15]. It is currently unknown whether the same effect applies to transplant patients and if prednisone should be substituted with dexamethasone in SOT recipients with COVID-19. Immunosuppression can probably be reintroduced after symptoms and signs of COVID-19 have significantly improved. As no specific data exist for SOT recipients, the use of specific therapy against SARS-CoV-2, such as the antiviral remdesivir, and anticoagulation should probably be recommended as for non-transplant patients according to institutional protocols.

The COVID-19 pandemic has had important implications on transplant programs throughout the world. A substantial decline in transplantation activity has been reported worldwide, especially for living-donor transplants, with some centers completely suspending all living-donor transplant programs [7,12,16,17]. In addition, the risk of donor-derived or post-transplant infection has led some transplantation societies to recommend a temporary suspension of all elective living-donor and non-urgent deceased-donor transplantations [12,18]. However, it should be noted that patients undergoing dialysis in hospital-based dialysis units are substantially more likely to contract COVID-19, and disease clusters have been

reported in dialysis units [19]. Furthermore, patients with end-stage renal disease and those on dialysis are at an increased risk for severe COVID-19 and for COVID-19-related mortality [20]. Therefore, the decision whether to perform elective transplantations during the COVID-19 pandemic should balance those contrasting risks and each patient should be individually considered. High-risk transplantations, particularly those requiring intensified immunosuppression such as lymphocyte-depleting agents, rituximab, and plasmapheresis should probably be avoided at this time.

Finally, although national data on the morbidity of COVID-19 among transplant patients in Israel is still lacking, one fatal case of a 55-year-old man who died from COVID-19 13 years after undergoing kidney transplantation was covered by the national media as he was the chairman of Matnat Chaim (Gift of Life), which is a not-for-profit organization responsible for encouraging and coordinating over 900 altruistic kidney donations. His death has had an impact on the transplant patient population and serves as a powerful reminder of the effects of COVID-19 and the importance of adhering to the recommended preventive measures.

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Capsule

Baricitinib plus remdesivir for hospitalized adults with COVID-19

Kalil et al. conducted a double-blind, randomized, placebo-controlled trial evaluating baricitinib plus remdesivir in hospitalized adults with COVID-19. All of the patients received remdesivir (≤ 10 days) and either baricitinib (≤ 14 days) or a placebo (control). The primary outcome was the time to recovery. The key secondary outcome was clinical status at day 15. The authors concluded that baricitinib plus remdesivir was superior to remdesivir alone in reducing recovery time and accelerating improvement in clinical status among patients with COVID-19, notably among those receiving high-flow oxygen or noninvasive ventilation. The combination was associated with fewer serious adverse events.

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