EDITORIAL

The dangers of immunosuppression and solid organ transplant in the SARS-CoV-2 pandemic era

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SARS-CoV-2 represents a relevant issue for many patients worldwide and is connected with several serious health problems.[1] When the SARS-CoV-2 pandemic status was declared in 2020,[2] the transplant community immediately raced to create safety protocols for their solid organ transplant (SOT) recipients. Shortly after, clear evidence emerged that SARS-CoV-2 can cause profound, and often fatal, illness in these patients, independent of graft function,[3,4] and that immunosuppression plays a relevant role in the evolution of severe SARS-CoV-2 infection.[5]

In the current issue of *Polish Archives of Internal Medicine* (*Pol Arch Intern Med*), Kolonko et al[6] present the results of their study on 2091 SOT recipients, including patients after kidney (n = 1372), liver (n = 246), and heart (n = 473) transplant, who regularly attended the outpatient transplant clinics in the 2 regional transplant centers of Katowice and Zabrze in Poland. Of this cohort, the authors reported 201 patients (9.6%) with an established diagnosis of SARS-CoV-2 infection during the period from March 2020 to March 2021 (112 kidney transplant, 56 heart transplant, and 33 liver transplant recipients). According to the results, COVID-19 cases were significantly more common among patients who had recently undergone kidney or heart transplant than in the remaining patients. Moreover, blood tacrolimus levels measured during or shortly after COVID-19 were significantly increased relative to predose trough levels in a relevant number of kidney transplant recipients, thus often necessitating a tacrolimus dose reduction.

The observations of Kolonko et al[6] are in line with previous pieces of evidence being part of a continuous reminder that SARS-CoV-2 infection represents a threat to SOT recipients.

As for the higher risk of infection in patients with a shorter time since transplant, an important aspect to underline is that this phenomenon was reported in kidney and heart transplant cases, namely, in patients typically receiving heavier immunosuppression regimens (eg, triple maintenance therapy). Secondly, the immunosuppression levels are typically higher during the first months after transplant. Therefore, the results reported by Kolonko et al[6] should be considered as representative of higher immunosuppressive regimens.

A large multicenter study from Brazil explored the data of 1680 kidney transplant recipients diagnosed with SARS-CoV-2 infection, showing that the recent use of high-dose steroids was an independent risk factor for hospitalization (odds ratio [OR], 1.866; $P = 0.003$) and death (OR, 1.534; $P = 0.022$).[7] In a population of 855 kidney transplant recipients from the United Kingdom, of whom 89 (10.4%) tested positive for SARS-CoV-2 antibodies, noninfected patients were more likely to receive a tacrolimus monotherapy vs double or triple immunosuppressive therapy ($P < 0.01$).[8] In a large European population (n = 243) of liver transplant recipients with SARS-CoV-2 infection, patients on triple therapy more commonly had severe infections requiring intensive care unit admission compared with those receiving monotherapy or two immunosuppressants ($P = 0.011$).[9]

As for the metabolism of tacrolimus, a study from the United States including 102 SOT recipients showed an increase in tacrolimus levels after SARS-CoV-2 infection.[10] While the mechanism of this association is unclear, SARS-CoV-2 infection may be associated with higher tacrolimus levels due to inflammatory processes impacting cytochrome P450 3A4 activity, gastrointestinal alterations, or acute kidney injury. The interaction

between tacrolimus and antiviral drugs or their side effects (ie, diarrhea) should also be considered a potential cause of increased tacrolimus levels.[11]

Therapies for SARS-CoV-2 infection are continuously being developed, with the routine use of monoclonal antibodies, antiviral agents, and vaccines. The vaccinal strategy has represented a welcome change to the SARS-CoV-2 pandemic.[12] However, also in vaccinated SOT recipients, immunosuppressants and time to transplant were related to reduced antibody response.[13] Despite the overall inferior efficacy of the antiviral strategies and the inferior outcomes reported in SOT recipients affected by severe SARS-CoV-2 infection, the benefit of organ transplant still outweighs the risks linked to the virus in patients with end-organ disease. Therefore, the effort of social distancing and vaccine implementation among the general population is mandatory to protect the "fragile" patients, such as SOT recipients. The immunosuppression in these patients has been a double-edged sword, requiring an accurate real-time control with the intent to minimize metabolic alterations and side effects resulting from high-level immunosuppression. The management of SOT recipients with SARS-CoV-2 infection remains challenging. In the time of a global crisis, the transplant community is called to join forces and develop strategies to mitigate risks in this population.

ARTICLE INFORMATION

DISCLAIMER The opinions expressed by the author(s) are not necessarily those of the journal editors, Polish Society of Internal Medicine, or publisher.

CONFLICT OF INTEREST None declared.

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