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REVIEW ARTICLE

Impact of Immunosuppression on the Severity of SARS-CoV-2 Infection in Renal Transplant Recipients

Tainá Veras de Sandes-Freitas[1,2], Lúcio Requião-Moura[3,4], Hélio Tedesco-Silva[3,4]

1. Universidade Federal do Ceará, Fortaleza (CE), Brazil.

2. Hospital Geral de Fortaleza, Fortaleza (CE), Brazil.

3. Universidade Federal de São Paulo, São Paulo (SP), Brazil.

4. Fundação Oswaldo Ramos – Hospital do Rim, São Paulo (SP), Brazil.

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Correspondence author:
taina.sandes@gmail.com

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Abstract: Kidney transplant patients have a high case fatality rate following severe acute respiratory syndrome 2 (SARS-CoV-2) infection. In addition, the vaccine immune response is lower and less durable, which makes them more susceptible to severe forms, even when vaccinated. Evidence suggests that in addition to advanced age and the high prevalence of comorbidities often associated with worse prognosis, such as diabetes, obesity, and cardiovascular disease, prolonged immunosuppression exerts an independent effect on outcomes. In fact, the cellular and humoral adaptive immune response, which is inhibited by immunosuppression, is a key step in resolving SARS-CoV-2 infection. On the other hand, lymphocyte inhibition could modulate the aberrant production of proinflammatory cytokines that result in severe lung impairment, mitigating the severity of the condition. In addition, some immunosuppressive drugs have antiviral properties, potentially applicable to coronavirus. This narrative review aimed to discuss the available evidence on the impact of immunosuppressive drugs on COVID-19 outcomes in kidney transplant recipients.

Descriptors: COVID-19; Kidney Transplantation; Immunosuppression.

INTRODUCTION

Evidence accumulated since the beginning of the COVID-19 pandemic has shown that kidney transplant patients infected by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have high mortality. When considering the first two years of the pandemic, 2020 and 2021, the lethality rate among transplanted individuals in the various world registries was around 20 to 25%, which was six to eight times the lethality reported for the nontransplanted population (3 to 5%). More recently, with almost 80% of the Brazilian population with a complete vaccination schedule (two or three doses) and predominance of the Omicron variant, the lethality among transplant recipients in Brazil is about 9 to 10%, which is 20 times the rate reported for the non-transplanted population (0.3 to 0.6%).[1-3]

It is well known that kidney transplant patients are afflicted with multiple comorbidities, which have been known to negatively impact the outcomes of COVID-19, such as renal dysfunction, hypertension, diabetes mellitus, cardiovascular disease and obesity, in addition to advanced age;[4] however, evidence suggests that some factor outside of age and comorbidities has negatively influenced the outcomes of these patients. As an example, kidney transplant patients followed at the Kidney Hospital in São Paulo city (Brazil) diagnosed with COVID-19 were compared with infected individuals among the inhabitants of the state of São Paulo stratified by age groups. In all groups, the lethality rate of transplant recipients was significantly higher, even in the 20 to 29 age group, in which a lower prevalence of comorbidities is expected.[5]

In another Brazilian study, kidney transplant recipients were compared with individuals with chronic dialysis kidney disease matched for age, sex, ethnicity, body mass index, presence of comorbidities, and geographic location of the center. As a result, transplant recipients had a 6% higher risk of death within 30 days with each day of follow-up after diagnosis.[6]

In addition to the worse clinical outcome after infection with the new coronavirus, transplant patients have prolonged viral clearance and lower vaccine response, notably lower rates of seroconversion and faster decline in neutralizing antibody titers when compared to the general population. [5,7-10] As a result, recent evidence shows that transplant patients who have received one or two doses of SARS-CoV-2 vaccine have similar clinical outcomes to unvaccinated patients, reinforcing the need for supplemental doses in this group of individuals.[11]

Evidence leads to the hypothesis that there is a likely independent effect of immunosuppressive drugs in influencing the outcomes of SARS-CoV-2 infection, either by downregulating and prolonging viral replication, modulating cytokine production and inflammation arising from the cellular adaptive immune response, reducing the humoral immune response, or by some other effect yet to be explored. [12] It should be noted that other factors not directly related to the modulating effect of viral load and immune response may impact the outcomes of COVID-19. As an example, some drug classes are associated with higher incidence of lymphopenia and coinfections, which are implicated in worse prognosis of COVID-19.[13,14]

Despite the higher overall lethality rate, it should be noted that when immunosuppressed patients who required hospitalization were compared with equally severely immunocompetent patients, there appeared to be no differences in mortality, which makes understanding the role of immunosuppression in outcomes even more intriguing, reinforcing the idea that the effect of immunosuppression is determinant in the early stages of the disease.[15-19]

In this narrative review, the available evidence about the potential impact of immunosuppressive drugs commonly used in kidney transplantation on the outcomes of SARS-CoV-2 infection is explored, with a focus on understanding the modulating role of immunosuppression on COVID-19 outcomes.

IMMUNE RESPONSE TO SARS-COV-2 INFECTION

For us to explore the impact of immunosuppressive drugs on COVID-19, a brief review of the immune response to SARS-CoV-2 infection is essential.

To exert its pathogenic effect, SARS-CoV-2 is internalized in target cells through the interaction between the viral S-protein and the cells' angiotensin-converting enzyme 2 (ACE2) receptors. Within the endosomes of infected cells, RNA is replicated and new virions are produced and released from the cell by exocytosis to then infect new cells. After the initial phase of viral replication, the innate immune system is triggered as the first line of defense, with release of proinflammatory cytokines, such as tumor necrosis factor alpha (TNF-α), interferon-gamma (IFN-γ) and interleukins 1, 6, and 18 (IL-1, IL-6, IL-18). Next, the adaptive immune response is initiated, with two main responses:

- production of cytotoxic T lymphocytes and production of cytokines, such as IL-2, IFN-γ, and TNF-α;
- Differentiation of B lymphocytes into plasma cells and production of neutralizing antibodies.[20]

The occurrence of severe forms of COVID-19 is related to deregulation of the innate and adaptive immune response, with reduced type I IFN activity and, consequently, inadequate control of viral replication; aberrant cytokine production, generating hyperinflammation (cytokine storm); lymphopenia and cell exhaustion, compromising the response of NK cells and T and B lymphocytes; dysregulation of the myeloid response, with excessive and aberrant production of dendritic cells, monocytes, and neutrophils; and heterogeneity of the adaptive immune response to natural infection and vaccines.[21]

It is noteworthy that the adaptive immune response is the main target of immunosuppressive drugs, which have the primary goal of preventing rejection by curbing lymphocyte activation and antibody production.

RABBIT ANTITHYMOCYTE GLOBULIN (THYMOGLOBULIN)

Rabbit antithymocyte globulin (ATG, thymoglobulin) is a polyclonal antibody that exerts its immunosuppressive effect predominantly by depleting T lymphocytes through cell lysis, apoptosis, and opsonization. In addition, thymoglobulin induces apoptosis of B and NK cells.[22]

Since lymphopenia was consistently associated with worse prognosis in patients with COVID-19, restricting the use of this drug as induction therapy during the pandemic was widely discussed in transplant centers around the world.[13] On the other hand, induction therapy with ATG is potentially associated with lower incidence of late graft function and ensures an initial immunosuppressive regimen of greater efficacy in preventing acute rejection, with less need for subsequent high-dose steroid and/or ATG treatments and shorter hospital stay.[23,24]

The scarce evidence available suggests that the use of ATG in rejection induction or treatment protocols during pandemic COVID-19 is safe, and should not be avoided or delayed in patients without infection.[25,26] There is no description of the use of ATG in patients with symptomatic active SARS-CoV-2 infection; however, two Brazilian studies have reported the use of ATG as induction therapy in asymptomatic individuals undergoing transplantation with positive SARS-CoV-2 reverse transcriptase followed by polymerase chain reaction (RT-PCR). In both cohorts, the clinical outcomes were favorable.[27,28]

CORTICOSTEROIDS

One of the main immunosuppressive mechanisms of corticosteroids, often used in maintenance immunosuppressive regimens, is inhibition of the activity of cytoplasmic factor kappa B (NF-κB), which is responsible for activating the DNA synthesis of several cytokines, such as IL-2, which induces T-lymphocyte proliferation.[29] At high doses, corticosteroids can act by mechanisms independent of intracellular receptor binding, affecting the physicochemical properties of the cell membranes of inflammatory cells. Corticosteroids also have a potent anti-inflammatory action, modulating T-cells, monocytes, and macrophages, reducing the production of pro-inflammatory mediators produced by these cells and stimulating the release of anti-inflammatory mediators, as well as suppressing coagulation factors.[30]

Previous studies with SARS-CoV and Middle East respiratory syndrome (MERS-CoV) have pointed to higher mortality in patients treated on steroids, with increased risk of secondary infection and prolonged viral clearance. Regarding SARS-CoV-2, the literature is controversial, and the effect of the steroid appears to be associated with disease stage and severity.[31] While evidence suggests the benefit of using corticosteroids in patients with severe forms of COVID-19, notably those on mechanical ventilation,[32] other studies demonstrate prolongation of viral load and worse prognosis when the drug is used in the early stages and in patients with nonsevere forms of the disease.[33]

It should be noted that the data cited refer to the use of steroids in high doses and for a short period of time, similar to the schemes adopted in the treatment of rejection episodes. Evidence regarding the chronic use of steroids at the low doses traditionally employed in maintenance regimens, such as 5 mg of prednisone per day, is sparse. An analysis of the Brazilian multicenter COVID-19 registry in kidney transplant recipients suggested a protective effect of steroid use as part of the maintenance immunosuppressive regimen, with a lower risk of death at 28 days however, this was a lower-weight predictor, i.e., the magnitude of its protective effect was much lower than that of other predictors. In addition, only 6% of the cohort was on steroid-free regimens, making this variable to be analyzed with caution.[34]

CALCINEURIN INHIBITORS: CYCLOSPORINE AND TACROLIMUS

Cyclosporine and tacrolimus exert their immunosuppressive effect by inhibiting the phosphatase activity of the cytoplasmic protein calcineurin (CNI), preventing the gene transcription of inflammatory interleukins, especially IL-2, and preventing the consequent activation of T lymphocytes. For this effect to occur, cyclosporine and tacrolimus bind to the cytoplasmic proteins cyclophilin and FKBP, respectively, forming complexes that inhibit calcineurin activity.[35]

Similar to what is described for human immunodeficiency virus (HIV), *in vitro studies* indicate binding of SARS-CoV to the immunophilins cyclophilin and FKBP during the process of internalization into the target cell. Thus, CNIs would be potential competitors for binding to these proteins, and this effect would result in reduced viral replication.[36,37] Additionally, it has also been shown, both *in vitro* and *in vivo*, that cyclosporine induces a potent antiviral immune response by inducing IFN-lambda-dependent release of IFN regulatory factor 1 (IFN type III), resulting in gene-dependent IFN-stimulated antiviral reprogramming of the lung epithelium, with preservation of barrier function after MERS-CoV infection.[38] The antiviral effect was also demonstrated for SARS-CoV-2 in *in vitro*/*ex-vivo* and *in vivo* experiments.[39]

Furthermore, as potent inhibitors of lymphocyte activation and consequent interleukin production, CNIs could act by inhibiting the inflammatory response arising from adaptive immunity, attenuating the cytokine storm that results in hypoxemia and morbidity and mortality in COVID-19. Considering this reasoning, a Spanish study retrospectively evaluated the outcomes of oral or intravenous cyclosporine treatment for nontransplant patients who required hospitalization after COVID-19 infection. As a result, patients treated with cyclosporine had significantly lower mortality.[40] Preliminary evidence in transplanted individuals also revealed that those on CNI had better outcomes.[41,42]

The potential beneficial effect of CNIs on viral replication and modulation of the inflammatory response is countered by a potential negative effect on the humoral adaptive immune response, demonstrated by lower neutralizing antibody production after vaccination with the immunizers BNT162b2 (Pfizer-Biontech), mRNA-1273 (Moderna) and ChAdOx1-nCoV-19 (AstraZeneca). In these studies, the likelihood of seroconversion after vaccination was lower in patients taking tacrolimus *versus* cyclosporine, notably in those taking daily doses greater than 3 mg.[43,44]

AZATHIOPRINE

Azathioprine, after conversion in the liver to 6-mercaptopurine, acts as an analog of purine bases, and is incorporated as a false base into cellular DNA. Thus, it blocks the *de novo* and salvage pathways of purine synthesis, inhibits DNA and RNA synthesis, and consequently blocks cell activation and proliferation.[45]

Previous *in vitro* studies demonstrated that the thiopurine analogues 6-mercaptopurine and 6-thioguanine exhibit an inhibitory effect on the replication of SARS-CoV by selective and reversible competition for a viral *papain-like protease*.[46,47] More recently, this effect has also been demonstrated for SARS-CoV-2.[48]

However, clinical evidence in patients with rheumatologic diseases points to a worse prognosis and higher mortality in patients with COVID-19 on chronic azathioprine use when compared to those on tumor necrosis factor inhibitors (anti-TNF).[49] In addition, azathioprine has a myelotoxic effect, and lymphopenia is a variable consistently associated with worse prognosis in patients with COVID-19.[13]

There is no robust evidence on the impact of azathioprine use on cellular, humoral and clinical vaccine response. It is emphasized that this class of drugs has limited effect on B lymphocyte activation and, therefore, on antibody production.[50] Previous studies with vaccines against *influenza* and hepatitis A virus have not been consistent in demonstrating impaired immune response in patients taking azathioprine.[51,52]

MYCOPHENOLATE SODIUM AND MOFETIL

Mycophenolic acid, the active form of mycophenolate sodium and mofetil, is a selective, noncompetitive, reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH), a limiting enzyme in the *de novo* synthesis of nucleotides, which prevents the division of different cell lines, mainly activated lymphocytes.[53]

Previous *in vitro* studies suggested a potential effect of mycophenolic acid in inhibiting the replication of MERS-CoV by noncompetitive inhibition by the viral *papain-like* protease.[54-56] More recently, similar antiviral effect has been demonstrated *in vitro* for SARS-CoV-2,[57] but *in vivo* experiments and clinical studies testing mycophenolate in experimental models and individuals with MERS-CoV infection have not confirmed this effect.[58] Regarding the potential impact of mycophenolate on SARS-CoV-2 infection, an analysis of the Brazilian multicenter COVID-19 registry in kidney transplant recipients demonstrated that patients taking mycophenolate as part of the maintenance immunosuppressive regimen had a higher lethality rate when compared to patients taking azathioprine and inhibitors of the *mammalian target of rapamycin* (mTOR).[59] In addition, mycophenolate, such as azathioprine, is a drug implicated in the development of lymphopenia.

Unlike azathioprine, mycophenolic acid has a direct inhibitory effect on B lymphocytes, attenuating antibody production. In fact, as demonstrated with other vaccines,[52] mycophenolate-containing immunosuppressive regimens have been consistently associated with lower neutralizing antibody formation after vaccination against COVID-19. This effect is greater the longer the exposure to the drug.[43]

MTOR INHIBITORS: SIROLIMUS AND EVEROLIMUS

The mTOR inhibitors (imTOR), sirolimus and everolimus, act by inhibiting the activity of the protein kinase mTOR, blocking the response to cytokine stimulation and inhibiting the progression from G1 to S phase of the cell cycle of various cells, including lymphocytes.[60]

The imTOR have known antiviral effects, vastly demonstrated for cytomegalovirus (CMV), the polyomavirus (BK virus) and human papillomavirus (HPV). Several mechanisms are implicated in this antiviral effect, such as: modulation of the innate immune response; inhibition of cell proliferation, a necessary reservoir for replication of obligate intracellular viruses; attenuation of immunosenescence; enhancement of memory CD8 T-cell function and response; and enhancement of CD4 T-cell response and, consequently, antigen-specific antibody production.[61]

As for viruses of the Coronaviridae family, *in vitro studies* revealed that SARS-CoV-2 utilizes the Akt/mTOR/HIF-1 pathway for its replication.[62] In addition to the specific action on viral replication and immune response, other potential beneficial effects of imTOR on COVID-19 would be to reduce cytotoxic T-cell proliferation and consequent cytokine production, ameliorating the cytokine storm, similar to what has been described for CNIs. In addition, the imTOR have the potential effect of preserving the growth and activities of regulatory T cells (Treg), which could act to reduce the aberrant immune response typical of severe forms of the disease.[63] There is also speculation about a potential antifibrotic effect reducing pulmonary interstitial fibrosis. This antifibrotic effect, arising from reduced expression of *plasminogen activator inhibitor* 1 (PAI-1), has been widely explored in the past for patients with renal graft dysfunction and interstitial fibrosis and tubular atrophy, formerly called chronic graft nephropathy.[64,65]

As opposed to the potential beneficial effects cited, the imTOR, as well as azathioprine and mycophenolate, are associated with lymphopenia. In addition, this class of drugs has known pulmonary toxicity, manifested by interstitial pneumonitis, lymphocytic alveolitis, bronchiolitis obliterans with organizing pneumonia, pulmonary fibrosis, or alveolar hemorrhage.[66]

In the clinical context, recent evidence from the Brazilian multicenter study of COVID-19 in kidney transplant recipients demonstrated that in patients using CNI-based regimens, the concomitant use of imTOR was independently associated with a lower risk of 90-day death compared to azathioprine and mycophenolate.[59]

Similar to mycophenolate, the imTOR act by blocking the development of memory B cells. Therefore, it would be expected that patients taking these drugs would show lower neutralizing antibody production after vaccination against SARS-CoV-2. Paradoxically, evidence suggests that the imTOR are associated with improved humoral and cellular immune response following vaccines using messenger RNA platform. It is speculated that this effect is related to the immunomodulatory effect on memory CD8 T cells and CD4 T cells.[67,68]

DRUG INTERACTIONS

Among the drugs currently used in the management of COVID-19, ritonavir deserves mention because of its potential for pharmacological interaction with immunosuppressants. Ritonavir, used in combination with other antivirals, such as nirmatrelvir, has potent inhibitory effect on the CYP4A and glycoprotein-P (gp-P) enzymes, significantly increasing the concentration of CNIs and imTOR.[69] In addition, steroids, when in high doses, induce CYP3A and gp-P activity, reducing tacrolimus concentration.[70] Despite the potential for pharmacologic interaction with immunosuppressants, drugs with no proven efficacy in the management of COVID-19 were not addressed here.

MANAGEMENT OF IMMUNOSUPPRESSION

Considering the body of evidence available to date and that immunosuppressive drugs are critical to the prevention of acute and chronic rejection, it follows:[34,71-77]

- There is no evidence to support changes in the immunosuppressive induction and/or maintenance protocol of transplant centers in order to reduce the risk of SARS-CoV-2 infection;
- No preemptive changes should be made to the maintenance immunosuppressive regimen of stable renal transplant patients in order to decrease the risk of SARS-CoV-2 infection;
- No change in immunosuppressive regimen should be made for patients who have had contact with people who developed COVID-19, as well as for those who tested positive for SARS-CoV-2 and are asymptomatic, oligosymptomatic or with mild forms, on outpatient treatment;
- Patients with SARS-CoV-2 infection can be monitored remotely, using the warning signs for escalated therapeutic interventions;
- Patients with mild to moderate forms without requiring hospitalization but with intense lymphopenia should be evaluated for reduction or temporary discontinuation of antiproliferative drugs, which are myelotoxic;
- For patients with moderate forms requiring hospitalization, regardless of lymphocyte count, reduction or temporary discontinuation of the antiproliferative drug should be considered, especially in those on mycophenolate;
- Complete discontinuation of immunosuppression may be considered in patients with severe forms, invasive mechanical ventilation, and/or organ dysfunction. Despite being a common practice and recommendation, it is important to point out that there is no evidence about the real benefit of this strategy, and it is possible that the reduction of immunosuppression in this phase is a late intervention;
- Kidney transplant recipients who develop SARS-CoV-2 infection are at increased risk of acute renal dysfunction, requiring frequent serial monitoring and possibly graft biopsy for diagnostic confirmation;
- It is recommended to return to immunosuppressive drugs as soon as possible after the patient's clinical recovery, in view of the increased risk of acute rejection;
- There is no evidence to support increasing the dose/exposure to tacrolimus or cyclosporine in order to reduce viral replication or modulate the inflammatory response;
- There is no evidence to support conversion from tacrolimus to cyclosporine or from mycophenolate to imTOR preemptively or for the therapeutic purpose against COVID-19;
- Although suggested by some authors, there is not enough robust evidence on the risk *versus* benefit of temporarily stopping mycophenolate before vaccination with the aim of improving vaccine immune response;

- There is no evidence on the management of patients with COVID-19 or concomitant acute rejection;
- Attention should be paid to therapeutic monitoring of immunosuppressants during treatment of COVID-19 with drugs that have the potential for pharmacological interaction.

FINAL CONSIDERATIONS

Kidney transplant patients have a higher risk of mortality, prolonged viral clearance, and a shorter and less durable vaccine immune response. It is not yet completely clear how immunosuppressive drugs modulate these outcomes, and it is likely that this effect is a determinant in the early stages of the disease, contributing to viral replication or aberrant immune response. Nevertheless, the management of the maintenance immunosuppressive regimen in patients with COVID-19 should be judicious and individualized, taking into consideration the patient's immune risk, clinical picture, and predictors of poor prognosis.

AUTHORS' CONTRIBUTION

Relevant scientific and intellectual contribution to the study: Sandes-Freitas TV, Requião-Moura L, Tedesco-Silva H; **Conception and design:** Sandes-Freitas TV; **Writing the initial version of the manuscript:** Sandes-Freitas TV; **Critical revision and approval of the final version of the manuscript:** Sandes-Freitas TV, Requião-Moura L, Tedesco-Silva H.

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