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Immunosuppression and SARS-CoV-2 Infection in Kidney Transplant Recipients

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Abstract. Kidney transplant recipients (KTRs) infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) may have an increased risk of mortality compared with the general population and hemodialysis patients. As these patients are immunosuppressed, it might seem obvious to attribute this excess mortality to the impaired immunity induced by immunosuppression. In line with this reasoning is the low immune response, both cellular and humoral, that KTRs mount in response to the anti–SARS-CoV-2 vaccine; however, acute respiratory distress syndrome associated with coronavirus disease 2019 is triggered by a state of inflammation and cytokine release syndrome that lead to pulmonary damage and increased mortality. In that context, immunosuppressive treatment dampening the immune response could, in theory, be potentially beneficial. This review aims at analyzing the current knowledge on the impact of immunosuppressive treatment on mortality in SARS-CoV-2–infected KTRs, the optimal management of immunosuppression in the coronavirus disease 2019 era, and the vaccine response and management in immunosuppressed KTRs.

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The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has shaken the world since its initial outbreak in December 2019. As of November 2021, >261 000 000 cases and 5 200 000 deaths have been reported by the World Health Organization, and the numbers continue to rise.[1] Mortality rates by country—provided by the Johns Hopkins University—range from 0.1% to 9.2% with important geographic variations.[2]

Kidney transplant recipients (KTRs) infected with SARS-CoV-2 have shown increased death rates. Indeed, data derived from 3 meta-analyses demonstrated mortality rates ranging from 18.6% to 23%, respectively.[3-5] Moreover, in a multivariate analysis for predictors of mortality in 10 926 coronavirus disease 2019 (COVID-19)–related deaths in England, solid organ transplant (SOT) recipients had the highest hazard ratio of 3.53 (95% confidence interval, 2.77-4.49) compared with hazard ratio of other infected patients including those with comorbidities such as cancer, hematological malignancy, chronic respiratory disease, rheumatoid diseases, and so on.[6] A nationwide cohort in Denmark showed similar results[7]; however, these studies do not allow us to accurately define the increased mortality rate in KTRs, as SOT recipient groups were heterogeneous and the exact number of KTRs included was not reported. As patients undergoing transplantation receive immunosuppressive treatment to prevent rejection, it might seem obvious to attribute the excess mortality encountered by KTRs infected with SARS-CoV-2 to the impaired immunity secondary to immunosuppression. In line with this reasoning is the lower immune response, both cellular and humoral, that KTRs mount in response to the anti–SARS-CoV-2 vaccine[8-10]; however, complications associated with SARS-CoV-2 infection—mainly acute respiratory distress syndrome (ARDS)—are triggered by a state of dysregulated inflammation and cytokine release syndrome that lead to pulmonary damage and increased mortality.[11-13] In that context, immunosuppressive treatment dampening the immune response could be potentially beneficial.

This review aims at analyzing the current knowledge on (1) the impact of immunosuppressive treatment on mortality, (2) the optimal management of immunosuppression in the COVID-19 era, and (3) the vaccine response and management in immunosuppressed KTRs.

Impact of Immunosuppression on Mortality From COVID-19 Infection in KTRs

Studies from Europe, England, United States, Canada, and South America have reported a mortality rate ranging

from 20% to 32% in KTRs compared with 1% to 14% in the general population, after adjustment for age and comorbidities.[14-23] When compared with hemodialysis patients, the mortality of KTRs also seems higher.[15,17] Increased mortality in KTRs may indirectly suggest a negative impact of immunosuppression. Indeed, both innate and adaptive immunity are activated following SARS-CoV-2 infection and are necessary to clear the virus.[24,25] Immunosuppressive agents given after KT affect both innate and adaptive immunity and might impair the immune control of the viral replication.[26] In favor with this assumption, a Spanish national study[27] reported that a SARS-CoV-2 infection occurring in the first 60 d after KT—when the immunosuppressive burden is the most intense—was associated with a significantly increased mortality rate of 45.8%. In agreement with this finding, a report from the European Renal Association COVID-19 Database comparing mortality in KTRs and hemodialysis patients showed that, in a fully adjusted model for age, sex, frailty, and comorbidities, the risk of mortality was higher in KTRs and increased during the first posttransplant year, without, however, association between immunosuppressive treatments and mortality.[17] A large Brazilian multicenter cohort study including 1680 SARS-CoV-2–infected KTRs (65.1% requiring hospitalization) reported a 90-d death rate of 21%.[28] In the multivariate analysis, the use of tacrolimus (Tac) and mycophenolic acid (MPA)—the most commonly used immunosuppressive combination[29]—was independently associated with the risk of death. Although these studies indirectly suggest an impact of immunosuppression, others have failed to demonstrate differences in the outcome between patients transplanted <1 y ago and those transplanted for a longer time,[16] as well as patients receiving induction therapy with lymphocyte depleting agents versus nondepleting agents,[16] suggesting that the degree of immunosuppression does not have a major impact on disease severity and outcome.[30]

Moreover, a cytokine release syndrome—arising from an inadequate immune response implicating interleukins, the complement, and intense antibody response to the virus—has been identified as responsible for negative outcomes of pneumonia, in which case immunosuppressive agents, including calcineurin inhibitors (CNIs), MPA, and glucocorticoids, could also theoretically be beneficial.[31] In fact, glucocorticoids are currently one of the treatments to have proven efficacy in patients admitted for severe COVID-19 pneumonia.[32] To delineate the role of comorbidities versus immunosuppression on mortality rates, recent studies have compared KTRs infected with COVID-19 to nontransplanted patients with similar comorbidities. Chaudhry et al[33] first showed a similar rate of mortality, need of intensive care unit, and mechanical ventilation support in COVID-19 hospitalized SOT recipients compared with nontransplant controls, suggesting that the transplant status by itself does not confer an increased predictive risk of mortality or severe disease. More recently, studies comparing the clinical outcomes of COVID-19 in patients with SOT to a propensity-matched cohort of nontransplanted patients with similar comorbidities showed similar severity of infection and mortality.[18-20,34] These studies conclude that long-term immunosuppression does not seem to increase the risk of developing severe forms of COVID-19; however, it must be underlined that in almost all studies, immunosuppression was decreased when KTRs were hospitalized, although in a nonhomogeneous way. Tables 1 and 2 summarize the main studies—including at least 100 KTRs—that have compared the outcomes of COVID-19 in KTRs versus matched control groups. It is worth noting that the high heterogeneity of these studies in terms of patients included (SOT recipients versus KTRs alone), study design, type, and selection of the control group, and periods of inclusions is most likely one of the main explanations for the contrasting conclusions.

TABLE 1.

Studies (including at least 100 transplanted patients) showing an increased death rate in transplanted patients vs controls

Publications	Country	Time of inclusion	Population study	Control group	Main findings
Goffin et al[17]	Europe – ERACODA database	February 1– December 1, 2020	496 KTRs	-1174 hemodialysis patients	-In a fully adjusted model, the risk was 78% higher in KTRs (HR, 1.78; 95% CI, 1.22-2.61) than in hemodialysis patients. -This association was similar in patients tested because of symptoms (fully adjusted model: HR, 2.00; 95% CI, 1.31-3.06). -This risk was dramatically increased during the first posttransplant year.
Fisher et al[22]	United States	March 10– September 1, 2020	128 hospitalized SOT recipients	-Hospitalized immunocompetent general population (multicenter retrospective cohort study, n = 38 944) -Coarsened exact matched control cohort: 3907	-Patients with a history of SOT were more likely to die within the study period than matched non-SOT recipients (21.9% and 14.9%, respectively; OR, 1.93; 95% CI, 1.18-3.1).
Caillard et al[23]	France	March 1–April 30, 2020	306 hospitalized KTRs	-Hospitalized immunocompetent general population (single-center retrospective cohort study, n = 795) -Matched for age and risk factors for severe COVID-19 or mortality	-Thirty-day COVID-19–related mortality was significantly higher in KTRs (17.9% vs 11.4%, respectively, $P = 0.038$).

CI, confidence interval; COVID-19, coronavirus disease 2019; ERCODA, European Renal Association COVID-19 Database; HR, hazard ratio; KTR, kidney transplant recipient; OR, odds ratio; SOT, solid organ transplant.

TABLE 2.

Studies (including at least transplanted 100 patients) showing similar death rates in transplanted patients vs controls

Publications	Country	Time of inclusion	Population study	Control group	Main findings
Chavarot et al[18]	France	February 26–May 22, 2020	100 hospitalized KTRs	-Hospitalized immunocompetent general population (multicenter retrospective cohort study, n = 2878) -Propensity score matched (1:1)	-Similar survival between KTRs and matched nontransplant patients with respective 30-d survival of 62.9% and 71% (P = 0.38)
Mamode et al[20]	United Kingdom	March–April 2020	121 hospitalized KTRs	52 hospitalized waitlisted patients	-Similar mortality rates (30% in KTRs vs 27% in controls, P = 0.71)
Pereira et al[21]	United States	March 10–May 30, 2020	117 hospitalized SOT recipients (56% of KTRs)	-Hospitalized immunocompetent general population (single-center retrospective cohort study, n = 2714) -Propensity score matched (3:1)	-Mortality (23.08% in SOT recipients vs 23.14% in controls, P = 0.21) was similar in both groups
Hadi et al[19]	United States	January 20–September 30, 2020	2307 SOT recipients (75% of KTRs), 715 requiring hospitalization	-Immunocompetent general population (multicenter retrospective cohort study, n = 231 047) -One-to-one matching for diabetes, hypertension, chronic lung diseases, race, nicotine dependence, heart failure, ischemic heart disease, and gender	-No difference in mortality at 30 d (6.45% vs 5.29%; RR, 1.22; 95% CI, 0.88-1.68) or 60 d postdiagnosis (RR, 1.05; 95% CI, 0.83-1.32)

CI, confidence interval; KTR, kidney transplant recipient; RR, relative risk; SOT, solid organ transplant.

Thus, at the current moment, although immunosuppression is a heavy contributor to the comorbidities affecting KTRs that make them at risk of complications and fatal outcome, it is still unclear whether immunosuppression by itself leads to an increased mortality in KTRs.

Management of Immunosuppression in SARS-CoV-2–infected KTRs: Guidelines and Uncertainties

Lowering immunosuppression—especially antimetabolite drugs—in case of symptomatic SARS-CoV-2 infection has been applied by most KT centers.[35] Table 3 summarizes the main guidelines available regarding the management of immunosuppression in SARS-CoV-2–infected KTRs.[36-41]

However, because randomized data are lacking, the optimal strategy of immunosuppression reduction, as well as its safety and efficacy, is not well defined. Immunosuppression minimization seems logical to unleash the antiviral T-cell response to control the infection.[25] In contrast, maintaining baseline immunosuppression is also a reasonable approach to mitigate the development of an uncontrolled overactivation of the immune response that is associated with the development of ARDS.[11-13] A randomized controlled trial comparing maintenance versus reduction of immunosuppression (NCT04420364) has been set up, but inclusions were terminated early because of lack of recruitment.

Safety concerns also exist on the middle- and long-term immunological consequences of immunosuppression minimization. Indeed, in other settings, as in BK virus infection,[42] a prolonged and intense minimization has been associated with an increased risk of developing de novo donor-specific antibodies (DSAs). Little is known about the potential risk of DSA development after COVID-19. A recently published case series from 2 KT centers in Spain reported the clinical follow-up of 47 hospitalized KTRs who survived COVID-19. Eighty-three percent had at least 1 immunosuppressive drug withdrawn—mostly the antimetabolite—for a median time

TABLE 3.

Guidelines regarding management of immunosuppression in COVID-19 KTRs

Guidelines	Key recommendations
TTS[40]	-No strong recommendation -Calibration of dose reduction has to be balanced with the risk of acute rejection
ERA[37]	-Maintain IS treatments unchanged in KTRs <60 y without pulmonary infiltrates. -In all other cases, MPA should be stopped, as well as CNI and mTORi if concomitant fever or hypoxia
AST[36]	-Consider immunosuppression reduction
BTS[38]	-Stop antiproliferative agents, and consider CNI reduction
FST[41]	-Nonhospitalized patients: 50% reduction of antimetabolite dose (or complete withdrawal on case-by-case basis), stop mTORi, maintain CNI doses (T_0 Tac 4–7 ng/mL, T_0 Csa 50–125 ng/mL) and steroids, and stop belatacept in acute phase of the disease -Hospitalized patients (without ARDS): stop antimetabolite, mTORi, belatacept, maintain steroids, and CNI (T_0 Tac 4–6 ng/mL, T_0 Csa 50–75 ng/mL) -ARDS: just maintain steroids -After clinical recovery: consider IS increasing

AST, American Society of Transplantation; ARDS, acute respiratory distress syndrome; BTS, British Transplant Society; CNI, calcineurin inhibitor; COVID-19, coronavirus disease 2019; Csa, cyclosporine A; ERA, European Renal Association; FST, French Society of Transplantation; IS, immunosuppression; KTR, kidney transplant recipient; MPA, mycophenolic acid; mTORi, mechanistic target of rapamycine; Tac, tacrolimus; TTS, The Transplant Society.

of 17 d. Up to 3 mo after discharge, no rejection episode or emergence of de novo DSAs were observed, and no significant changes occurred in the calculated panel reactive antibodies.[43] Nevertheless, longer follow-up studies with larger cohorts are necessary to assess the safety of minimization strategies.

Immunosuppressive Drugs and COVID-19: Harmful or Potential Adjuvant Therapy?

A triphasic course in COVID-19 disease has been described.[24] In the first phase, patients have mild symptoms, such as dry cough, malaise, and fever. An adequate response of the innate and adaptive immune systems can eliminate the virus and preclude disease progression to the next stages.[25] In the second phase, viral multiplication and localized inflammation of the lung tissue occur, causing viral pneumonia. A minority of patients with COVID-19 will undergo a transition to the third and most severe phase of illness: a syndrome of systemic hyperinflammation, also referred to as the cytokine storm syndrome, associated with high levels of proinflammatory cytokines release, such as interleukin (IL)-2, IL-6, IL-7, and tumor necrosis factor-alpha. In this phase, patients can develop ARDS and multiorgan failure, which are the main causes of death.[11-13]

In vitro investigations show that some immunosuppressive drugs have antiviral effects against coronaviruses. How immunosuppressive drugs commonly used after KT can potentially affect COVID-19 is discussed below.

Corticosteroids

Corticosteroids are widely used after KT. They have a wide range of anti-inflammatory and immunomodulatory effects, including inhibition of the synthesis of proinflammatory cytokines, reduction of leukocyte trafficking, and induction of T-lymphocytes apoptosis.[44] They impair innate, T-cell, and humoral immunity.[26]

Corticosteroids have been tested in immunocompetent patients infected by SARS-CoV-2 in at least 8 cohort studies and 1 open-label randomized trial. Six cohort studies showed that steroid use was associated with a better clinical outcome in patients with COVID-19[13,45-49]; however, 2 cohort studies reported opposite results.[50,51] They found that steroid use was associated with a higher risk of blood stream infections[50] and a lower remission rate.[51] These conflicting results may have resulted from selection bias because of nonrandomization. The RECOVERY trial was an open-label controlled study comparing dexamethasone versus standard of care in hospitalized COVID-19 patients. It showed that dexamethasone was associated with reduced 28-d mortality in patients requiring oxygen supplementation.[32] Effectiveness of steroids in severe COVID-19 was also demonstrated in a meta-analysis.[52] Since then, dexamethasone has been the standard of care in patients with COVID-19 requiring supplemental oxygen; however, as KTRs were excluded from most studies—including RECOVERY—the benefit of increasing steroids in KTRs with symptomatic COVID-19 is still to be proven.

CNIs

CNIs—Tac and cyclosporine A—are the cornerstone of most immunosuppressive regimens used after KT. They impact innate, cell-mediated, and humoral immunity.[26] In vitro studies suggest that CNIs have antiviral effects on coronaviruses. Cyclosporine A has been shown to inhibit the replication of several coronaviruses in vitro at noncytotoxic concentrations and independently of its immunosuppressive effect.[53,54] A genome-wide analysis of protein–protein interactions between SARS-CoV (SARS-CoV-1) and human host proteins identified FK506 (Tac)-binding proteins as one of the interaction partners for SARS-CoV proteins.[55] In addition, both FK506 treatment and knock down of FK506-binding proteins 1A and 1B inhibited SARS-CoV replication in vitro.[56] Finally, cyclophilins, the binding proteins of cyclosporine A, catalyze the *cis/trans* isomerization of propyl peptide bonds. This is an essential step in the correct folding of proteins, such as cellular and viral proteins.[57] This function of cyclophilin is found to be important for the replication of SARS-CoV-2.[31]

However, there is no clinical evidence supporting that CNIs may improve the clinical outcomes of COVID-19 in KTRs or in the general population. There is also no evidence that reducing or interrupting CNIs improve the clinical outcome of SARS-CoV-2–infected KTRs. A phase 2 clinical trial is ongoing to test the efficacy of conversion from Tac to voclosporin—a third-generation CNI—to reduce the time of viral clearance in SARS-CoV-2–infected KTRs with mild to moderate symptoms on dual immunosuppressive treatment of steroids and Tac (NCT04701528). Current recommendations regarding management of CNI consider reducing doses or drug cessation depending on the severity of the infection (Table 3).

Antimetabolites

MPA and azathioprine are the most commonly used antimetabolites after KT. Both drugs inhibit purine synthesis, affecting T- and B-cell proliferation.[26] MPA was shown to inhibit viral replication of 4 different coronaviruses (but not SARS-CoV-2) in cell culture.[58] One in vitro study found that MPA inhibits SARS-CoV-2 replication in VeroE6/TMPRSS2 cells.[59] In another study,[60] human pluripotent stem cells were differentiated into lung organoids and then infected with SARS-CoV-2. In these lung organoids, MPA inhibited viral replication of SARS-CoV-2. To the best of our knowledge, there are no data about azathioprine.

Most guidelines recommend considering MPA cessation in KTRs presenting symptomatic COVID-19. In a large multicenter cohort study of SARS-CoV-2–infected KTRs in Brazil, MPA, when associated with Tac, was an independent risk factor of mortality[28]; however, there is currently no strong clinical evidence showing that MPA interruption modifies the outcome of patients.

Mechanistic Target of Rapamycine Inhibitors

Sirolimus and everolimus are inhibitors of the mechanistic target of rapamycin (mTORi). They inhibit protein synthesis, cell cycle progression, and cell growth,[61] impacting mostly innate and cell-mediated immunity.[26] The use of mTORi after KT is associated with a reduced incidence of several viral infections, such as cytomegalovirus and BK virus.[62,63] mTORi's were shown to inhibit MERS-CoV replication in vitro.[64] A work based on network drug repurposing suggested sirolimus as a potential treatment for COVID-19.[65] At least 3 clinical trials are ongoing (NCT04341675, NCT04461340, and NCT04948203) to evaluate the effectiveness of mTORi initiation in the general population hospitalized for COVID-19. In KTRs, mTORi did not emerge as protective against the development of severe COVID-19 outcomes; however, it is important to keep in mind that these drugs were interrupted most of the time in hospitalized KTRs with severe diseases

by fear of their potential negative impact on the pulmonary involvement associated with COVID-19.

Tocilizumab

Tocilizumab, an anti–IL-6 receptor, has shown promising results in the treatment of active and chronic antibody-mediated rejection in KTRs.[66,67] IL-6 is an important proinflammatory cytokine involved in the acute phase response and differentiation and function of B and T cells.[68] IL-6 is also an important actor in the cytokine storm associated with severe forms of COVID-19.[11-13] Consequently, tocilizumab has been investigated in COVID-19 patients in several cohort studies and a phase 3 placebo-controlled trial. In 3 cohort studies, tocilizumab use was associated with lower mortality and intensive care unit admission rates[69,70]; however, other cohort studies reported contradictory results.[50,71-75] A phase 3 placebo-controlled trial showed that tocilizumab treatment in patients hospitalized with COVID-19 pneumonia was effective to improve a composite end point including mechanical ventilation initiation or death by day 28[76]; however, in another phase 3 placebo-controlled trial, tocilizumab was not superior to the placebo to improve clinical status in patients hospitalized for severe COVID-19.[77] Finally, a meta-analysis showed that tocilizumab was superior to usual care or the placebo to improve a composite end point of progression to mechanical ventilation, extracorporeal membrane oxygenation, or death.[78] Nevertheless, the effectiveness of tocilizumab to improve mortality alone has still to be demonstrated. Small case series suggest that tocilizumab might be used safely with moderate efficacy in COVID-19 KTRs. Pereira et al[79] showed in a case series of 29 hospitalized SOT recipients with severe COVID-19 that tocilizumab could be used safely but was not associated with decreased incidence of 90-d mortality compared with a matched cohort of SOT recipients who did not receive the drug.

Other Immunosuppressive Drugs

Induction immunosuppression at KT typically consists of basiliximab or thymoglobulin.[80] Thymoglobulin is a T cell–depleting agent, especially used in sensitized recipients. Basiliximab is a CD25 receptor antagonist. Thymoglobulin has been associated with an increased risk of viral infection—cytomegalovirus and BK virus—compared with basiliximab.[81] There are currently no published data about the impact of induction therapy on COVID-19. The TANGO trial[16] reported the outcomes of 144 KTRs hospitalized for COVID-19 and did not find a significant difference between KTRs who received induction therapy with lymphocyte depleting agents versus those who did not.

Rituximab, a monoclonal anti-CD20 antibody, is commonly used in HLA- or ABO-incompatible KTs or as treatment of antibody-mediated rejection. A French multicenter cohort study recently showed that treatment with rituximab in patients with inflammatory rheumatic and musculoskeletal diseases was associated with more severe COVID-19[82]; however, published data on KTRs treated with rituximab are lacking.

Belatacept inhibits T-cell activation through costimulation blockade, allowing a CNI-free regimen. Its impact on the risk of developing severe COVID-19 infection has not been well evaluated so far. Although some authors have suggested that belatacept might mitigate the cytokine storm, resulting in a mild form of COVID-19 in KTRs, evidence is very weak and not currently tested in clinical trials.[83] The French Society of Transplantation recommends belatacept cessation in KTRs infected with SARS-CoV-2[41] (Table 3).

Immunosuppression and Anti–SARS-CoV-2 Vaccines

Great hopes were placed in the early vaccination of all immunocompromised patients to reduce the rate of severe forms of COVID-19; however, disappointing results emerged from KTR cohort studies regarding the humoral response rates after 2 doses of mRNA vaccines that ranged from 29.9% to 54% (Table 4).[9,85,87,89,90] These results contrast with the robust humoral response rates observed in the general population[91] and also in chronic dialysis populations.[92-94] Cellular response rates were also low. Bertrand et al[8] showed a 57.8% T-cell response rate in 26 KTRs after 2 doses of the BNT162b2 vaccine, using an ELISpot immunoassay. Cucchiari et al[9] demonstrated a 54.7% T-cell response rate after the second dose of the mRNA-1273 vaccine in 117 SARS-CoV-2–naive transplant patients, also using an ELISpot immunoassay. We recently reported a cellular response rate of 32.2% (Interferon-Gamma-Release-Assay test) in a cohort of 90 SARS-CoV-2–naive KTRs 1 mo after the second dose of the mRNA BNT162b2 vaccine.[10] Case series of severe SARS-CoV-2 infections in fully vaccinated KTRs have been reported.[95,96] A recent large multicenter study showed that compared with 101 million fully vaccinated adults in the United States, fully vaccinated SOT recipients (n = 18.215) had an 82-fold higher risk of breakthrough infection and 485-fold higher risk of breakthrough infection with associated hospitalization and death.[97] These data emphasize the importance of the adaptive immune response in the defense against the virus. Regarding such poor results, a third dose of mRNA vaccine was tested in a case series and 1 randomized trial and resulted in a substantial increase of humoral response rates at around 70%[84,86-88] (Table 4). Nevertheless, a nonnegligible proportion of KTRs remains with no humoral response even after 3 doses.

Risk factors affecting the humoral response rates after 2 and 3 doses of mRNA vaccine have been suggested from cohort studies (Table 4). The use of MPA seems to be associated with poor response rates. Although not very surprising, as it has already been reported for other vaccines such as influenza,[98] it is a challenging problem because MPA is widely used in KTRs.

Scarce data exist on the impact of other immunosuppressive drugs on the response rate after vaccination. A French group recently reported a low rate of humoral response rates at 6.4% after 3 doses of mRNA vaccine in KTRs treated with belatacept.[99] Also, patients treated with rituximab for rheumatic disease show very low humoral response rate after vaccination.[100] A group of experts of antineutrophil cytoplasmic antibodies vasculitis recently suggested a time window of at least 6 mo between rituximab administration and anti–SARS-CoV-2 vaccination.[101] To the best of our knowledge, there is no formal recommendation in the KT field. Mechanistic targets of rapamycin were reported to increase the humoral response after pneumococcal, tetanus, and influenza vaccines, as they increase CD8+ effector memory T cells[102,103]; however, the potential positive impact of mTORi on the COVID-19 vaccine-induced humoral response rate has yet to be translated into clinical data.

Less is known regarding the clinical effectiveness of vaccine in SOT recipients; however, 2 recently published studies from

TABLE 4.

Immune response after anti–SARS-CoV-2 vaccine in KTRs

Publication	Study population	Vaccine	After 2 doses	After 3 doses	Risk factor impacting humoral response
Cucchiari et al[9]	133 KTRs and kidney-pancreas transplant recipients	mRNA-1273	29.9%[a]		
Benotmane et al[84]	205 KTRs	mRNA-1273	48%[b]	49% of patients with no or low humoral response after 2 doses	-After 2 doses: Patients with a first KT, a longer time from transplantation, better kidney function, and less immunosuppression were more likely to seroconvert. -After 3 doses: Patients with no response after 2 doses (compared with those with weak response) and patients treated with and association of Tac–MPA–steroids (compared with other IS regimens) were less likely to respond.
Boyarsky et al[85]	658 SOT recipients	47% mRNA-1273 53% BNT162b2	54%[b]		-The use of antimetabolite was associated with poor humoral response
Kamar et al[86]	101 SOT recipients	BNT162b2	40%[b]	68%	-Patients who do not respond after 3 doses were older, had a higher degree of immunosuppression, and had lower graft function.
Masset el al[87]	456 KTRs and pancreas transplant recipients	BNT162b2	49.7%[b]	69.2%	-After 2 doses: The use of antimetabolites or steroids, older age, impaired kidney function, and KT ≤4 y were independent risk factors for nonresponse. -After 3 doses: Lymphocyte count <1500/μL and impaired kidney function were independently associated with the absence of response.
Hall et al[c,88]	60 KTRs	mRNA-1273	11%[d]	55%	

[a]Two weeks after the second dose.
[b]One month after the second dose.
[c]Placebo-controlled randomized trial including 120 KTRs demonstrated that a booster third dose (n = 60) of the mRNA-1273 vaccine given 2 mo after the second dose was associated with higher rates of seroconversion, anti-RBD Ab titers, and virus neutralization 1 mo after injection compared with placebo (n = 60).
[d]Two months after the second dose.
Ab, antibody; IS, immunosuppression; KT, kidney transplantation; KTR, kidney transplant recipient; MPA, mycophenolic acid; RBD, receptor-binding domain; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SOT, solid organ transplant; Tac, tacrolimus.

the United States[104] and United Kingdom[105] suggested that vaccinated SOT recipients have a reduced risk of developing symptomatic[104] and lethal forms[105] of SARS-CoV-2 infection compared with nonvaccinated SOT recipients. These preliminary results are encouraging but need validation. Moreover, correlation between vaccine-induced immune response and subsequent clinical protection is not well described yet and deserves further investigation.

CONCLUSIONS

KTRs infected with COVID-19 may have an increased risk of mortality compared with the general population and hemodialysis patients. Attributing this increased mortality to immunosuppression alone is imprudent, as a direct relationship has not been demonstrated so far. What is, however, clearly reported is that immunosuppression can reduce the humoral and cellular responses to vaccination; however, the interpretation of the data derived from the rapidly growing number of studies is complex because of the high heterogeneity in the use of antibody assays and neutralization platforms. Thus, until proven otherwise, immunosuppression reduction is a consideration in the early stages of infection. Handling immunosuppression in case of COVID-19 infection in KTRs should integrate the stage of infection, strength of immunosuppression, and comorbidities. Further studies will help clarify the implication of immunosuppressive drugs on KTRs' outcomes. The relationship between immunogenicity of vaccines and subsequent clinical protection needs further clarification to adapt our vaccine strategy in SOT recipients. Finally, the combination of different preventive strategies (eg,

vaccination and preventive monoclonal antibody infusion) should be tested in future clinical trials.

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