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ORIGINAL ARTICLE

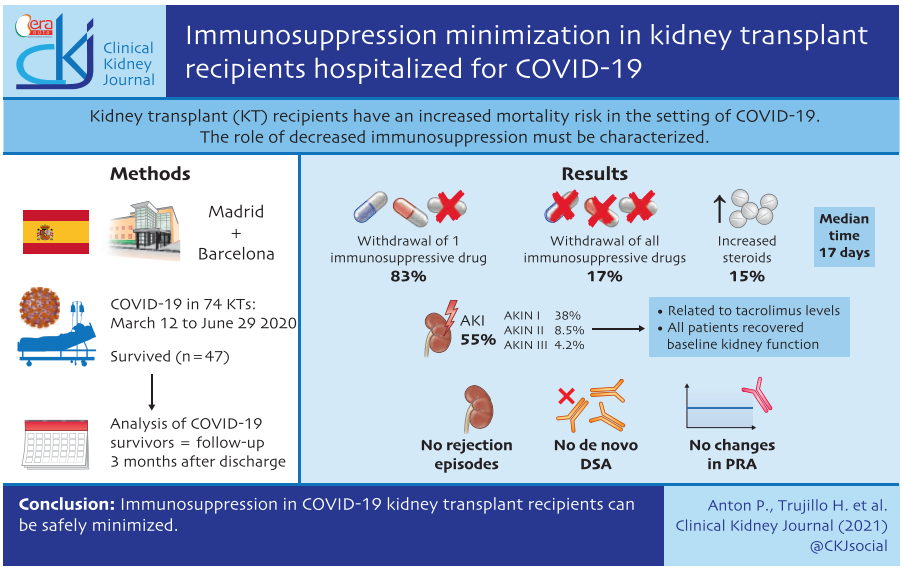
Immunosuppression minimization in kidney transplant recipients hospitalized for COVID-19

Paula Anton Pampols[1], Hernando Trujillo [2], Edoardo Melilli [1], Blanca Urban[3], Justo Sandino [2], Alexandre Favá[1], Eduardo Gutierrez[2], Oriol Bestard [1], Esther Mancebo[4], Angel Sevillano[2], Josep M. Cruzado[1] and Enrique Morales [2]

[1]Department of Nephrology, IDIBELL, Bellvitge University Hospital, Barcelona, Spain, [2]Department of Nephrology, University Hospital "12 de Octubre", Madrid, Spain, [3]Department of Immunology, Bellvitge University Hospital, Barcelona, Spain and [4]Department of Immunology, University Hospital "12 de Octubre", Madrid, Spain

Correspondence to: Edoardo Melilli; E-mail: emelilli@bellvitgehospital.cat, Josep M. Cruzado; E-mail: jmcruzado@bellvitgehospital.cat

GRAPHICAL ABSTRACT



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ABSTRACT

Background. Immunosuppressed patients such as kidney transplant recipients (KTs) have increased mortality risk in the setting of coronavirus disease 2019 (COVID-19). The role and management of chronic immunosuppressive therapies during COVID-19 must be characterized.

Methods. Herein, we report the follow-up of a cohort of 47 KTs admitted at two Spanish Kidney Transplant Units, who survived COVID-19. The impact of the management of immunosuppression during COVID-19 on graft function and immunologic events was evaluated.

Results. At least one immunosuppressive agent was withdrawn in 83% of patients, with antimetabolites being the most frequent. Steroids were generally not stopped and the dose was even increased in 15% of patients as part of the treatment of COVID-19. Although immunosuppressive drugs were suspended during a median time of 17 days, no rejection episodes or *de novo* donor-specific antibodies were observed up to 3 months after discharge, and no significant changes occurred in calculated panel reactive antibodies. Acute graft dysfunction was common (55%) and the severity was related to tacrolimus trough levels, which were higher in patients receiving antivirals. At the end of follow-up, all patients recovered baseline kidney function.

Conclusions. Our observational study suggests that immunosuppression in KTs hospitalized due to COVID-19 could be safely minimized.

Keywords: acute kidney injury, allograft rejection, coronavirus disease 2019, donor-specific antibodies, immunosuppression, kidney transplantation

INTRODUCTION

Immunosuppressed patients, in particular solid-organ transplant recipients (SOTs), have an increased risk of viral and bacterial infections as a consequence of diminished T-cell immunity. In the early days of the current pandemic, it was suggested that kidney transplant recipients (KTs) could have severe manifestations of coronavirus disease 2019 (COVID-19) due, at least in part, to chronic immunosuppressive therapy [1–3]. More recently, several studies have confirmed a substantially worse prognosis in this population [4], with a large European cohort reporting a mortality risk 92 times higher in KTs with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection as compared with their uninfected counterparts and a 28% greater risk compared with dialysis patients [5].

Spain was one of the most affected countries during the first wave of the COVID-19 pandemic, and transplant units coped with a significant number of infected and hospitalized KTs without evidence-based strategies concerning therapeutic management [6]. It has been proposed that management of viral infections after solid-organ transplantation should include antiviral drug therapies and immunosuppression reduction, since progression to severe disease has been correlated with overimmunosuppression. Consequently, a reduction of immunosuppressive agents appears as a rational strategy to allow the development of specific immunity [7]. In fact, an expert consensus document suggests a progressive withdrawal of immunosuppression depending on the severity of the disease [8], and previous works have already described the withdrawal of at least one immunosuppressive drug in KTs with COVID-19, and this strategy does not seem to have an impact on patient survival [1–3, 6]. On the contrary, KTs with COVID-19 present lower CD3, CD4 and CD8 cell counts than the general population, which further supports an immunosuppression minimization approach for the management of the infection [2]. Despite the overwhelming number of current publications on COVID-19 and kidney transplantation, there is scarce information on the evolution of alloimmune humoral response after reduction of immunosuppression in KTs hospitalized due to SARS-CoV-2 infection. Moreover, to the best of our knowledge, no data on the evolution of kidney graft function in COVID-19 survivors has been reported. This is of special relevance given that acute kidney injury (AKI) has been frequently described among KTs with COVID-19 [9, 10].

Herein, we report 3-month follow-up of 47 KTs who survived COVID-19 in two Spanish Kidney Transplant Units. We aimed to evaluate the impact of immunosuppression reduction/withdrawal during the course of COVID-19 on kidney graft function and to assess the influence of immunosuppression reduction/withdrawal on the possible appearance of *de novo* donor-specific antibodies (DSAs) or changes in calculated panel reactive antibodies (cPRAs).

MATERIALS AND METHODS

Study population

This is a two-centre observational study. All COVID-19-positive KTs hospitalized between 12 March and 29 June 2020 were included. COVID-19 diagnosis was confirmed by positive results on real-time reverse transcriptase–polymerase chain reaction (RT-PCR) on nasal and/or pharyngeal swab samples. Swab tests were not available in four patients. In the latter cases, a presumptive diagnosis was made based on computed tomography scan or chest X-ray findings and compatible clinical presentation. Hospitalization criteria included need for oxygen therapy, radiographic evidence of pulmonary infiltrates, kidney graft dysfunction and recent onset of symptoms (<7 days).

Therapies for COVID-19 were quite homogeneous among the two institutions and varied according to the new data that have become known over time. Immunosuppression management was based on antimetabolite [mycophenolate mofetil (MMF)/mycophenolic acid (MPA)] withdrawal at admission or in some cases only when lymphopaenia was present and was later reintroduced when total lymphocyte counts improved or according to the physician's discretion. Tacrolimus (TAC) or mammalian target of rapamycin inhibitors (mTORi) interruption was

reserved for extremely severe cases [intensive care unit (ICU) admission, acute respiratory distress syndrome].

We analysed data from patients who were discharged after COVID-19 and had follow-up data available at 3 months after discharge. KTs with an estimated glomerular filtration rate (eGFR) ≤15 mL/min/1.73 m^2 as measured by the Chronic Kidney Disease Epidemiology Collaboration equation and patients who did not survive COVID-19 were excluded from the analysis.

Serum creatinine (SCr), eGFR, proteinuria, microhaematuria, lymphopaenia and TAC trough levels were retrospectively collected at 3 and 6 months before admission, at hospital admittance and at discharge. Then, we prospectively measured the aforementioned variables at 3 months after discharge. AKI was defined according to the Kidney Disease: Improving Global Outcomes classification [11].

Measurements of human leukocyte antigen (HLA) Class I (A, B) and Class II (DR, DQ), of both the recipient and the donor, were performed by DNA-based low-resolution typing with sequence-specific primers. All samples were tested by single-antigen bead assay (SAB; One Lambda) to detect donor-specific anti-HLA IgG by single-antigen Classes I and II flow beads assay kit. The test was considered positive if mean fluorescence intensity (MFI) was >500 or if MFI/MFI lowest bead was >5. In the presence of DSA, the missing alleles were inferred from their haplotype associations with HaploStats [12]. Pre-COVID-19 SAB tests were performed between 6 and 12 months before admission, while post-COVID-19 SAB tests were performed 3 months after discharge.

This study was conducted in accordance with the amended declaration of Helsinki and was approved by the hospital ethical review boards (PR230/20).

Statistical analysis

Continuous variables were expressed as mean ± standard deviation or median and interquartile range (IQR) and categorical variables as total number (*n*) and percentage (%). Comparison between groups was performed using Pearson's χ^2 test for categorical data and Fisher's exact test was applied when the number of cases was fewer than five. One-way analysis of variance and *t*-tests were used for normally continuous distributed data, and nonparametric Kruskal–Wallis test and Mann–Whitney *U*-test for non-normally distributed variables. P-values were two-tailed and statistical significance level was established at $P < 0.05$. SPSS 20.0 software (SPSS Inc., Chicago, IL, USA) and GraphPad Prism version 6.0 (GraphPad Software, San Diego, CA, USA) were used for data management and analysis.

RESULTS

During the observation period, 74 patients were admitted to our institutions due to SARS-CoV-2 infection. Twenty-four of them died and were excluded from the analysis. Additionally, three patients with baseline eGFR ≤15 mL/min/1.73 m^2 who started haemodialysis during admission were ruled out, since immunosuppression withdrawal was carried out as part of a protocol after kidney graft failure and kidney function recovery was not expected (Figure 1). Ultimately, 47 patients were suitable for the final analysis.

Five out of 47 (10.6%) patients required ICU management and 4/47 (8.5%) invasive mechanical ventilation. Baseline (pre-admission) eGFR was 46 mL/min/1.73 m^2 (mean of two determinations) and proteinuria was minimal. The main clinical characteristics of the study population are detailed in Table 1. Regarding immunological features, most patients had baseline cPRA of 0%, four patients (8.5%) had known DSA before admission and six (12.7%) had a history of rejection episodes (one humoral and five cellulars). Median time from kidney transplantation to COVID-19 diagnosis was 109 months.

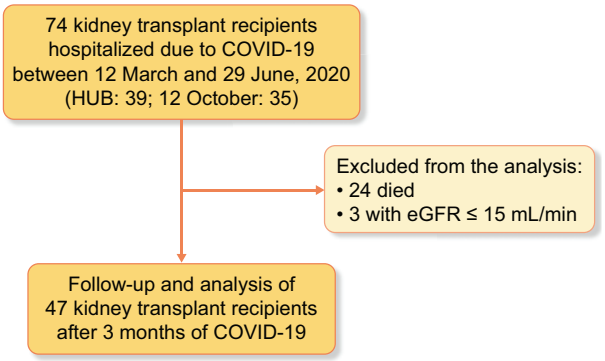

FIGURE 1: Flow chart of the study. Only subjects who required hospital admission were included.

Table 1. Baseline clinical characteristics of the study population

Sex (male/female), *n* (%)	18/29 (39/61)
Age at COVID-19 diagnosis (years), mean ± SD	59 ± 12
Ethnicity (Caucasian/other), *n* (%)	40/7 (85/15)
Type of donor (deceased/living), *n* (%)	41/6 (87/13)
Number of transplants (1/>1), *n* (%)	40/7 (85/15)
Induction therapy, *n* (%)	
None	13 (27)
Thymoglobulin	17 (36)
Basiliximab	17 (26)
Heart disease (Y/N), *n* (%)	11/36 (23.4/76.6)
Pulmonary disease (Y/N), *n* (%)	7/40 (14.9/85.)
Hypertension (Y/N), *n* (%)	4/43 (8.5/91.5)
Diabetes mellitus (Y/N), *n* (%)	13/34 (27.7/72.3)
Obesity (BMI >30 kg/m^2 Y/N), *n* (%)	14/33 (29.8/70.2)
RAASi, *n* (%)	
None	28 (59.6)
ACE inhibitors	13 (27.7)
Angiotensin receptors blockers	6 (12.8)
Anticoagulation treatment (Y/N), *n* (%)	8/39 (17/83)
Time from transplantation to COVID-19 diagnosis (months), IQR	109 (30–191)
cPRA %, median (IQR)	0 (0–18)
cPRA >90 (%)	5 (10.6)
DSA Class I	3 (6.4)
DSA Class II	1 (2.1)
DSA Classes I and II	4 (8.5)
Previous rejection episode	
All (*n* %)	6 (12.8)
Cellular (%)	5 (10.6)
Humoral (%)	1 (2.1)
eGFR before admission (mL/min/1.73 m2), median (IQR)	46 (32–66)
CKD stage (%)[a]	
1–2	14 (31)
3a	7 (16)
3b	15 (34)
4	8 (17)
Urinary protein creatinine ratio (g/mol), median (IQR)	16.5 (9–34.4)

[a]Three patients were excluded because kidney function was not stable due to recent transplantation (<6 months).
BMI, body mass index; RAASi, renin–angiotensin–aldosterone system inhibitors; ACE, angiotensin-converting enzyme.

Immunosuppression management before, during and after COVID-19

Most patients were taking calcineurin inhibitors (CNI)-based immunosuppression, mainly accompanied by antimetabolites, and 68% were on steroids. During admission, withdrawal of at least one immunosuppressive drug was common (83%), while total immunosuppression withdrawal was performed in 17% of cases. The percentage of withdrawal for each immunosuppressive agent and the length of withdrawal (days) is presented in Table 2. Patients with MMF/MPA withdrawal had more severe lymphopaenia during hospital stay (median lymphocyte nadir during admission 720 ± 387 versus 451 ± 216, P = 0.02) and duration of immunosuppression withdrawal was longer for antimetabolites as compared with other drugs. Of note, 15% of patients received high-dose intravenous steroids. Figure 2 displays the immunosuppression reduction strategy for each patient of the cohort.

Graft function evolution

During a median hospital stay of 14 days (IQR 9–25), 26 (55%) patients developed AKI; 18 (38%) cases Stage I, 4 cases Stage II (8.5%) and 2 cases (4.2%) Stage III. One AKI episode was of obstructive nature due to anastomotic ureteral stricture in a patient transplanted 3 months before admission. The empirical treatment for COVID-19 used during the first wave of the pandemic according to AKI status during hospitalization is shown in Figure 3. Notably, more AKI episodes were observed in patients receiving antivirals (except for remdesivir); however, this was not significant (32% versus 19%, respectively, P = 0.3). Not surprisingly, the use of antivirals had a strong relationship with high TAC trough levels, as can be seen in Figure 4. Median TAC trough levels were higher in patients receiving such drugs compared with no antiviral therapy [9 (IQR 8.1–10.9) versus 35.6 (IQR 14.6–44), P = 0.009]. Consequently, patients who received antivirals had higher rates of TAC withdrawal (54% versus 18%, P = 0.03). Of interest, AKI was not associated with the use of renin–angiotensin–aldosterone system

Table 2. Baseline immunosuppression and management during COVID-19

Baseline IMS therapy, *n* (%)	
TAC/MMF/prednisone	20 (42.6)
TAC/mTORi/prednisone	4 (8.5)
mTORi/MMF/prednisone	4 (8.5)
TAC/MMF	8 (14.9)
TAC/mTORi	2 (4.3)
mTORi/MMF	3 (6.4)
TAC/prednisone	2 (2.1)
TAC monotherapy	1 (2.1)
MMF/prednisone	1 (2.1)
Cyclosporine/prednisone	1 (2.1)
mTORi/prednisone	1 (2.1)
Follow-up (months), median (IQR)	4 (3–5)
Any IMS withdrawal (Y/N)	38/9 (80.9/19.1)
All IMS withdrawal (Y/N)	8/39 (17/83)
TAC withdrawal[a] (Y/N)	10/27 (27/73)
Day TAC withdrawal, median (IQR)	13 (5–21)
Antimetabolite withdrawal (*n* = 36) (Y/N)	31/5 (86/14)
Day antimetabolite withdrawal, median (IQR)	20 (11–31)
mTORi withdrawal (*n* = 14) (Y/N)	8/6 (57/42)
Day mTORi withdrawal, median (IQR)	15 (4–21)

[a]Thirty-seven patients were on TAC.
IMS, immunosuppression.

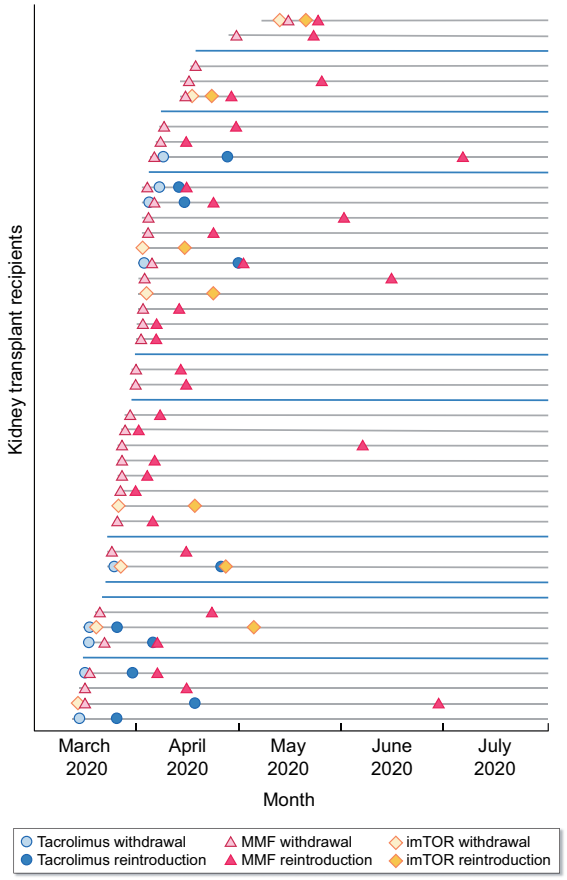

FIGURE 2: Management of immunosuppression. Each line corresponds to a patient. Blue lines represent patients without immunosuppression minimization/withdrawal.

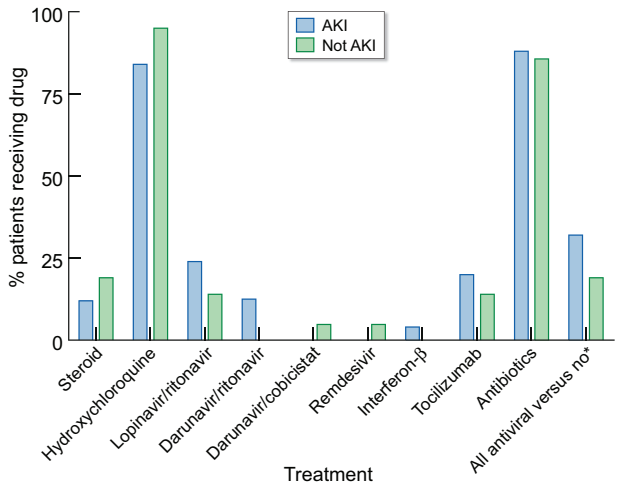

FIGURE 3: Treatment for COVID-19 (distribution according to AKI during hospitalization). *Except remdesivir.

inhibitors before admission (56% versus 44%, P = 0.68). On the contrary, the severity of AKI was related to TAC trough levels [TAC trough levels 9.1 (IQR 6.9–12.6) for no AKI, TAC trough levels 9.4 (IQR 8.2–29) for AKI I, TAC trough levels 26 (IQR 15–45) for AKI II–III, P = 0.026; Figure 5]. Globally, 23.4% of patients had TAC trough levels >20 μg/L, with all cases returning to baseline levels at 3 months after discharge [median TAC trough levels of 10.2 μg/L (IQR 8.6–19.9) at admission; median TAC trough levels of 6.1 μg/L (IQR 5.2–7.8) at 3 months]. Proteinuria did not exhibit relevant changes before and after COVID-19 (Δ 0.6 ± 4 g/mol). Finally, all patients with AKI recovered baseline kidney graft function as shown by SCr evolution in Figure 6. One patient who did not develop AKI during admission experienced an AKI episode 3 months after COVID-19, but in the context of an acute graft pyelonephritis. No patient developed *de novo* DSA at 90 days after discharge. The MFI levels before and after COVID-19 for patients with known DSA previous to admission are presented in Figure 7. One patient exhibited an important reduction of MFI DSA against Class I, while a low MFI titre DSA against Class II disappeared, and cPRA decreased from 64% to 18%. Notably, this patient did not undergo immunosuppression reduction as COVID-19 clinical presentation was mild. Overall, cPRA remained unchanged in most patients, with the exception of two cases where cPRA increased from 0% to 1% and 18%, respectively, whereas cPRA reduction was observed in two patients (one previously mentioned and another with a decrease from 30% to 0%; Figure 8).

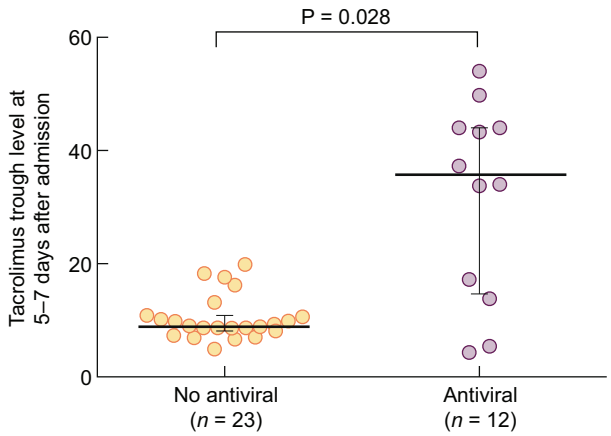

FIGURE 4: Use of antiviral drugs (excluding remdesivir) and tacrolimus trough levels at 5–7 days since admission.

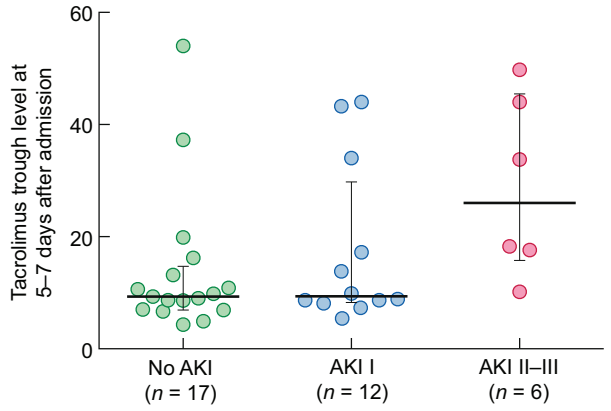

FIGURE 5: AKI stage and tacrolimus trough levels.

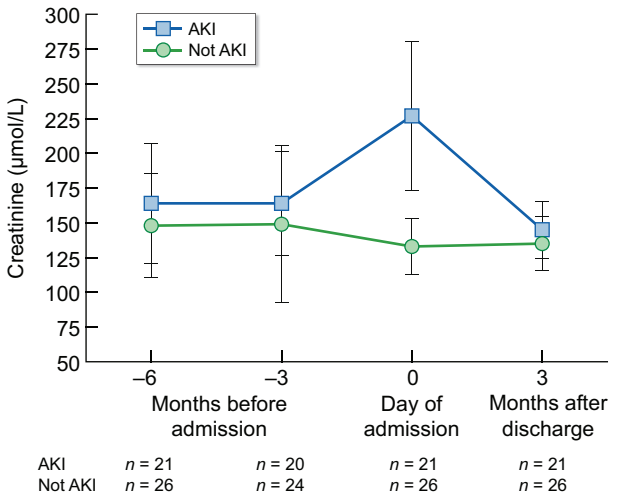

FIGURE 6: SCr evolution at different time points (3 and 6 months before admission and 3 months after discharge).

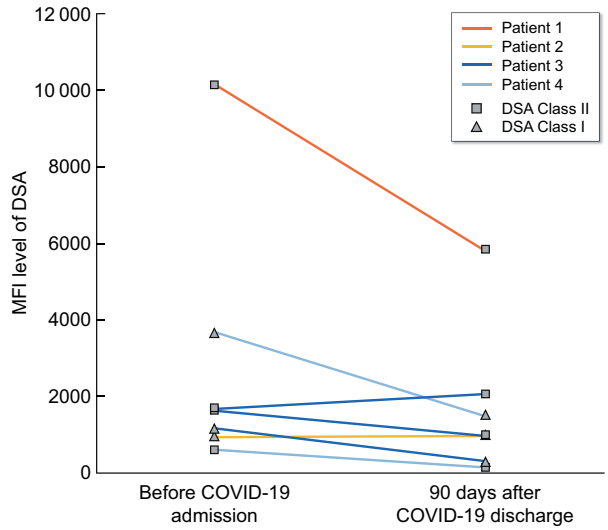

FIGURE 7: Evolution of MFI of DSAs before and after COVID-19.

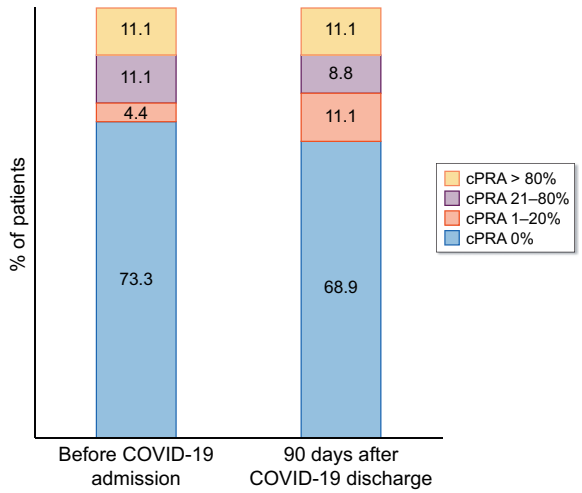

FIGURE 8: Evolution of cPRAs before and after COVID-19.

DISCUSSION

In this study, we have found that an immunosuppressive minimization strategy in KTs with COVID-19 appears safe as no rejection episodes or appearance of *de novo* DSA or relevant changes in cPRA at 90 days after discharge were observed. KTs are susceptible to severe manifestations of COVID-19 due to their immunosuppressive status [2, 3]. Maggiore *et al.*, on behalf of the DESCARTES Working Group of the ERA-EDTA, proposed a progressive approach of immunosuppression withdrawal depending on the severity of SARS-CoV-2 infection [8]. It is important to note that the latter recommendation is based on expert opinion, and no previous study has analysed the impact of such strategy. However, since the immune response to infections is reduced in immunosuppressed patients, such as KTs, it seems rational to temporarily reduce or withdraw immunosuppression. In fact, the vast majority of published studies regarding KTs management and outcomes in the setting of COVID-19 have reported performing some kind of immunosuppression minimization [13]. Interestingly, a recent large multicentre international observational study by the TANGO International Transplant Consortium found no significant association between withdrawal of immunosuppression and mortality in KTs with COVID-19 [9].

In our study population, most patients had at least one immunosuppressive agent withdrawn, with the exception of steroids. A recent systematic review by Marinaki *et al.* [14], including 420 KTs with COVID-19, reported that reduction/withdrawal of immunosuppression was done in 58% patients and all immunosuppressive agents were maintained in only 5%. In our case, 80.9% of patients were managed with immunosuppression reduction, while 19.1% maintained the complete immunosuppressive regimen (Table 2). CNI and mTORi were stopped depending on the severity of the disease, with an observed reduction rate of 27% and 57%, respectively. This is in line with the work by Marinaki *et al.*, where similar reduction rates (32% and 58%, respectively) were described. Also, the drug that was most commonly withdrawn was MMF (91%), similar to our study where MMF/MPA represented 86% of the cases. Of note, in some cases, the interruption of antimetabolites in our cohort was reactive to the degree of lymphopaenia, which could account for the longer withdrawal time of antimetabolites as compared with other immunosuppressive agents. Another retrospective study including 773 SOTs with COVID-19 found a significant association between antimetabolite withdrawal and better survival; however, no data on alloimmune response or longer follow-up were provided [15]. In spite of immunosuppression minimization, none of our patients developed *de novo* DSA or acute rejection episodes after a median time of 4 months after COVID-19 hospitalization. Moreover, one hypersensitized patient with DSA before COVID-19 (who did not experience immunosuppression withdrawal) presented a notable reduction in MFI of DSA. These observations suggest that SARS-CoV-2 infection probably decreases immunity to a great extent, including alloimmune response. Nonetheless, Akilesh *et al.* [16] recently reported two cases of humoral rejection in KTs with COVID-19. One patient had histological features of chronic humoral rejection, while the other presented microangiopathy lesions. In both cases, the biopsy was performed on a deferred basis (graft dysfunction was present at the time of admission) and the patients had a previous history of rejection and DSA. Considering this, in our opinion, the possibility of SARS-CoV-2 infection as a trigger for the development of rejection remains purely speculative. In fact, our data suggest that withdrawal of immunosuppressants in the course of illness and their later reintroduction is safe in KTs. Furthermore, since dexamethasone at high doses is currently recommended for the treatment of moderate–severe COVID-19 [17], withdrawal of antimetabolites or other immunosuppressive agents is probably advisable to prevent complications associated with overimmuno-suppression.

AKI is a well-known complication of COVID-19 and its presence has been associated with higher mortality risk. Patients needing kidney replacement therapy (KRT) and patients with chronic kidney disease (CKD) had the lowest probability of recovering kidney function [18, 19]. In addition, AKI incidence in KTs with COVID-19 is high, with most studies reporting an incidence of nearly 50% [6, 9]. To date, the pathophysiology of COVID-19-associated AKI has not been clearly established. Proposed mechanisms include decreased kidney perfusion, viral cytopathic effect, coagulation dysfunction and microangiopathy. Also, interaction of different drugs leading to CNI nephrotoxicity in KTs is another possible mechanism [6]. In our study, the severity of AKI was closely related to TAC trough levels, and these were higher in patients taking antivirals treatment. It is worth noting that some of these treatments are no longer recommended for COVID-19 management, such as the case of ritonavir/lopinavir. These drugs interact strongly with CYP3A4 and might cause a marked increase of TAC levels, leading to a higher rate of kidney dysfunction. In general, TAC trough levels during hospitalization in our study population were higher when compared with pre-admission levels, suggesting that other factors such as diarrhoea and/or change in volume distribution could be related to CNI nephrotoxicity. Interestingly, all patients recovered baseline kidney function at 3 months after discharge, including the few patients with more severe AKI. These data contrast with studies by Ng *et al.* [19] and Gupta *et al.* [20], in which 30–34% of patients with AKI remained dialysis-dependent at discharge. This discrepancy could be explained by several factors, including the low prevalence of severe AKI in our cohort, the relatively good eGFR before admission and the exclusion of patients with eGFR inferior to 15 mL/min/1.73 m^2. Besides, most patients admitted at our centres that required ICU management and KRT did not survive, and therefore were also excluded from the analysis. This is in line with the high mortality reported for SOTs requiring ICU admission [15].

Our study has several limitations. The follow-up period was relatively short. Nonetheless, a longer follow-up time would probably not alter the results since immunosuppression was reintroduced in all patients. Secondly, due to the low-resolution HLA typification we have employed, we had to infer the allele of DSA using the HaploStats program to minimize the possibility of errors in some cases. Thirdly, time from transplantation in our cohort was significantly higher than that reported in other studies, thus, our results may not be applicable to recent KTs. Finally, the small sample size of our study precludes establishing definitive associations.

In conclusion, our study has found that temporary withdrawal of immunosuppressive treatments in KTs with COVID-19 appears to be safe, since no patients experienced rejection episodes or developed *de novo* DSA. Additionally, most of AKI events in our cohort were probably due to CNI nephrotoxicity rather than directly associated with COVID-19. At the end of follow-up, all patients with AKI who survived recovered baseline graft function.

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CONFLICT OF INTEREST STATEMENT

None declared.

DATA AVAILABILITY STATEMENT

Data available on request from the authors.

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