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BRIEF COMMUNICATION

AJT

# Should cyclosporine be useful in renal transplant recipients affected by SARS-CoV-2?

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Minimization of immunosuppression and administration of antiretrovirals have been recommended for kidney transplant recipients (KTRs) with coronavirus disease 2019 (COVID-19). However, outcomes remain poor. Given the likely benefit of cyclosporine because of its antiviral and immunomodulatory effect, we have been using it as a strategy in KTRs diagnosed with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). We studied 29 kidney transplant recipients (KTRs) who were admitted to our institution with COVID-19 between March 15and April, 24, 2020. Mycophenolate and/or mammalian target of rapamycin inhibitors (mTORi) were discontinued in all patients. Two therapeutic strategies were compared: Group 1, minimization of calcineurin inhibitors (N = 6); and Group 2, cyclosporine-based therapy (N = 23), with 15 patients switched from tacrolimus. Hydroxychloroquine was considered in both strategies but antivirals in none. Six patients died after respiratory distress (20.6%). Five required mechanical ventilation (17.2%), and 3 could be weaned. Nineteen patients had an uneventful recovery (65.5%). In group 1, 3 of 6 patients died (50%) and 1 of 6 required invasive mechanical ventilation (16.7%). In group 2, 3 of 23 patients died (12.5%). Renal function did not deteriorate and signs of rejection were not observed in any patient on the second treatment regime. In conclusion, immunosuppressant treatment based on cyclosporine could be safe and effective for KTRs diagnosed with COVID-19.

**KEYWORDS**

clinical research/practice, health services and outcomes research, kidney transplantation / nephrology, kidney disease: infectious, immunosuppressant

**Abbreviations:** ARDS, acute respiratory distress syndrome; COVID-19, coronavirus disease 2019; CsA, cyclosporine; H, hydroxychloroquine; ICU, intensive care unit; IQR, interquartile range; IST, immunosuppressant treatment; IL-6, interleukin-6; IMV, invasive mechanic ventilation; IG, intravenous immunoglobulin; KT, kidney transplantation; MMF/MPA, mycophenolate mofetil/mycophenolic acid; mTORi, mammalian target of rapamycin inhibitors; RT-PCR, reverse transcription polymerase chain reaction.; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SpO2/FiO2, pulse oximetry saturation/fraction of inspired oxygen ratio.

## 1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a novel viral disease with tens of thousands of infected patients worldwide.[1] Clinically, when symptomatic, the disease is characterized by fever, cough, lymphopenia, dyspnea, and, eventually, respiratory distress and multiorgan failure in severe cases.[1,2] Mortality in the general population is about 1%-6% but it is higher among patients with previous comorbidities (15%). [3] Recent publications have demonstrated that the clinical course of this disease among transplanted patients is more aggressive, with mortality being as high as 14%-25% [4-8] Besides, renal function also appears to be affected.[4,9] To date, recommendations include the use of antivirals and downgrading immunosuppressive treatment,[10-12] but the evidence supporting these recommendations is weak. Hypothetically, conversion to cyclosporine (CsA) could improve outcomes in kidney transplant (KT) patients with COVID-19 as CsA has both antiviral power (including with severe acute respiratory syndrome coronavirus [SARS-Cov] species) and immunomodulatory effect.[13] Besides, CsA may help to avoid graft rejection during the infection.

Therefore, we aimed to describe the initial experience in a referral kidney transplantation center treating renal transplants infected with COVID-19 with cyclosporine.

## 2 | MATERIALS AND METHODS

### 2.1 | Study population and design

We included all kidney transplant patients with polymerase chain reaction (PCR)-confirmed SARS-CoV-2 infection who were referred to our institution (a referral kidney transplantation center) between March 15 and April 24, 2020. Final follow-up date was May 19, 2020. Clinical, laboratory, and radiologic data were collected. All laboratory and imaging tests were performed as part of standard of care. The degree of severity of COVID-19 on admission was determined by the need for oxygen therapy and the presence of pneumonia in X-ray. We also considered analytical changes, especially inflammatory and renal function parameters. Inflammatory parameters including PCR, procalcitonin, D dimer, ferritin, lactate dehydrogenase (LDH), and interleukin-6 (IL-6) of patients were monitored on admission and on a daily basis.

Respiratory function was assessed by means of the pulse oximetry saturation/fraction of inspired oxygen (SpO2/FiO2) ratio, which has a good correlation with the partial pressure of arterial oxygen (PaO2)/FiO2 ratio (SpO2/FiO2 = 64 + 0.84 x PaO2/FiO2).[14]

Unfavorable outcome was defined by the presence of progressive respiratory failure; ie sustained worsening of the SpO2/FiO2 ratio and/or development of acute respiratory distress syndrome (ARDS) resulting in need of intensive care unit (ICU) admission and/or death.

### 2.2 | Patient management

All KT recipients presenting at the emergency room or outpatient clinic with suggestive symptoms or signs were tested for SARS-CoV-2 infection. The diagnosis of COVID-19 was made by means of real time reverse transcription polymerase chain reaction (RT-PCR) in nasopharyngeal swab or sputum samples according to established methods.

### 2.3 | Therapy approach

#### 2.3.1 | I. Adjustment of immunosuppressive regimen

Group 1: Minimization of Immunosuppressive Therapy.

Following current recommendations [10-12] we tended to downgrade immunosuppressive therapy; therefore, mycophenolate and/or rapamycin were discontinued and the dose of calcineurin inhibitors was reduced.

Group-2: Cyclosporine-based immunosuppression therapy.

Given the poor evolution of the first patients with SARS-Cov-2 treated with standard regimes, our previous experience with CsA in other viral infections such as polyomavirus BK nephropathy infection, and the theoretical benefits of cyclosporin in COVID-19,[13] we decided to change the strategy of immunosuppressive therapy: we maintained cyclosporin at low doses when it was part of the patients' usual treatment, and those on tacrolimus or mammalian target of rapamycin inhibitors (mTORi) were switched to cyclosporin. CSA target concentration was around 50-100 ng/mL.

#### 2.3.2 | II. Antiviral and immunomodulatory therapy

Both protocols included the use of hydroxychloroquine, 400 mg twice daily orally for the first 24 hours, followed by 200 mg twice daily for 5-10 days. Antivirals were not administered in any group.

Moreover, high doses of steroids were used if evidence of progressive respiratory, radiologic, or inflammatory profile worsening appeared. Our local protocol included a 4-day cycle of methyl-prednisolone with a recommended dosing of 250-125-125-125 mg. Still, individual dosing was left up to the attending physician.

Tocilizumab was added if Il-6 was > 60 pg/mL. Initial local protocols recommended a first dose of 600 mg or 400 mg (according to patient´s weight), followed by 2 other doses of 400 mg. Protocols were subsequently modified and a single dose of 600 mg or 400 mg according to weight was recommended. Patients with IgG < 700 mg/dl received an intravenous immunoglobulin (IG) cycle (10 g/kg).

#### 2.3.3 | III. Other coadjuvant therapies

Antibiotics were prescribed if bacterial superinfection was suspected. Ceftriaxone was the preferred antibiotic but was modified based according to antibiograms.

**TABLE 1** Baseline and on admission characteristics

| | Baseline characteristics | | | | Admission features | | | |
|---|---|---|---|---|---|---|---|---|
| | Patient. (Admission date) | Gender /Age (years) | Transplantation date (n previous transplant) | Cardiovascular risk factors | Day of symptoms when admission | X-ray | Oxygen Requirement | Renal function CKD-EPI mL/min (AKI) |
| Group 1 | P 1 (03.13.2020) | F (74) | 2005 (1) | HBP, DL, OB, DM | 2 (F*) | BPS | None | 80.0 (No) |
| | P 2 (03.16.2020) | M (50) | 2003 (1) | HBP, DL | 4 (F*, M*) | No infiltrates | None | 36.0 (No) |
| | P 3 (03.17.2020) | M (71) | 2012 (2) | HBP, DL | 4 (F*, C, M*, D) | No infiltrates | None | 15.0 (No) |
| | P 5 (03.17.2020) | F (66) | 2008 (1) | DL, OB | 7 (F*, C, M*, D, Dy) | LPS | NG | 21.0 (Yes) |
| | P 6 (03.17.2020) | F (66) | 2011 (1) | HBP, OB | 0 (CF) | No infiltrates | None | 80.0 (No) |
| | P 7 (03.19.2020) | F (63) | 2018 (1) | HBP, DL, OB | 4 (M*, Dy) | No infiltrates | None | 44.0 (No) |
| Group 2 | P 4 (03.17.2020) | M (66) | 2014 (1) | HBP, DL | 8 (F*, C, M*, Dy) | No infiltrates | None | 27.7 (No) |
| | P 8 (03.19.2020) | M (75) | 2006 (1) | HBP, DL | 0 (CF) | No infiltrates | None | 46.0 (No) |
| | P 9 (03.25.2020) | M (71) | 2009 (1) | HBP, DL, OB, DM | 12 (F*, C, M*, Dy) | LPS | NG | 33.0 (Yes) |
| | P 10 (03.26.2020) | M (68) | 2006 (1) | HBP, DL, DM | 1 (F*, C, M*, D, Dy) | BPS | NG | 93.0 (No) |
| | P 11 (03.27.2020) | M (45) | 2005 (1) | HBP, DL | 4 (F*, M*, D, Dy) | BPS | VM | 11.0 (Yes) |
| | P 12 (03.27.2020) | M (63) | 2020 (1) | HBP, DL, DM | 7 (F*, C, M*, D, Dy) | BPS | VM | 11.9 (Yes) |
| | P 13 (03.27.2020) | M (79) | 2006 (1) | HBP, DM | 30 (F*, C, M*, D, Dy) | No infiltrates | None | 16.0 (Yes) |
| | P 14 (03.30.2020) | M (28) | 2012 (1) | HBP, DL | 10 (F*, C, M*, D) | LPS | None | 30.0 (Yes) |
| | P 15 (03.31.2020) | F (48) | 2001 (1) | HBP, DL, OB | 7 (F*, C, M*) | BPS | None | 91.6 (No) |
| | P 16 (04.01.2020) | F (38) | 2015 (4) | HBP, DL | 7 (F*, M*, Dy) | LPS | None | 17.0 (Yes) |
| | P 17 (04.02.2020) | M (69) | 2018 (1) | HBP, DL, OB | 7 (F*, C, T, M*) | LPS | None | 48.0 (Yes) |
| | P 18 (04.02.2020) | M (63) | 2011 (1) | HBP, DL, OB, DM | 5 (F*, C, D, Dy) | LPS | None | 30.0 (Yes) |
| | P 19 (04.04.2020) | F (69) | 2019 (1) | HBP, DL, OB, DM | 0 (CF) | LPS | None | 13.0 (Yes) |
| | P 20 (04.06.2020) | M (63) | 2019 (1) | HBP, OB, DM | 5 (F*, C, D) | BPS | None | 9.40 (No) |
| | P 21 (04.06.2020) | F (56) | 2006 (1) | HBP, DL, OB | 7 (C, M*, D) | LPS | None | 43.5 (No) |
| | P 22 (04.06.2020) | M (63) | 2018(2) | HBP, DL, OB, DM | 3 (M*, Dy) | BPS | VM | 8.0 (Yes) |
| | P 23 (04.06.2020) | M (43) | 2013 (1) | HBP, DL, OB, DM | 7 (F*, C, D) | BPS | None | 21.3 (Yes) |
| | P 24 (04.07.2020) | M (73) | 2019 (1) | HBP, DL, OB, DM | 10 (F*, M*) | No infiltrates | None | 25.0 (No) |
| | P 25 (04.09.2020) | M (65) | 2010 (1) | HBP | 1 (F*, M*, D) | No infiltrates | None | 19.0 (Yes) |
| | P 26 (04.10.2020) | M (80) | 2007 (1) | HBP, DL, OB | 3 (F*, C, Dy), | BPS | NG | 25.0 (No) |
| | P 27 (04.14.2020) | F (80) | 2018(1) | HBP, DL. OB | 6 (M*) | No infiltrates | None | 31.7 (No) |
| | P 28 (04.14.2020) | F (64) | 2019 (1) | HPB, DL | 2 (C, D, Dy) | No infiltrates | None | 71.6 (No) |
| | P 29 (04.24.2020) | F (78) | 2000 (1) | HBP, DL, | 3 (M*, C, D, Dy) | LPS | None | 20.7 (Yes) |

Abbreviations: AKI, acute kidney injury; BPS, bilateral patchy shadowing; C, cough; CF, casual findings of pulmonary infiltrates in computed tomography; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; D, diarrhea; DL, dyslipidemia; DM, diabetes mellitus; Dy, dyspnea; F*= fever; F, female; HBP, hyper blood pressure; LPS, local patchy shadowing; M*= myalgias; M, male; NG, nasal glasses (2-3 lpm); OB, obesity; VM, venturi mask (8-10 lpm).

In addition, we prescribed anticoagulant drugs in patients with D dimer above 3000 ng/mL. Our local protocols included enoxaparin or tinzaparin at prophylactic doses, adjusted at weight and renal function.[15]

### 2.4 | Statistical analysis

Categorical variables were expressed with absolute/relative frequency and quantitative with median and interquartile rank, and were compared with nonparametric test according to their distribution. Statistical analysis was performed with SPSS (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. IBM Corp., Armonk, NY)

## 3 | RESULTS

Patients´ characteristics and pathological features on admission are summarized in Table 1. Tables 2 and Table 3 show the clinical, radiologic, and analytical evolution during the in hospital stay. Table 4 summarizes the differences between the group of patients with minimization of immunosuppression (Group 1, n = 6) and the group of patients who were being already treated with cyclosporine or converted from previous immunosuppressants to cyclosporine (group 2, n = 23). All patients were followed until May 19, 2020. Median time of follow-up was 43 days (interquartile range [IQR] 35-54 days).

Twenty-six patients (89.65%) were symptomatic on admission and the median time from the onset of symptoms to admission was of 5 days (IQR 2.5-7). Most common symptoms were fever (n = 20, 69%), myalgia (n = 21, 72.4%), cough (n = 17, 58.6%), dyspnea (n = 14, 48.3%), and diarrhea (n = 14, 48.3%) (Table 1).

On admission, only 7 patients (24.1%) required supplemental oxygen therapy (Table 1), though 18 finally received it throughout the hospitalization (62%) (Table 3). Among them, 9 cases had high PaO2/FiO2 ratio (31%) (Table 3).

We did not detect any statistically significant baseline clinical difference between the two groups.

Inflammatory parameters are shown in Table 2 and Table 4. Patients with poor prognosis (death or invasive mechanical ventilation requirement) had higher inflammatory parameters and peak levels tended to be later on the course of the disease ($P < .05$) (Table 2).

Initially, the most common pattern on chest X-ray was bilateral (n = 9, 31%) and local (n = 9, 31%) patchy shadowing. Initial imaging tests were normal in 11 patients (37.9%) (Group = 1 4 patients, 66.75% and Group = 2 7 patients, 29.2%). Nineteen patients (65%) suffered a radiological worsening during the hospitalization (Table 3).

Fourteen patients (48.2%) presented with acute kidney injury on admission (Table 1). Ten patients recovered their baseline renal function at the end of follow-up (71.4%%). The 4 patients who did not recover baseline renal function died. Three of them needed renal replacement therapy in the first days of admission (10.3%) because these patients already had a baseline Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) < 15 mL/min (Table 3). These patients belonged to Group 2. We have not observed any episode suggestive of acute rejection in any group of patients.

Baseline characteristics and admission features of both groups are summarized in Table 4. Given the small sample size we cannot draw any robust conclusion regarding differences between the groups, but patients in Group 2 appear to be more seriously affected (Table 4).

**TABLE 2** Inflammatory parameters evolution

| | | Total (n = 29) Median, (IQR) | Unfavorable evolution (n = 9) Median, (IQR) | Favorable evolution (n = 20) Median (IQR) | *P* |
|---|---|---|---|---|---|
| RCP | On admission | 3.01 (0.6-9.8) | 6.46 (2.26-14.8) | 2.59 (0.3-7.32) | .153 |
| | Max levels | 8.3 (1.9-12.7) | 12.3 (8-25.5) | 4.15 (1.34-10.12) | .017 |
| | Max levels day | 3 (1-8) | 7 (2.25-11.75) | 2 (1-5) | .065 |
| PCT | On admission | 0.16 (0.07-0.70) | 0.32 (0.16-2.63) | 0.12 (0.07-0.49) | .066 |
| | Max levels | 0.22 (0.1-1.04) | 1.37 (0.32-20.63) | 0.12 (0.08-0.42) | .005 |
| | Max levels (day) | 3 (1-5) | 6 (2.25-11.75) | 1 (1-3) | .019 |
| D dimer | On admission | 1429 (754-2358) | 2001 (967-9315) | 1333 (585-2235) | .238 |
| | Max levels | 1926 (1620-5249) | 5691 (3273-20020) | 1749 (1427-2275) | .003 |
| | Max levels(day) | 6.0 (1.3-11.7) | 10.5 (5.5-14.0) | 1.5 (1-8) | .019 |
| Ferritin | On admission | 647 (348-1642) | 597 (478-1986) | 698 (285-1678) | .562 |
| | Max levels | 1226(496-2027) | 1698 (1392-2441) | 884 (350-1981) | .039 |
| | Max levels day | 7 (1.5-9.5) | 11 (5.75-12) | 3 (1-8) | .009 |
| LDH | On admission | 488 (360-712) | 719 (434-789) | 462 (330-606) | .043 |
| | Max levels | 713 (457-981) | 1154 (897-1353) | 549 (443-729) | .001 |
| | Max levels day | 8 (3.0-12.0) | 11.5 (8.5-12) | 4 (1-10) | .047 |
| IL-6 | Max levels | 62.0 (13.3-122.7) | 115 (77.2-168.25) | 37 (14.4-107.75) | .047 |

Regarding immunosuppressive therapy approach, most patients were previously treated with sodium mycophenolate (N = 22, 75.8%), tacrolimus (N = 19, 65.5%), and low doses of steroids (N = 23, 79.3%) (Table 3). Mycophenolate and/or rapamycin were discontinued in all patients and the dose of tacrolimus was reduced in the first patients.

Initial strategy with the first patients showed poor outcomes (see Table 3). However, we observed an acceptable infection course in one of those patients (patient p4), who was previously on cyclosporine (p4). In the management of patients with viral infections, such as polyomavirus BK nephropathy, our unit had good outcomes with the switch to cyclosporine from tacrolimus. In addition, it has been suggested that CsA could be beneficial in the treatment of SARS-CoV infection.[13] For all these reasons, we decided to modify our therapeutic strategy and prescribe cyclosporine systematically.

In the overall cohort, 23 patients (79.3%) received cyclosporine and prednisone during the infection. Six were already treated with cyclosporine prior to SARS-CoV-2 infection, and 19 patients (65.5%) were switched from their usual immunosuppressive therapy to this combination. Fifteen patients were switched to CsA from tacrolimus (Table 3). At the moment of submission of this manuscript, 14 patients (48.2%) were kept on treatment with cyclosporine. Median levels of cyclosporine during hospitalization were 60 ng/mL (IQR 40-82.50 ng/mL). In general, doses of CsA were lower during the treatment with hydroxychloroquine (median 50 mg/24 h), compared with doses after discontinuation (median 150 mg/24 h).

Regarding SARS-CoV-2 specific treatment, all patients except 2 received hydroxychloroquine and all of them received antibiotics. (Table 3 and Table 4).

We used early administration of high-dose of steroids in 18 patients (62.1%) and tocilizumab in 9 (31%). Also, 8 patients received immunoglobulins (27.6%). Twenty-four patients were treated with anticoagulants at prophylactic doses (82.75%). (Table 3 and Table 4).

Table 4 summarizes principal outcomes. At this point, 6 patients had died because of ARDS (20.7%). Five patients (17.2%) required mechanical ventilation at some point of the progression of the disease but 3 of them were weaned and transferred to the hospitalization ward and then discharged. In total, 23 patients (79.3%) had a favorable evolution and were discharged.

Mortality was higher in immunosuppression minimization strategy group as compares to cyclosporine strategy group: 3/6 (50%) Vs. 3/23 (13%), respectively (Table 4).

## 4 | DISCUSSION

There is a dearth of information about the impact of the COVID-19 infection on kidney transplant recipients (KTRs). Little is known about optimal treatment for these patients. Current recommendations include the use of antivirals and minimization of immunosuppression.[10-12] We aimed to report our experience treating 29 transplanted COVID-19 patients, 23 of whom had their immunosuppressive treatment strategy based on cyclosporine. To date there is no other report describing experience in renal transplant patients using this strategy.

Recently published reports [4-8] suggest that SARS-CoV-2 infection may have a more severe course in KTRs and different clinical presentation as compared to general population. We found, accordingly with previous reports, that gastrointestinal symptoms and myalgias were more frequent in KTR (48.3%). Dyspnea, which has been associated with a poor prognosis [2,8] was also very common among our patients (48.3%).

SARS-CoV-2 mortality is around 2.3% in healthy population, but it is higher in patients with preexisting comorbidities (5.6%-10.5%).[3] KTRs are in this group of patients, as they usually have a higher prevalence of comorbidities, which largely increase mortality by themselves. Data on mortality due to SARS-Cov-2 among KTRs is limited, and it has been reported to rank between 13% and 27.8%.[5-9] Global mortality in our patients was 20.7% (6/29), but among patients who had received cyclosporine as immunosuppressant treatment, it was 13% (3 patients out of 23), Nevertheless, it is difficult to draw robust conclusions from these studies given the small sample size.

According to Siddiqi [16] et al, SARS-Cov-2 disease shows up in three stages: Stage I, early infection; II, pulmonary involvement; and III, systemic hyperinflammation. The last stage, which has the poorest outcomes, might be associated with a hyperinflammatory state or cytokine-release syndrome.[13,16] Therefore, a comprehensive approach to clinical phenotyping has to be done to distinguish the phase where the viral pathogenicity is dominant and the moment when the host inflammatory response becomes predominant. Hence, antivirals proposed to SARS-Cov-2 treatment,[17] could be more useful at the first stage, when viral replication is more important. Therapy in phase III might include the use of immunomodulators to reduce systemic inflammation, such as steroids, tocilizumab or anakinra, and immunoglobulins.[13,16-18] Cyclosporine could also be considered in this stage.[13,16-18]

Lopinavir/ritonavir in combination with hydroxychloroquine is widely used to reduce the viral replication.[10-12] However, a recent trial comparing lopinavir/ritonavir vs. placebo found no significant benefits in terms of viral clearance and survival between the two arms.[19] It is important to note that most of the patients included in the trial (just as our series) were admitted in an advanced stage of the disease with a significant inflammatory status. At that point, patients probably would have benefited not from antiviral treatments but from an inflammation targeted approach.[18] Furthermore, the utility of lopinavir/ritonavir in transplanted patients could be limited given their interactions with calcineurin inhibitors [7] and the risk of QTc prolongation. Both side effects are boosted if combined with hydroxychloroquine.

It is possible that conversion to cyclosporine might be an option in the SARS-CoV-2 management in KTRs. First, CsA could have an antiviral effect in patient with coronavirus infection. CsA is a well-known immunosuppressive drug that binds to cellular cyclophilins to inhibit calcineurin. The inhibition of calcineurin blocks the transcription of genes encoding cytokines such as interleukin-2. This effect is useful as immunomodulator and immunosuppressant agent in kidney transplant recipients. Interestingly, many viruses require cyclophilins for replication, including the coronavirus, so cyclosporine could suppress its replication.[20] In vitro investigations have demonstrated an early block in SARS-CoV replication associated to CsA.[21]

**TABLE 3** Treatment and evolution

| Treatment | | | | | | | Evolution | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Patients | | Onset IST | Initial change on IST | Change to CsA (day from admission) | Other treatments | TZ (day/oxygen/ doses) | Anti-C | Renal function (hemodialysis day from admission) | X-ray worsening (day) | Oxygen requirement (on set/max/end follow-up) | Actual status |
| Group1 | P 1 | FK + MPA | Low dose FK | No | H, IG | No | No | Stable | Yes (5), BPS | None/R | Death |
| | P 2 | FK + MPA | Low dose FK | Yes (24) | H, STB, TZ | Yes (8/R) (1200mg) | Yes | Stable | Yes (8), BPS | None/IMV/None | ICU/ Discharge |
| | P 3 | FK + RAPA+P | P | Yes (15) | H, STB, TZ | Yes (8/ None) (1200 mg) | Yes | Stable | Yes (8), BPS | None/None | Discharge |
| | P 5 | EV + MPA+P | P | No | IG | No | No | AKI no recovered | Yes (5), BPS | NG/R | Death |
| | P 6 | P | P | No | H, STB | No | Yes | Stable | Yes (12), BPS | None/VM | Death |
| | P 7 | FK + MPA+P | Low dose FK | No | H, IG | No | No | Stable | No | None/NG/None | Discharge |
| Group 2 | P 4 | CsA + MPA+ P | CsA + P | Previously | H, IG | No | No | Stable | Yes (7), LPS | None/None | Discharge |
| | P 8 | RAPA + MPA+P | CsA + P | Yes (7) | H | No | Yes | Stable | Yes (7), LPS | None/None | Discharge |
| | P 9 | FK + RAPA | CsA + P | Yes (3) | H, STB | No | Yes | AKI recovered | Yes (9), BPS | NG/NG/None | Discharge |
| | P 10 | FK + MPA+P | CsA + P | Yes (5) | H, STB, TZ | Yes (8/R) (600 mg) | Yes | Stable | No | NG/IMV/None | ICU/ Discharge |
| | P 11 | CsA + MPA+P | CsA + P | Previously | H, STB, TZ | Yes (2/R) (600 mg) | Yes | HD (1) | Yes (5), BPS | VM/IMV | ICU/ Death |
| | P 12 | FK + MPA+P | CsA + P | Yes (3) | H, IG, STB, TZ | Yes (2/ VM) (600 mg) | Yes | HD (3) | Yes (16), BPS | VM/IMV | ICU/ Death |
| | P 13 | CsA + AZA+P | CsA + P | Previously | H, STB | No | Yes | AKI recovered | Yes (7), LPS | None/NG/None | Discharge |
| | P 14 | EV + MPA+P | CsA + P | Yes (1) | H | No | Yes | AKI recovered | No | None/None | Discharge |
| | P 15 | FK + RAPA | CsA + P | Yes (1) | H, STB | No | Yes | Stable | Yes (6), BPS | None/NG/None | Discharge |
| | P 16 | FK + RAPA+P | CsA + P | Yes (1) | H, STB, TZ | Yes (4/R) (400 mg) | Yes | AKI recovered | Yes (4), BPS | None/IMV/None | ICU/ Discharge |
| | P 17 | FK + MPA+P | CsA + P | Yes (1) | H, STB | No | Yes | AKI recovered | Yes (6), BPS | None/NG/None | Discharge |
| | P 18 | FK + MPA+P | CsA + P | Yes (1) | H, STB, TZ | Yes (1/ None) (600 mg) | Yes | AKI recovered | No | None/None | Discharge |
| | P 19 | FK + MPA+P | CsA + P | Yes (1) | H, IG | No | Yes | AKI recovered | Yes (2), LPS | None/None | Discharge |
| | P 20 | FK + MPA+P | CsA + P | Yes (1) | H, IG, STB, TZ | Yes (1/ NG) (600 mg) | Yes | Stable | Yes (2), BPS | None/NG/None | Discharge |
| | P 21 | FK + MPA+P | CsA + P | Yes (1) | H, STB, TZ | Yes (5/ None) (600 mg) | Yes | Stable | Yes (5), LPS | None/None | Discharge |

(Continues)

**TABLE 3** (Continued)

| Patients | Treatment | | | | | Evolution | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Onset IST | Initial change on IST | Change to CsA (day from admission) | Other treatments | TZ (day/oxygen/doses) | Anti-C | Renal function (hemodialysis day from admission) | X-ray worsening (day) | Oxygen requirement (on set/max/end follow-up) | Actual status |
| P 22 | CsA + MPA+P | CsA + P | Previously | H, STB | No | Yes | HD (2) | Yes (4), BPS | VM/CPAP | Death |
| P 23 | FK + MPA+P | CsA + P | Yes (1) | H, STB | No | Yes | AKI recovered | No | None/NG/None | Discharge |
| P 24 | CsA + MPA+P | CsA + P | Previously | H | No | No | Stable | No | None/None | Discharge |
| P 25 | FK + MPA+P | CsA + P | Yes (1) | H | No | Yes | AKI recovered | No | None/None | Discharge |
| P 26 | FK + MPA | CsA + P | Yes (1) | STB | No | Yes | Stable | No | NG/None | Discharge |
| P 27 | FK + RAPA+P | CsA + P | Yes (1) | H | No | Yes | Stable | No | None/None | Discharge |
| P 28 | FK + MPA+P | CsA + P | Yes (1) | H, STD | No | Yes | Stable | Yes (6) BPS | None/NG/None | Discharge |
| P 29 | CsA + MPA | CsA + P | Previously | H, IG | No | Yes | AKI recovered | No | None/None | Discharge |

Moreover, it has been suggested that cyclosporine could slow down the replication of other viruses such as human immunodeficiency virus type 1 (HIV-1),[13] hepatitis C virus,[13] and polyoma BK virus.[22] There is limited evidence of antiviral effect of CsA in vivo, but it has been suggested that switching from tacrolimus to low-dose CsA may be an effective therapy for BK virus nephropathy.[23] However, the evidence for in vitro CsA associated antiviral effects are limited, and other effects (eg, less immunosuppressive power, reduced mycophenolic acid exposure in CsA-treated patients) may be likely contributors to the observed effects in clinics more than any direct antiviral effects. Second, cyclosporine has also been used to successfully treat hemophagocytic lymphohistiocytosis (HLH) and to inhibit nuclear factor of activated T cell–mediated IL-2 gene transcription, reducing cell proliferation and the concomitant production of other cytokines.[13] Given that SARS-CoV-2 is associated with cytokine-release syndrome, cyclosporine might be helpful in the hyperinflammatory phase of SARS-CoV-2 infection.[13] Indeed, CsA has been suggested to be beneficial in other SARS-Cov-2 manifestations, such as inflammatory intestinal lesions.[24] Finally, cyclosporine may help to avoid graft rejection during the infection. Although an antiviral effect has also been reported for other immunosuppressants such as mTORi,[25] their lung side effects [26] could make these drugs less suitable. For all these reasons, we believe that cyclosporine is useful in KTR with SARS-CoV-2. Our clinical observations support this hypothesis given that the mortality was lower in the group of patients treated with CsA, (50% vs 13%, $P = .047$). Moreover, the analytical worsening (43.5% vs 100%, $P = .017$) and oxygen-therapy requirements (basal: 16.1% vs 43.5%, $P = .037$) were also lower in this group. However, it is difficult to draw robust conclusions because of the small size of sample.

The role of high-dose steroids in this disease remains controversial, because their use within the first phase could delay viral clearance.[27] However, in patients with an inflammatory status due to SARS-Cov-2 infection, corticoids might be beneficial.[28] Small series have reported a lower mortality in patients treated with steroids as compared with those who were not [5] (13% vs 25%). These findings are inconclusive due to the limited sample sizes. We added low-dose prednisone as a coadjuvant immunosuppressor to cyclosporine in 4 patients who had not taken it previously, and boluses were administered in 18 patients (62.1%) to try to control the aberrant immune response secondary to SARS-CoV-2. Other investigators have used high doses of steroids [5,6] but in a lower proportion of patients as compared with our series.

Tocilizumab [29] and immunoglobulins were also used with the same purpose.[30] Some authors [4-8] also used this IL-6 inhibitor in KTR with fairly good outcomes. According to recent investigations,[18] we tried to prescribe tocilizumab early when indicated, as the later it is given the poorer its effect could be. Immunoglobulins have also been used in renal transplanted patients.[6] They could have some utility, as they could modulate the immune system during the hyperinflammatory phase.[13,17,18] Finally, taking into account the prothrombotic state of this disease,[15] we added anticoagulant treatment in selected patients. Akakin et al [6] described the use of apixaban, but it is not used in other series.[5-8]

**TABLE 4** Features admission and outcomes by immunosuppression strategy

| Baseline characteristics | | Total N = 29 | Minimization N = 6 | Cyclosporin N = 23 | *P* |
|---|---|---|---|---|---|
| Age, m (IQR) | | 66 (59-72) | 66 (59-71) | 65 (56-73) | .845 |
| Female Gender, n (%) | | 12 (41.4) | 4 (66.7) | 8 (34.8) | .198 |
| Transplantation time mo., m(IQR) | | 99.22 (26-171) | 99 (26.6-159) | 102 (27.14-171) | .862 |
| Risk factors > 3, n (%) | | 18 (62.1) | 2 (33.3) | 16 (69.6) | .164 |
| Admission characteristics | | | | | |
| Symptoms days, m (IQR) | | 5 (2.5-7) | 4 (1.5-4.75) | 6 (3-7) | .192 |
| Dyspnea, n (%) | | 12 (44.4) | 2 (33.3) | 13 (52.2) | .361 |
| X-ray abnormalities | No infiltrates, (%) | 11 (37.9) | 4 (66.75) | 7 (29.2) | .344 |
| | BPS, n (%) | 9 (31) | 1 (16.7) | 8 (34.8) | |
| Oxygen requirement | Basal n, (%) | 22 (75.9) | 5 (83.3) | 17 (73) | .642 |
| | VM/R/CPAP n, (%) | 3 (10.3) | 0 (0) | 3 (13) | |
| D dimer (ng/mL), m (IQR) | | 1429 (754-2358) | 1066 (844-1042) | 1627 (602-2691) | .146 |
| Ferritin (ng/mL), m (IQR) | | 647 (348-1682) | 554 (67-2764) | 725(403-1684) | .380 |
| LDH, IU/l, m (IQR) | | 488 (360-712) | 443 (399-535) | 584 (330-719) | .742 |
| CKD-EPI, mL/min, m (IQR) | | 25.0 (16.75-45) | 41. (19-80.5) | 25 (16.43) | .212 |
| AKI, n (%) | | 14 (48.2) | 1 (16.7) | 13 (56.5) | .169 |
| Treatments | | | | | |
| Hydroxychloroquine | | 27 (93.1) | 5 (83.3) | 22 (95.7) | .377 |
| Steroids bolus, n (%) | | 18 (62.1) | 3 (50) | 15 (62.5) | .646 |
| Cumulative steroid doses, mg, m (IQR) | | 735 (375-1260) | 1033 (125-1250) | 735 (375-1455) | 1.000 |
| Tocilizumab, n (%) | | 9 (31) | 2 (33.3) | 7 (30.4) | 1.000 |
| IG, n (%) | | 8 (27.6) | 3 (50) | 5 (21.5) | .300 |
| Anticoagulation, n (%) | | 24 (82.2) | 3 (50) | 21 (91.3) | .046 |
| Outcomes | | | | | |
| Radiologic worsening, n (%) | | 19 (65.5) | 5 (83) | 14 (60.9) | .633 |
| Analytical worsening, n (%) | | 16 (55.2) | 6 (100) | 10 (43.5) | .017 |
| Ferritin max, ng/mL, m (IQR) | | 1226 (496-2027) | 2090 (1190-3482) | 923 (443-1887) | .140 |
| LDH max, IU/l m (IQR) | | 713(457-981) | 1167 (768-1466) | 645 (448-829) | .021 |
| AKI recovered, n (%) | | 10 (34.48) | 0 (0) | 10 (43.4) | .145 |
| AKI with HD, n (%) | | 3 (10.3) | 0(0) | 3 (13) | .145 |
| Oxygen requirement increase | Yes, n (%) | 16 (55.2) | 5 (83.3) | 11 (47.8) | .119 |
| | Day, m (IQR) | 4 (2-7) | 8 (3.5-5) | 3.5 (5.5-10) | .006 |
| Max oxygen requirement | Basal, n (%) | 11 (37.9) | 1 (16.7) | 10 (43.5) | .035 |
| | NG, n (%) | 9 (31) | 1 (16.7) | 8 (34.8) | |
| IMV, n (%) | | 5 (17.2) | 1 (16.7) | 4 (17.4) | 1.000 |
| Death, n (%) | | 6 (20.7) | 3 (50) | 3 (13) | .047 |
| Discharge, n (%) | | 23 (79.3) | 3 (50) | 20 (87) | |

Abbreviations: AKI, acute kidney injury; BPS, bilateral patchy shadowing; max, maximum; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CPAP, continuous positive airway pressure; HD, hemodialysis, IG, immunoglobulins; IMV, invasive mechanical ventilation; IQR, interquartile range; m, median; NG, nasal glasses (2-3 lpm); R, reservoir (15 lpm); VM, venturimask (8-10 lpm).

Actual status (May 19, 2020), Units: D dimer (ng/mL): normal range < 500 ng/mL, ferritin (ng/mL) normal range 30-350 ng/mL, LDH, lactate dehydrogenase (UL/l), normal range 240-480 U/ l. Day, day of oxygen requirement increase from admission.

## 5 | CONCLUSIONS

Given that SARS-CoV-2 infection has two principal phases—a purely viral infection and an inflammatory process with different prognostic and therapeutic implications—it is relevant to identify the stage of the disease and prescribe specific treatment.

Among KTRs the immune system is altered by the immunosuppressive medication, and the balance between control of infection and inflammation can be even more complex.

Cyclosporine can be useful at any moment during the course of the disease given its effect on the inhibition of viral replication, maintenance of kidney graft and down regulation of the immune response.

Other adjuvant therapies may include the use of tocilizumab, high-dose steroids, immunoglobulins and anticoagulation treatment.

Our current treatment protocol appears to be associated with favorable outcomes, but longer follow-up of a larger cohort of patients is needed.

## DISCLOSURE

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

## DATA AVAILABILITY STATEMENT

No data are available.

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## REFERENCES

1. Wang W, Tang J, Wei F, et al. Updated understanding of the outbreak of 2019 novel coronavirus (2019-nCoV) in Wuhan. *China J Med Virol*. 2020;92(4):441-447.
2. Guan W-J, Ni Z-Y, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med*. 2020;382(18):1708-1720.
3. Sun P, Lu X, Xu C, et al. Understanding of COVID-19 based on current evidence. *J Med Virol*. 202092(6):548-551.
4. Coates PT, Wong G, Drueke T, et al. Early experience with COVID-19 in kidney transplantation. *Kidney Int*. 2020;97(6):1074-1075.
5. Pereira MR, Mohan S, Cohen DJ, et al. COVID-19 in solid organ transplant recipients: initial report from the US epicenter [published online ahead of print 2020]. *Am J Transplant*. 2020.
6. Akalin E, Azzi Y, Bartash R, et al. Covid-19 and kidney transplantation [published online ahead of print 2020]. *N Engl J Med*. 2020.
7. Fernández-Ruiz M, Andrés A, Loinaz C, et al. COVID-19 in solid organ transplant recipients: a single-center case series from Spain [published online ahead of print 2020]. *Am J Transplant*. 2020.
8. Husain SA, Chang JH, Early CDJ, et al. Description of coronavirus 2019 disease in kidney transplant recipients in New York [published online ahead of print 2020]. *J Am Soc Nephrol*. 2020.
9. Zhang H, Chen Y, Yuan Q, et al. Identification of kidney transplant recipients with coronavirus disease 2019 [published online ahead of print 2020]. *Eur Urol*. 2020.
10. López V, Vázquez T, Alonso-Titos J, et al. Recommendations on management of the SARS-CoV-2 coronavirus pandemic (Covid-19) in kidney transplant patients [published online ahead of print 2020]. *Nefrologia*. 2020.
11. Guidance on the management of transplant recipients diagnosed with or suspected of having covid 19. British Transplant Society. Update 24th April 2020. https://bts.org.uk/wp-content/uploads/2020/04/Clinical-management-of-transplants-and-immunosuppression-updated-24th-April-FINAL.pdf. Accessed May 23, 2020
12. Alberici F, Delbarba E, Manenti CH, et al. Management of patients on dialysis and with kidney transplant during SARS-COV-2 (COVID-19) pandemic in Brescia. *Italy. Kidney Int Rep*. 2020;5(5):580-585.
13. Willicombe M, Thomas D, McAdoo S. COVID-19 and calcineurin inhibitors: should they get left out in the storm? *JANS*. 2020;31(6):1145-1146.
14. Rice TW, Wheeler AP, Bernard GR, et al. Comparison of the SpO2/FiO2 ratio and the PaO2/FiO2 ratio in patients with acute lung injury or ARDS. *Chest*. 2007;132(2):410-417.
15. Bikdeli B, Madhavan MV, Jimenez D, et al. COVID-19 and tthrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up. *J Am Coll Cardiol*. 2020;S0735–1097(20):35008-7.
16. Siddiqi HK, Mehra MR. COVID-19 illness in native and immunosuppressed states: a clinical-therapeutic staging proposal. *J of Heart and Lung Transplant*. 2020;39(5):405-407.
17. Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic treatments for coronavirus disease 2019 (COVID-19) a review [published online ahead of print 2020]. *JAMA*. 2020.
18. Mehta P, McAuley DF, Brown M, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet*. 2020;395:1033-1034.
19. Cao B, Wang Y, Wen D, et al. A trial of lopinavir-ritonavir in adults hospitalized with severe COVID-19. *N Engl J Med*. 2020;382(19):1787-1799.
20. Tanaka Y, Sato Y, Sasaki T. Suppression of coronavirus replication by cyclophilin inhibitors. suppression of coronavirus replication by cyclophilin inhibitors. *Viruses*. 2013;5(5):1250-1260.
21. Wilde AH, Zevenhoven-Dobbe JC, van der Meer Y, et al. Cyclosporin A inhibits the replication of diverse coronaviruses. *J Gen Virol*. 2011;92(Pt11):2542-2548.
22. Li YJ, Weng CH, Lai WC, et al. A suppressive effect of cyclosporine A on replication and noncoding control region activation of polyomavirus BK virus. *Transplantation*. 2010;89(3):299-306.
23. Chen X, Li J, Deng RH, et al. The therapeutic effect of switching from tacrolimus to low-dose cyclosporine a in renal transplant recipients with bk virus nephropathy. *Biosci Rep*. 2019;39(2):BSR20182058.
24. Rosen MH, Axelrad J, Hudesman D, et al. Management of acute severe ulcerative colitis in a pregnant woman with COVID-19 infection: a case report and review of the literature. *Inflamm Bowel Dis*. 2020;izaa109.
25. Bowman LJ, Brueckner AJ, Doligalski CT. The role of mTOR inhibitors in the management of viral infections: a review of current literature. *Transplantation*. 2018;102(2S Suppl 1):S50-S59.
26. Morelon E, Stern M, Israël-Biet D, et al. Characteristics of sirolimus-associated interstitial pneumonitis in renal transplant patients. *Transplantation*. 2001;75(2):787-790.
27. Lee N, Allen Chan KC, Hui DS, et al. Effects of early corticosteroid treatment on plasma SARS-associated coronavirus RNA concentrations in adult patients. *J Clin Virol*. 2004;31(4):304-309.
28. Villar J, Ferrando C, Martínez D, et al. Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial. *Lancet Respir Med*. 2020;8(3):267-276.
29. Xu X, Han M, Li T, et al. Effective treatment of severe COVID-19 patients with tocilizumab. *Proc Natl Acad Sci USA*. 2020;117(20):10970-10975.
30. CaoW LX, Bai T, Fan H, et al. High-dose intravenous immunoglobulin as a therapeutic option for deteriorating patients with coronavirus disease Open Forum. *Infect Dis*. 2020;7(3):ofaa102.

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