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# How should I manage immunosuppression in a kidney transplant patient with COVID-19? An ERA-EDTA DESCARTES expert opinion

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## INTRODUCTION

After severe acute respiratory syndrome coronavirus (SARS-CoV) in 2003 and Middle East respiratory syndrome–related coronavirus (MERS-CoV) in 2012, the world is now facing a third rapidly spreading coronavirus outbreak, caused by SARS-CoV-2 [1–3]. Coronavirus disease 2019 (COVID-19) was declared a global pandemic by the World Health Organization [4] and has already led to >3 million reported cases and >230 000 deaths worldwide [5].

Viral infections pose an important risk of morbidity and mortality in patients after organ transplantation [6]. Indeed, immunosuppression, which is crucial for preventing alloimmune reactions, impairs host defense mechanisms. Respiratory virus infections, such as respiratory syncytial virus, may progress more rapidly to pneumonia in organ transplant recipients, with a tendency to more severe disease and prolonged shedding of potentially infectious virus. Immunosuppression also increases the severity of both adeno- and influenza viruses (reviewed in Razonable [7] and Manuel *et al.* [8]).

With regard to COVID-19, all kidney transplant recipients (KTRs) must strictly follow the general hygiene measures recommended for the general population, including frequent hand washing, social distancing measures and wearing of masks in crowded places [9]. COVID-19 induces variable clinical courses in normal hosts but seems to progress more rapidly in immunocompromised hosts, with greater rates of intensive care unit admissions and death [10]. The largest series reported to date from Europe and the USA are shown in Table 1 [11–17]. Although there might be a bias towards selection of the most severe cases (apart from one study in which only a minority of patients had severe disease [17]), the mortality rates were between 23% and 28%, which is close to the rate of 21% reported from a cohort of 5700 hospitalized patients in New York [18], but certainly higher than the ≤5% usually reported for COVID-19-infected patients [11]. These articles describe various strategies for the management of immunosuppressive therapy, based on a stepwise reduction of immunosuppression according to the severity of the disease. Due to the heterogeneity of the reported strategies, it is of course impossible to draw generalizable conclusions about the best practice to follow.

A European initiative, promoted by ERA-EDTA and the DESCARTES working group (WG) has recently started and is aiming to rapidly collect data about treatments and outcomes of COVID-19 disease in KTRs [9]. In the meantime, how to deal with immunosuppression among KTRs is left to clinical judgement and common sense, taking into consideration the risk of a serious, potentially fatal disease along with the risk of acute rejection and possibly graft loss. Interestingly, none of the series has reported acute rejection and graft loss as a consequence of immunosuppression reduction (Table 1), but this

**Table 1. Largest case series reported of kidney transplant recipients with COVID-19**

| Study | Location | Time frame (2020) | No. of KTs | Hospitalized (%) | Immunosuppressive strategy | High-dose steroids (%) | Anti-IL-6R Ab; other monoclonal Abs | Follow-up days | Mortality (%) | Rejection or raft failure |
|---|---|---|---|---|---|---|---|---|---|---|
| Akalin *et al.* [11] | Montefiore, USA | 16 March–1 April | 36 | 78 | Withdrawal of MPA/AZA, Tac withheld in severely ill patients | 2 | 2% tocilizumab; 21% leronlimab | 21 (14–28) | 28 | Not reported |
| Pereira *et al.* [12][a] | Columbia University, USA | 13 March–3 April | 46 | 76 | Moderately decrease the overall amount of immunosuppression with a particular emphasis on decreasing or stopping MPA/AZA | 24 | 21% tocilizumab | 20 (14–24) | 23 | Not reported |
| Columbia University KT program [13] | Columbia University, USA | Up to 27 March | 15 | 100 | Stop MPA/AZA while continuing tacrolimus (4–7 ng/mL) and prednisone | 7 | 7% tocilizumab | 7 (3–11) | Incomplete follow-up | Not reported |
| Fernández-Ruiz *et al.* [14][a] | Madrid, Spain | 5 March–23 March | 8 | 100 | Stop CNI and mTORi upon initiation of LPV/r (given in 50% of the pts)<br>Target Tac 5-10 ng/mL<br>Steroids reduced by 50%<br>MPA/AZA decreased | 11 | 6% tocilizumab | 18 (14–28) | 28 | Not reported |
| Alberici *et al.* [15] | Brescia, Italy | Up to 24 March | 20 | 100 | Stop all immunosuppressive treatment<br>LPV/r, DRV/r given in 95% of the pts<br>Increased dose of steroids | 55 | 30% tocilizumab | Median follow-up 7 days | 25 | Not reported |
| Banerjee *et al.* [16] | London, UK | 1 March–31 March | 7 | 71 | MPA stopped<br>CNI stopped in ventilated patients | 0 | 0% | N.A. | Incomplete follow-up | Not reported |
| Lubetzky *et al.* [17] | WCM, USA | 13 March–20 April | 54 | 72 | MPA stopped (61%) in hospitalized patients<br>Tacrolimus reduced (46%) in hospitalized patients | 9 | 4% | 21 (5–43) | 13 | Not reported |

Follow-up (days) is reported as median (range) unless otherwise specified.

[a]Apart from the number of KTRs, reported data from Pereira *et al.* [12] refer to 90 solid organ transplants combined and from Fernández-Ruiz *et al.* [14] to 18 solid organ transplants combined.

KT, kidney transplantation; Ab, antibody; LPV/r, lopinavir/ritonavir; DRV/r, darunavir/ritonavir; MPA, mycophenolate sodium or mofetil; AZA, azathioprine; tocilizumab, anti-IL-6 mAb; leronlimab, CCR5 antagonist; N.A., not available.

**Table 2. Management of immunosuppression in patients who are beyond 3–6 months after transplantation**

| | |
|---|---|
| **1. Asymptomatic patients: no knowledge of COVID-19 status (ambulatory, stable patients)** | |
| No pre-emptive/proactive change of immunosuppressive medications | |
| **2. Asymptomatic patients, swab pos for COVID-19** | |
| If it is a high-risk patient: age ≥70 years, or comorbidities or risk factors (diabetes, cardiac or pulmonary disease, heavy smoking, BMI >30 kg/m$^2$, eGFR <30 mL/min/1.73 m$^2$, lymphocyte depletion therapy within previous 3–6 months): consider reducing/stopping AZA/MPA/mTORi if on triple therapy | |
| **3. Mild disease: the patient is alert, has only mild upper respiratory and/or gastrointestinal symptoms, temperature <38°C and does not refer symptoms suggestive of COVID-19 pneumonia such as dyspnoea, persistent chest pain and intensive cough; if available, oxygen saturation in room air is >95%, respiratory rate <25/min; no evidence of pneumonia on either chest X-ray or CT; no need for hospitalization** | |
| **If patient is on:** | |
| Triple therapy | Stop MPA/AZA/mTORi<br>Maintain CNI + steroids |
| Dual therapy (including steroids) | Continue dual therapy |
| Dual therapy (steroid-free) | |
| CNI + MPA | Consider replacing MPA with low-dose steroids |
| CNI + mTORi | Consider replacing mTORi with low-dose steroids |
| MPA + mTORi | Consider replacing MPA or mTORi with low-dose steroids |
| **• Consider CNI dose reduction (to the lower bound of the therapeutic range according to the immunological risk) if there is no clear improvement over the first 3–5 days** | |
| **• Cautiously restart previous immunosuppression 3–7 days after symptoms have cleared** | |
| **4. Evidence of mild COVID-19 pneumonia: oxygen saturation 94–95% in room air; respiratory rate 25–29/min; or suspect l esions on chest X-ray or CT scan** | |
| **a. High-risk patient: age ≥70 years, or comorbidities or risk factors (diabetes, cardiac or pulmonary disease, heavy smoking, BMI >30 kg/m$^2$, eGFR <30 mL/min/1.73 m$^2$, lymphocyte depletion therapy within previous 3–6 months)** | |
| Stop MPA/AZA/mTORi,<br>Stop CNI<br>Increase (or start) steroids 15–25 mg/day | |
| **• Cautiously restart previous immunosuppression (CNI first) 5–10 days after symptoms have cleared** | |
| **b. No high-risk patient (as defined above)** | |
| Stop MPA/AZA/mTORi<br>Maintain on dual therapy CNI-steroids<br>Reduce CNI trough levels to target CsA: 50 ± 15 ng/mL, Tac: 3 ± 1 ng/mL<br>Continue steroids in maintenance dose | |
| **• In patients starting antiretroviral treatment: stop CNI and monitor as detailed in the text** | |
| **• Cautiously restart previous immunosuppression 5-10 days after symptoms have cleared** | |
| **5. More severe COVID-19 pneumonia: oxygen saturation <94% in room air, respiratory rate ≥30/min, unstable or deteriorating course or requiring non-invasive ventilation or transfer to the intensive care unit (with or without mechanical ventilation)** | |
| Discontinue all immunosuppressive drugs<br>Increase/start steroids at 15–25 mg/day (or higher according to local practice). | |
| **• Consider continuing with low-dose CNI in patients with higher risk of rejection (e.g. <1 year after transplantation and/or highly immunized)** | |
| **• Cautiously restart previous immunosuppression (CNI first) 5–15 days after symptoms have cleared** | |

When available, risk stratification may additionally benefit from the results of lab parameters indicating severe inflammatory disease at risk of rapid progression, such as a high level of C-reactive protein, IL-6, ferritin and D-dimer.
MPA, mycophenolate mofetil, mycophenolic acid; AZA, azathioprine; CsA, cyclosporine; Tac, tacrolimus.

might be due to a too-short follow-up period. Furthermore, with KTRs amounting to only 0.1% of the general population, it is unlikely that evidence-based medicine will ever be produced for KTRs infected with COVID-19. Indeed, while >1000 studies about COVID-19 are registered in ClinicalTrials.gov (accessed 1 May 2020), none is devoted specifically to treatment of KTRs. While *in vitro* experiments suggest that coronavirus may require intact immunophilin pathways with a role for tacrolimus and cyclosporine to inhibit the growth of human coronaviruses [19, 20], the translation of these experimental findings in clinics remains to be seen. There is also the fear that complete withdrawal of immunosuppressive drugs may exacerbate the hyperinflammatory response that may occur in the late stages of COVID-19. After reading the expert opinions published by single centres (Table 1) and societies (French [21], Spanish [22], British [23], American [24]), and after extensive discussions between its members, the DESCARTES WG formulated suggestions for COVID-19-infected KTRs who are beyond 3–6 months after kidney transplantation (Table 2).

## MANAGEMENT OF DRUG-TO-DRUG INTERACTIONS, USE IN PATIENTS WITH RENAL FAILURE AND OTHER ISSUES RELEVANT TO THE USE OF ANTIVIRAL AND ANTI-INFLAMMATORY TREATMENT IN KTRs

Treatment of COVID-19 is based on antiviral drugs that inhibit SARS-CoV-2 proliferation and on immunomodulatory drugs that inhibit the hyperinflammatory syndrome that may cause adacute respiratory distress syndrome (ARDS) and life-threatening respiratory failure [25, 26]. In theory, antiviral drugs could be effective in restraining viral infection when given in the early phase of the infection, whereas immunomodulatory

drugs may show the strongest benefit when administered during the late hyperinflammatory phase of the disease. Herein we do not formulate any advice on the use of antiviral drugs, antibiotics or anti-inflammatory drugs in KTRs with COVID-19. For these issues, please refer to your infectivologist and local and/or national guidelines. Below, we discuss anti-COVID-19 therapies in the context of renal impairment and their potential effects on the exposure of concomitant immunosuppressive agents.

## ANTIVIRAL DRUGS FOR COVID-19

### Remdesivir

Remdesivir, which is administered intravenously, has a favourable clinical profile and no known drug-to-drug interactions (DDIs). However, the drug has not been studied in patients with kidney failure [estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 $m^2$], which has been an exclusion criterion so far [27].

### Hydroxychloroquine

Although a much-cited source [28] indicates that there is a possible increase in the exposure of cyclosporine, tacrolimus and mammalian target of rapamycin inhibitors (mTORis) during simultaneous use of chloroquine/hydroxychloroquine, a thorough PubMed search retrieved only two cases of increased cyclosporine levels. As chloroquine/hydroxychloroquine, which have a long half-life, are given for only 5–7 days, it is preferable but not mandatory to follow the trough levels of cyclosporine, tacrolimus and mTORis in this setting. No dose adjustment is mandatory in patients with kidney failure (eGFR <30 mL/min/1.73 $m^2$), although it is recommended to use with caution in this setting.

### Lopinavir–ritonavir and darunavir–cobicistat

Complete withdrawal of calcineurin inhibitor (CNI) and mTORi should be considered in every patient undergoing treatment with ritonavir- or cobicistat-boosted antiviral drugs. In fact, tacrolimus should be reduced to 1/20–1/50 in patients receiving ritonavir (and to 1/10 in patients receiving cobicistat) of the initial dose just to maintain constant blood levels [29, 30]. Therefore the dose should be reduced even further (i.e. even <1/50 of the initial dose) if the therapeutic plan is to 'reduce' CNIs rather than stop them. If the treatment with ritonavir-/cobicistat-based drugs is planned for only 5–7 days, then CNIs (and mTORis) should be withdrawn altogether and restarted no earlier than 24–48 h after ritonavir/cobicistat discontinuation at low dose. For longer ritonavir/cobicistat treatments (e.g. 2 weeks [31]), tacrolimus blood levels should be monitored daily and oral tacrolimus 0.5 mg/day administered only after blood levels have dropped below the desired lower bound (e.g. <5 ng/mL). It should also be noted that the hepatic clearance of tacrolimus may be further reduced in the course of multiple organ failure, making tacrolimus dose adjustments even more challenging. DDIs are milder for cyclosporine compared with tacrolimus, the dose reduction usually being 1/5 to maintain constant blood levels. No dose adjustment of lopinavir–ritonavir, darunavir–cobicistat is needed for renal failure. Nonetheless, it should be mentioned that a randomized trial on the use of lopinavir–ritonavir failed to show a clear benefit [31]; therefore, given the high risk of the DDIs in this category of patients, we recommend against their routine use in KTRs.

## ANTI-INFLAMMATORY DRUGS FOR COVID-19

Besides counteracting severe inflammation causing inflammatory lung injury and thrombotic complications in COVID-19, anti-inflammatory drugs in transplant recipients may have the additional benefit of protecting against rejection in patients who have withdrawn CNIs because of severe disease. However, they should be used with caution since suppression of inflammatory responses in the absence of effective antiviral therapy may cause uncontrolled infection [10].

### High-dose steroids

A randomized controlled trial is testing the safety/efficacy of steroids (NCT04273321). Until results are available, broad use of high-dose steroids is discouraged [32]. However, for the treatment of a hyperinflammatory state causing abrupt respiratory compromise, and in the absence of viable alternatives, their use may be considered on a case-by-case basis [33–35], even in KTRs.

### Tocilizumab and other anti-interleukin (IL)-6/IL-6R monoclonal antibodies (e.g. sarilumab)

After the preliminary successful experience of its use in China [36], and pending results from various clinical trials, tocilizumab is currently the most popular treatment used to counteract hyperinflammatory syndrome causing impending or ongoing respiratory compromise. In this severe clinical setting, usually transplant recipients had already withdrawn mycophenolate/azathioprine/mTORi along with CNIs before they were considered for tocilizumab administration. Tocilizumab should be used with caution if the white blood cell count is <1000/$mm^3$. Its elimination is not influenced by renal dysfunction.

### Intravenous immunoglobulins

High-dose intravenous immunoglobulins have been proposed for the use in patients with COVID-19 and deteriorating conditions to counteract inflammation and endothelial activation [37].

## INVESTIGATIONAL TREATMENT STRATEGIES

At the time of writing, clinical trials are ongoing for the evaluation of other promising antiviral drugs and anti-inflammatory drugs such as favipiravir [25, 26], umifenovir (arbidol) [25, 26, nelfinavir [25], ivermectin [38], baricitinib [a Janus kinase (JAK) inhibitor] [38], anakinra (an IL-1 receptor antagonist) [39] and colchicine [40]. Favipiravir and arbidol do not need to be adjusted for renal function. CYP3A4 is the major isoform involved in arbidol metabolism, therefore there may be potential

interaction, especially in patients taking cyclosporine and mTORi. In contrast, favipiravir does not have DDIs with CNIs and mTORi [26]. Baricitinib [25] is contraindicated with kidney failure (eGFR <30 mL/min/1.73 $m^2$) and may strongly increase the risk of infections in association with CNIs. Anakinra does not have DDIs with CNIs and mTORis and should be given every other day in patients with kidney failure (eGFR <30 mL/min/1.73 $m^2$).Colchicine is better avoided while the patient is receiving concurrent treatment with ritonavir–cobicistat-based antiviral therapy and its dose should be halved in patients with kidney failure (eGFR <30 mL/min/1.73 $m^2$). DDIs with tacrolimus are likely to be negligible, whereas concomitant administration of cyclosporine may warrant monitoring.

### Convalescent plasma therapy and hyperimmune immunoglobulins

Convalescent plasma therapy and hyperimmune immunoglobulins, namely the transfer of passive immunity from convalescent human plasma, offer the most promising novel therapeutic approaches for the treatment of COVID-19 [41, 42].

## CONFLICT OF INTEREST STATEMENT

None declared.

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