DESCARTES expert opinion regarding the management of immunosuppressive medication for kidney transplant patients during the COVID-19 pandemic.

General remarks

- By analogy with other infectious diseases, it is considered that kidney transplant patients under immunosuppression are at higher risk of poor outcomes, although this has not been proven/reported to date. ERA-EDTA has developed a registry for kidney transplant recipients that should help us to rationalize our algorithm. See https://www.era-edta.org/en/covid-19-news-and-information/#toggle-id-23
- The scheme below is only valid for patients who are more than 3 months after transplantation, with no recent history of acute rejection. These patients should be treated on a case-per-case basis.
- The scheme is meant as a template which allows adjustment according to local practice. It focuses on the management of immunosuppressive therapy without covering other important issues (e.g. diagnostic procedures and antiviral therapy, which should be aligned with local / national protocols).

Adjustment of immunosuppressive medication

1. Asymptomatic patients, no knowledge of COVID-19 status (ambulatory, stable patients):
   → No change of immunosuppressive medications

2. 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 dyspnea, 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:
   → If patient is on triple therapy: STOP MPA/AZA/mTOR, maintain on dual therapy CNI-steroids.
   → If patient is on dual therapy: continue dual therapy. If dual therapy is a steroid-free regimen: for CNI + MPA/mTORi, consider replacing MPA/mTORi with low dose steroids. If on 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.

3. Patients with evidence of mild COVID-19 pneumonia (oxygen saturation 94-95% in room air, respiratory rate 25-29/min; or suspect lesions on chest X-ray or CT scan):
   a. High risk patient because of age 70+, or because of comorbidities or risk factors (diabetes, cardiac or pulmonary disease, heavy smoking, BMI > 30 kg/m2, eGFR <30 ml/min/1.73m2, lymphocyte depletion therapy within previous 3-6 months):
      → STOP MPA/AZA/mTOR, STOP CNI, increase (or start) steroids 15-25 mg/day
   b. No high-risk patient (as defined above):
      → STOP MPA/AZA/mTOR, maintain on dual therapy CNI-steroids. Always reduce CNI levels to target CsA: 50±15 ng/ml, TAC: 3±1 ng/ml. Continue steroids in maintenance dose.
   c. In patients starting anti-retroviral treatment stop CNI, and monitor as shown in the paragraph below

4. Patients with 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 IS drugs, increase/start steroids at 15-25 mg/day (or higher according to local practice). Carefully consider to continue with low dose CNI in patients with higher risk of rejection.

Drug interactions between chloroquine/hydroxychloroquine, anti-retroviral drugs, and IS drugs:

1. Although a much cited source (www.covid19-druginteractions.org) indicates that there is a possible increase in the exposure of cyclosporine, tacrolimus, and mTOR inhibitors with chloroquine/hydroxychloroquine, a thorough Pubmed search retrieved only two cases of increased CsA levels. As chloroquine/hydroxychloroquine are given for only 5 days, it is preferable, but not mandatory to follow the trough levels of cyclosporine, tacrolimus, and mTOR inhibitors in this setting.
2. Patients starting anti-retroviral drugs that contain ritonavir or cobicistat must stop mTOR inhibitors and CNIs. If the aim is to continue tacrolimus, it should be administered only when blood levels are < 5 ng/ml, and the dose should not exceed 0.5 mg (overall dose reduction 1/50 or lower). Cyclosporine should be given only when levels are below 50 ng/mL (overall dose reduction 1/5 or lower, administered once a day).