COVID-19 in solid organ transplant recipients

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Dear Editor,

Coronavirus disease 2019 (COVID-19) in solid organ transplant (SOT) recipients poses a real challenge to the clinicians, since evidence-based treatment protocols on the immunosuppression management are urgently awaited. In our opinion, the excellent overview article of Kates et al.[1], analyzing the largest number of SOT recipients with COVID-19 so far, is a major step in this direction. The authors discuss the dilemma of immunosuppression in SOT recipients, which has been suggested to be beneficial in case of moderate to severe COVID-19 in preventing hyperinflammation (cytokine storm)[2]. The authors conclude that the mortality among SOT patients with COVID-19 is high. As stated in their study, the number of nonkidney organ transplant recipients is relatively low[1], especially concerning lung transplant recipients (LTR). In transplant centers in the USA there are relatively more unilateral lung transplantations as compared to Europe and the patients are generally older, have more comorbidity, and a higher BMI, which are all risk factors for unfavorable COVID-19 outcomes.

Kates et al. conclude that the intensity of the immunosuppression seems not influence mortality[1]. In our view, the potential influence of the immunosuppressive drug combination needs to be considered: In most centers mycophenolate mofetil (MMF) and azathioprine are strongly reduced or discontinued upon COVID-19 diagnosis. Some authors recommend discontinuing MMF for severe COVID-19 in SOT recipients[3]. This was based on experience with the influenza H1N1 pandemic, when MMF resulted in a reduced immune response in SOT recipients[4,5]. Is this favorable for COVID-19? On the other hand, calcineurin inhibitors (CNIs) appear to have a positive impact in moderate to severe COVID-19: Tacrolimus and cyclosporine have shown effectiveness in *in vitro* studies with other coronaviral diseases such as in Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS)[6].

The treatment of COVID-19 at the time of the study by Kates et al. was different than current experimental practice (remdesivir & steroids). The combination of lopinavir/ritonavir with tacrolimus could have lead to very high blood concentrations of tacrolimus. The same holds true for sirolimus. In order to maintain normal tacrolimus serum concentrations, the dose usually has to be reduced to 0.5-1.0 mg per week, a fraction of the previous dose. In case of treatment with hydroxychloroquine (HCQ), important QTc prolongation can be seen as drug-drug interactions with tacrolimus, cyclosporine or sirolimus. This can be even more complex in the ICU setting, if there is organ dysfunction, low serum albumin, high volume of distribution, a strong inflammation and dependency on vasopressors. All these factors can change the distribution, metabolism and pharmacokinetics of the immunosuppressive drugs as well as the antiviral drugs. Cardial adverse events can be easily falsely attributed to COVID-19 itself instead of considering them potential cardiac adverse events of the introduced medication.

In summary there are many open questions in COVID-19. With regard to cytokine storm in COVID-19, it is interesting to mention that there are currently two studies, investigating the role of CNI in immunocompetent patients with COVID-19: using tacrolimus in Barcelona, Spain[7], and cyclosporine in Philadelphia, USA[8].

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