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LETTER TO THE EDITOR

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Coronavirus disease 2019 and transplantation: The combination of lopinavir/ritonavir and hydroxychloroquine is responsible for excessive tacrolimus trough level and unfavorable outcome

To the Editor:

The ongoing outbreak of coronavirus disease 2019 (COVID-19) first reported in Wuhan has been declared global public health emergency and a pandemic by the World Health Organization. Faced with this novel coronavirus, scientists have been trying to use drugs that have not been validated by rigorous clinical trials, such as lopinavir/ritonavir (LPV/r) and hydroxychloroquine (HCQ). These drugs may be used tentatively for general population with COVID-19, but for solid organ transplant (SOT) recipients with long-term immunosuppressive therapy and drug-related metabolic diseases, antiviral drugs should be chosen with particular care. Notably, elderly SOT patients commonly have liver and kidney dysfunction of varying degrees, resulting in worse drug metabolism. Hence, the drug–drug interactions must be highly valued in SOT patients with COVID-19 treated with multiple drugs simultaneously.

Fernández et al[1] described 18 SOT recipients with COVID-19. Half of the patients were treated with LPV/r, usually in association with HCQ (8/9). However, results of close therapeutic drug monitoring in 5 patients indicated that target trough blood concentrations of tacrolimus (5-10 ng/mL) were achieved at 48-72 hours from the initiation of LPV/r therapy in only 1 patient (20.0%), with tacrolimus trough level after 72 hours increasing above 30 ng/mL in 3bv of 5 recipients. Additionally, Bartiromo et al[2] presented a case of a 36-year-old kidney transplanted woman with COVID-19, whose tacrolimus trough level turned to be extremely high (90.5 ng/mL) after antiviral therapy with LPV/r, along with HCQ and ceftriaxone. We consider the that combined therapeutic regimen of LPV/r and HCQ has an uncertain antiviral effect and even some potentially severe side effects in SOT recipients with COVID-19. Moreover, LPV/r and HCQ have a synergistic effect on tacrolimus, resulting in higher trough blood concentrations far beyond the expected range, which not only cause severe liver and kidney dysfunction and neurologic abnormalities but also greatly damage the function of the immune system, leading to prolonged virus shedding, and multiple organ function failure, which is the leading cause of death in COVID-19 patients.

No antiviral drug has yet been proven effective for the treatment of patients with COVID-19. Protease inhibitors, including LPV/r, are known inhibitors of cytochrome P450 3A (CYP3A) and p-glycoprotein. However, tacrolimus is a substrate for CYP3A and p-glycoprotein.[3] The concentration of tacrolimus may increase and last for a long time after the introduction of LPV/r, even if LPV/r is discontinued promptly.[4] Additionally, HCQ and tacrolimus are the common substrates of CYP3A. Combination of immunosuppressants and LPV/r or HCQ is unfavorable for the disease improvement and protection of allograft due to overimmunosuppression, even resulting in severe cardiac toxicity due to their synergistic effect.[5] Furthermore, the therapeutic window of calcineurin inhibitors is very narrow and susceptible to a variety of drugs. When tacrolimus exceeds a certain concentration, the side effects are extremely harmful. Besides, the monitor of tacrolimus trough blood concentration was not fully available during the pandemic. Hence, we do not recommend the simultaneous use of LPV/r and HCQ as an antiviral regimen in SOT recipients with COVID-19.

KEYWORDS

antibiotic: antiviral, clinical research/practice, complication: infectious, drug interaction, infectious disease, kidney transplantation/nephrology, liver transplantation/hepatology

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DISCLOSURE

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

Tian Xia

Yanfeng Wang

Zhongnan Hospital of Wuhan University, Wuhan, Hubei, China

Correspondence

Yanfeng Wang

Email: yanfengwang@whu.edu.cn

ORCID

Yanfeng Wang https://orcid.org/0000-0002-3859-0937

REFERENCES

1. 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. https://doi.org/10.1111/ajt.15929
2. Bartiromo M, Borchi B, Botta A, et al. Threatening drug-drug interaction in a kidney transplant patient with Coronavirus Disease 2019 (COVID-19) [published online ahead of print 2020]. *Transpl Infect Dis*. 2020. https://doi.org/10.1111/tid.13286
3. Prytuła A, van Gelder T. Clinical aspects of tacrolimus use in paediatric renal transplant recipients. *Pediatr Nephrol*. 2019;34(1):31-43.
4. Jain AB, Venkataramanan R, Eghtesad B, et al. Effect of coadministered lopinavir and ritonavir (Kaletra) on tacrolimus blood concentration in liver transplantation patients. *Liver Transpl*. 2003;9(9):954-960.
5. Ehud C, Matthew D, Eric S, et al. The QT interval in patients with SARS-CoV-2 infection treated with hydroxychloroquine/azithromycin. *medRxiv* preprint. 2020. https://doi.org/10.1101/2020.04.02.20047050