Important interactions of immunosuppressants with experimental therapies for novel coronavirus disease (COVID-19): how to act

LETTER TO THE EDITOR

Tanja R. Zijp¹, Martha L. Toren-Wielema¹, Prashant V. Nannan Panday¹, Jos G.W. Kosterink¹, Stefan P. Berger²,³, Daan J. Touw¹

¹Department of Clinical Pharmacy and Pharmacology, University Medical Center Groningen and University of Groningen, Groningen, The Netherlands;

²Department of Internal Medicine, Division of Nephrology, University Medical Center Groningen and University of Groningen, Groningen, the Netherlands;

³UMC Groningen Comprehensive Transplant Center, University Medical Center Groningen and University of Groningen, Groningen, the Netherlands;

Correspondence: Daan J. Touw, University Medical Center Groningen, Hanzeplein 1 (internal postcode EB70), Groningen, 9700RB, the Netherlands. Email: d.j.touw@umcg.nl

Author contributions: J.K., S.P., and D.T. conceived the idea for the article on ritonavir interaction; M.T.W. and P.N.P. conceived the idea to research chloroquine interaction; T.Z., M.T.W., P.N.P., and D.T. performed the literature research; T.Z. and D.T. wrote the first draft of the manuscript; T.Z., M.T.W., P.N.P., J.K., S.B., and D.T. revised the article critically for important intellectual content. All authors approved the final version of the manuscript.

Disclosure: The authors declare no conflicts of interest.

Funding: None.
Transplant recipients are prone to experience severe illness when infected with the new coronavirus disease (COVID-19). Importantly, two of the initially proposed drug regimens for experimental treatment of this disease, lopinavir/ritonavir and chloroquine, could have serious implications on the efficacy and safety of immunosuppressive therapy; moreover, no information is available on the third option, remdesivir. Timely dose adjustment is thus crucial in these patients, and although the drug-drug interactions are known and monitoring of drug levels is warranted, dosing guidance is lacking. Therefore, this letter highlights evidence on the relevant drug-drug interactions and recommends rigorous dose adjustments.

As there are no approved treatment options for severe COVID-19 symptoms, WHO experts recommended promising drugs for trial evaluation, including lopinavir/ritonavir combination, chloroquine, hydroxychloroquine, and remdesivir. Although lopinavir/ritonavir combination showed little benefit in a recent randomized clinical trial,\(^1\) information on their interaction may still be of interest for those who continue using them. Ritonavir is a fast and strong inhibitor of cytochrome P450 isoform 3A (CYP3A). This enzyme limits the uptake of numerous drugs in the intestine and accelerates hepatic drug clearance. The clinical
consequence of CYP3A inhibition by ritonavir is a strong increase in the biological availability and half-life of tacrolimus and cyclosporine. A study in healthy subjects showed an extreme 57-fold higher tacrolimus exposure, whereas cyclosporine exposure is less affected with a 6-fold increase.\footnote{2} Similar increases in exposure were confirmed in transplant patients with hepatitis C and human immunodeficiency virus.\footnote{3,4} Sirolimus and everolimus concentrations are also expected to increase when used in combination with ritonavir, but no concise data are available. Interaction of sirolimus and everolimus with the strong CYP3A inhibitor ketoconazole led to 10- and 15-fold increases in exposure, respectively.\footnote{5,6}

To prevent serious clinical toxicity, dose adjustment for tacrolimus and cyclosporine is essential. When a patient on tacrolimus treatment starts a ritonavir-containing regimen, the tacrolimus dose should immediately be lowered to 0.5 mg once per week or 0.2 mg twice per week.\footnote{2} Depending on the time after transplantation, higher maintenance dosages (0.5 to 1 mg per 48 h) may apply.\footnote{7} In case of ritonavir initiation during stable cyclosporine treatment, reduction to one-fifth of the total daily dose is recommended and should be administered once per day.\footnote{2} Although sirolimus dosage reductions to 1.5 mg per week and 1 mg per 14 days have been advised,\footnote{8} no case reports are available for everolimus. It is advised to frequently monitor immunosuppressant drug levels, at least right before dose administration. As the drugs’ half-lives are expected to increase, it could take several weeks until trough levels are stable (40 and 15 days for tacrolimus and cyclosporine, respectively).\footnote{2}

Consequently, ritonavir discontinuation requires an increase in the immunosuppressant dosage. As ritonavir irreversibly inhibits CYP3A, their interaction is assumed to slowly dissipate owing to the turnover of intestinal and hepatic CYP3A enzymes.\footnote{9} Calcineurin or mTOR inhibitor dosage may be gradually increased by 20% of the original dose each day.
after ritonavir cessation, and therefore the original dose could be reintroduced on the 5th day.

Frequent monitoring of trough levels is recommended to ascertain optimal treatment.

The antimalarial drugs chloroquine and hydroxychloroquine are other treatment options. The product information of chloroquine mentions that chloroquine increases the risk for QTc prolongation and that combination with cyclosporine potentially increases cyclosporine levels, as two dated case reports indicated a 3- to 4-fold increase in cyclosporine exposure.10 There are no publications available on the drug-drug interaction of chloroquine with tacrolimus, sirolimus, or everolimus. As previously mentioned, CYP3A inhibition caused a 10-fold greater increase in tacrolimus exposure compared with cyclosporine exposure. Thus, tacrolimus exposure might be affected by chloroquine in the same manner. Therefore, we advise to be vigilant of this possible interaction and to monitor calcineurin and mTOR inhibitor trough levels at both the start and discontinuation of chloroquine treatment.

There is no information on the possible effects of remdesivir, the third treatment option, on CYP3A. Frequent monitoring is needed when this drug is administered concomitantly with an immunosuppressant, and we urge to publish any experience with this combination.
References


