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EDITORIAL

Yes We Can (Use Nirmatrelvir/Ritonavir Even in High Immunological Risk Patients Treated with Immunosuppressive Drugs)!

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While other therapeutic alternatives exist, nirmatrelvir/ritonavir is an attractive option for treating severe acute respiratory syndrome coronavirus 2 infection owing to the availability of an oral formulation and the possibility for outpatient treatment. It has been shown to decrease the 28-day relative risk of hospitalisation by 89% (95% confidence interval 75–94) when taken within the first 3 days of symptomatic infection [1]. The drug is, therefore, of particular relevance for patients at high risk of severe disease, such as patients receiving immunosuppressive drugs for organ transplants or immunological conditions. However, the possibility of drug–drug interactions in this context has raised concerns [2]. Nirmatrelvir, a protease inhibitor (PI), is the pharmacologically active drug of the combination; ritonavir is a cytochrome P450 (CYP) and P-glycoprotein inhibitor used as a pharmacokinetic booster to prolong the half-life of nirmatrelvir. Use of nirmatrelvir/ritonavir with immunosuppressive drugs can be challenging, particularly with tacrolimus, the most commonly used immunosuppressive drug, which is a well-known substrate of CYP3A4/5 and P-glycoprotein. The challenge is even greater in patients with high immunological risk in whom a strict balance in immunosuppression should be maintained. Although tacrolimus accumulation leading to concentration-related adverse events is a risk with the combination with nirmatrelvir/ritonavir, concomitant use should not be avoided and would represent a lost opportunity for these patients.

With decades of experience in managing drug–drug interactions in the context of protease inhibitor-boosted therapy for treating patients with human immunodeficiency virus and hepatitis C virus, we have a path to safely combine tacrolimus and nirmatrelvir/ritonavir. Pharmacokinetic drug–drug interaction studies provide clues for adjusting tacrolimus dosage during PI co-treatment. Concomitant use of ritonavir results in a four-fold increase in tacrolimus bioavailability due to intestinal inhibition of the first-pass effect, as well as a large decrease in elimination through CYP3A4/5 inhibition where a ten-fold decrease in the elimination constant is observed [3, 4].

Based on this information, on the first day of nirmatrelvir/ritonavir treatment, one eighth of the usual daily dosage of tacrolimus could be used for the 5-day period of antiviral treatment. For example, for a patient treated with tacrolimus 6 mg twice daily (BID) with the immediate-release formulation, 1.5 mg can be administered once on day 1 before discontinuing tacrolimus during the entire antiviral treatment. Given the half-life of tacrolimus when combined with ritonavir (117–232 h), it is unlikely further administration will be required during the final 4 days of nirmatrelvir/ritonavir treatment. A recent case series shows a mean tacrolimus trough concentration of 7.2 ng/mL before the introduction of nirmatrelvir/ritonavir and of 5.4 ng/mL afterwards, which is consistent with previous data for the tacrolimus half-life when combined with ritonavir [5]. The present strategy would also allow maintaining a comparable 5-day total exposure (i.e. area under the drug concentration–time curve [AUC]) during the antiviral treatment, compared with the previous 5 days. Eventually, AUC is expected to be increased by a factor of 40 under ritonavir inhibition, the dose adjustment (considering the total dose of tacrolimus received by a patient during 5 days, a single one eighth of the daily dose on day 1 and then no other administration during the following days correspond to a 40 times decrease in the 5-day daily dose) is expected to balance the tacrolimus exposure, limiting overexposure while preventing rejection. In long-term treatment with ritonavir, dose recommendations for tacrolimus have been made; however, these are population based

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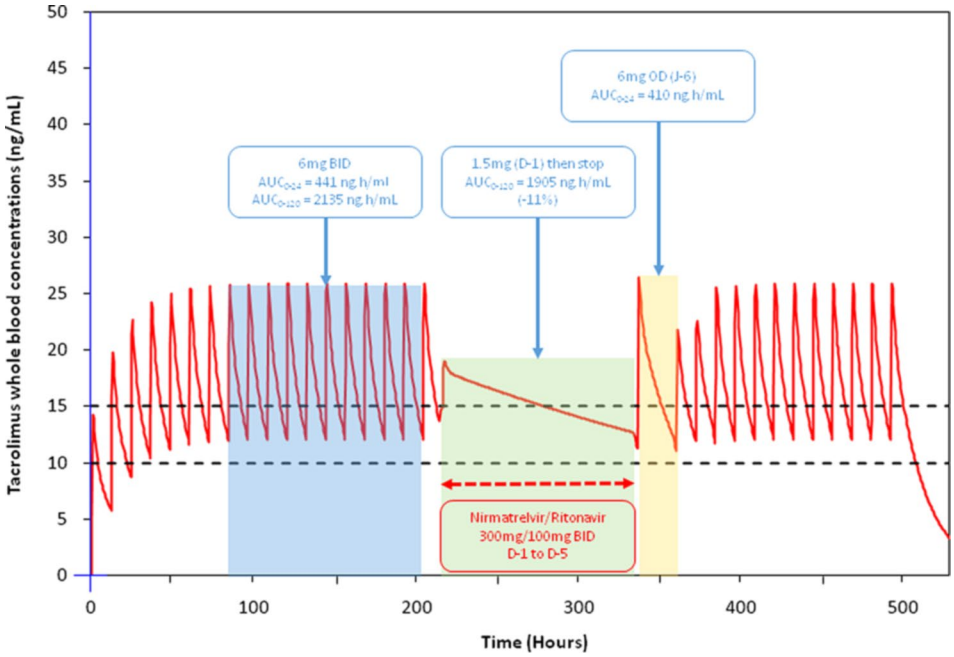

Fig. 1 Simulation of tacrolimus whole blood concentrations in a typical patient (aged 54 years, 175 cm, 75 kg) treated with tacrolimus immediate-release 6 mg twice daily (BID) and receiving ritonavir 100 mg/day from day 1 (D-1) to day 5 (D-5). Tacrolimus dosage is adjusted to one dose of 1.5 mg on D-1 and then 6 mg once daily (OD) on day 6, 4.5 mg BID on day 7 and 6 mg BID thereafter. Areas under the curve for tacrolimus concentrations calculated over 5 days ($AUC_{0–120}$) before and after drug interactions were close and so were 24-h areas under the curve of tacrolimus concentrations ($AUC_{0–24}$) before drug interactions and on day 6

and do not take into account patients' individual parameters [6]. Of note, the approach proposed in the present article can be applied with tacrolimus extended-release and LCP-Tacro formulations, making it very convenient for every therapeutic situation.

Another key issue is the tacrolimus dosage adjustment at the end of the PI treatment. After the cessation of ritonavir treatment, drug transport and CYP3A4/5 inhibition decrease progressively, as shown in a simulation study, with a 50% recovery capacity of metabolism after 24 h, and 75% after 48 h [7]. For this reason, tacrolimus should be reintroduced at the end of day 6 of nirmatrelvir/ritonavir at 50% of the initial dosage and 75% of the initial dosage on day 7. For a patient originally treated with tacrolimus 6 mg BID with the immediate-release formulation, this would mean 6 mg once daily on day 6 and 4.5 mg BID on day 7. Finally, the full initial dose could be restarted on day 8. Figure 1 shows a simulation of the example patient initially receiving tacrolimus 6 mg BID, performed using the software MWPHARM++ (version Mediware, Maastricht, The Netherlands).

Some patients may require less strict immunosuppression maintenance, and a more convenient option for treatment adaptation is proposed. In the light of the volume of distribution and clearance modifications, cessation of tacrolimus 12 h before the initiation of nirmatrelvir/ritonavir is a simple strategy to avoid overexposure. For example, if the last tacrolimus intake is in the morning, nirmatrelvir/ritonavir can be started in the evening and vice versa. Further, the decrease in tacrolimus exposure with this strategy may also be an intentional goal during the infection period. In simulations, a 24% decrease in the usual AUC is observed (data not shown).

Therapeutic drug monitoring should be proposed to patients as an additional tool during the concomitant use of ritonavir and tacrolimus. Some authors propose measuring the tacrolimus trough concentration on day 6 to decide whether immunosuppressive treatment can be restarted [8]. Another option is to propose two-point sampling to calculate the tacrolimus elimination slope, for example, on day 2 and day 3 of nirmatrelvir/ritonavir treatment. This allows a precise calculation of the moment when the tacrolimus concentration will drop below a predefined threshold, suggesting when to reintroduce tacrolimus and the dose to use [9]. We applied this strategy to a patient and determined a level of 3.7 ng/mL on day 2 and 3.5 ng/mL on day 3 of the antiviral treatment, and thus determined a half-life of 299 h, enabling us to predict a concentration of 2.9 ng/mL at the end of nirmatrelvir/ritonavir treatment. The suggested dosage adjustment strategies are based on pharmacokinetic mean population values and therapeutic drug monitoring will allow refinement to a truly individualized approach. Similar strategies can be applied to other immunosuppressive drugs such as cyclosporine and mammalian target of rapamycin inhibitors.

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