Management of nirmatrelvir/ritonavir and tacrolimus interaction in kidney transplant recipients infected by COVID-19: a three-case series

Carlos Guzmán Cordero, Maria Saez-Torres de Vicente

ABSTRACT

Objectives Nirmatrelvir/ritonavir may cause a clinically relevant drug-drug interaction (DDI) with immunosuppressive drugs, such as tacrolimus, which may condition the use of this antiviral in transplant patients. We aimed to describe the management of this interaction.

Methods Descriptive study in which renal transplant patients in treatment with nirmatrelvir/ritonavir and tacrolimus were included. They suspended tacrolimus the day before starting the antiviral treatment, and the decision to restart it was made based on their tacrolimus blood levels. Main variables studied to measure this DDI were tacrolimus blood concentration, dose adjustment and serum creatinine.

Results Three patients were included. During the study, tacrolimus levels elevation did not have repercussion in the serum creatinine, that remained stable in all patients. No patient required hospitalisation or showed signs of rejection.

Conclusions Our experience provides further evidence that this interaction should not be a contraindication to treatment with nirmatrelvir/ritonavir, and can be managed with close monitoring of tacrolimus levels.

INTRODUCTION

COVID-19 pandemic has had a major global impact on healthcare systems. Patients who have undergone solid organ transplants, specifically kidney transplants, are more likely to develop a serious clinical condition.

Lately, new drugs have been authorised for this disease. Among them, the virus protease inhibitor nirmatrelvir/ritonavir is used as an oral therapeutic option in patients with mild and moderate SARS-2-CoV disease and high risk of developing a severe condition. Administered at a dose of 300/100mg twice a day for 5 days, it has proven to reduce the hospitalisation and death risk by 89%, compared with placebo, when the therapy started within the first days of symptoms onset. The presence of ritonavir in this drug causes a fast, powerful inhibition of CYP3A4, that represents the main metabolic pathway of numerous drugs. This phenomenon makes it necessary the study of the possible interactions between nirmatrelvir/ritonavir and these drugs in order to avoid adverse effects.

One of the drugs that is more likely to be affected is tacrolimus, a cornerstone in the immunosuppressive treatment of kidney transplant patients, as it is metabolised by CYP3A4. It is a drug with a narrow therapeutic window, whose underdosaging can lead to a graft rejection and failure, and overdosing could cause adverse effects such as nephrotoxicity. Previous experience with ritonavir in transplants patients confirms the need for drastic tacrolimus dose reduction and monitoring of blood levels to avoid supratherapeutic concentrations. In a cohort of liver transplant recipients infected with hepatitis C virus who initiated treatment with a ritonavir-boosted direct-acting antiviral drug, tacrolimus dose reduction to 0.5 mg weekly was necessary.

There is just a few published cases about how to manage this drug-drug interaction (DDI). Some authors suggest to stop tacrolimus intake during the nirmatrelvir/ritonavir treatment, but it is not clear when to restart the immunosuppressive therapy. Our objective is to describe our experience following this strategy in the management of this DDI.

METHODS

This work is a descriptive study in which all renal transplant patients in treatment with nirmatrelvir/ritonavir and tacrolimus in our hospital (from the authorisation of nirmatrelvir/ritonavir in Spain in March 2022 until July 1, 2022) were included. Age, sex, transplant date, and immunosuppressive regime were obtained from our hospital’s electronic medical report. The main variables studied to measure the DDIs were tacrolimus blood concentration, which was obtained by chemiluminescent microparticle immunoassay (CMIA) analytical technique, the serum creatinine concentration, and dose adjustment of the immunosuppressive treatment.

Day one was defined as the first nirmatrelvir/ritonavir treatment day. All patients suspended tacrolimus intake the day before the beginning of the antiviral treatment (day −1) and completed the 5-day therapy. They were followed up for at least 20 days after the beginning of the antiviral treatment, underwent a closer monitoring than usual, having at least three determinations of tacrolimus blood concentrations and serum creatinine. The decision to restart the immunosuppressive treatment was made based on their tacrolimus blood levels. Tacrolimus goal level range depended on the patient’s immunological risk and the time from the transplant.

RESULTS

Three kidney transplant patients were included, who had had a previous determination of tacrolimus blood concentration and serum creatinine no more than 15 days before starting nirmatrelvir/
Guzmán Cordero C, Saez-Torres de Vicente M. Eur J Hosp Pharm 2022;0:1–3. doi:10.1136/ejhpharm-2022-003544

**Short report**

TAC dose adjustment pre-TAC* reintroduction daily dose

**Table 1**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age (nearest decade)</th>
<th>TAC* baseline concentration (ng/mL)</th>
<th>TAC* 1 (ng/mL)</th>
<th>TAC* 2 (ng/mL)</th>
<th>TAC* 3 (ng/mL)</th>
<th>TAC* formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study</td>
<td></td>
<td></td>
<td>Years from transplant</td>
<td>daily dose</td>
<td>daily dose</td>
<td>daily dose</td>
<td></td>
</tr>
<tr>
<td>Patient report</td>
<td>M</td>
<td>80</td>
<td>9.2 (day 6)</td>
<td>5 mg</td>
<td>47.1 (day 4)</td>
<td>16.2 (day 8)</td>
<td>Immediate release</td>
</tr>
<tr>
<td>Rose et al 12</td>
<td>M</td>
<td>40</td>
<td>3.6 (day 4)</td>
<td>6 mg</td>
<td>2.6 (day 4)</td>
<td>7.3 (day 20)</td>
<td>Immediate release</td>
</tr>
<tr>
<td>Wang et al 13</td>
<td>F</td>
<td>59</td>
<td>14.2 (day 2)</td>
<td>11 mg</td>
<td>7.3 (day 20)</td>
<td>&gt;60 (day 4)</td>
<td>Not listed</td>
</tr>
<tr>
<td>Prikis et al 10</td>
<td>M</td>
<td>60</td>
<td>1.5 (day 6)</td>
<td>5 mg</td>
<td>9.1 (day 4)</td>
<td>6.6 (day 3)</td>
<td>Extended release</td>
</tr>
</tbody>
</table>

*TAC corresponds to every tacrolimus blood concentration measurement.

**DISCUSSION**

The exclusion of kidney transplant patients in 45% of clinical trials of authorised drugs for COVID-19 treatment makes necessary a closer surveillance than would be in patients without this condition to avoid harmful consequences.

Experience is still limited, but there are already studies that show that treatment with nirmatrelvir/ritonavir has benefits in patients who have received solid organ transplants, reducing the rate of hospitalisation and death.

Tacrolimus levels control in transplant patients remains complicated. Levels need to be kept within specific narrow ranges, as underexposure increases the risk of graft rejection, while overexposure can lead to adverse effects such as nephrotoxicity, neurotoxicity, infections, malignancies, diabetes and gastrointestinal discomfort. At acutely high levels, tacrolimus can lead to elevated serum creatinine and acute kidney injury.

**Table 1 Characteristics of the patients report in our study, and other published studies**

- In patients 1 and 2, there was a remarkable increase in tacrolimus blood levels, which happened after its reintroduction. This is because of the persistence over time of CYP3A4 inhibition, which is only able to recover 27% of its activity 3 days after the last intake of ritonavir.

- Patient one restarted the treatment at his baseline dose (6 mg) on day 6, after completion of nirmatrelvir/ritonavir therapy. Owing to the increased tacrolimus blood levels, the dose was reduced by 1 mg until normalisation of concentrations, when the baseline regimen was reintroduced.

- In the case of patient 2, a decrease in tacrolimus concentration observed on day 4 led to the reintroduction of tacrolimus with a reduced dose (4 mg), and from day 5 to return to the usual regimen (6 mg). The day after terminating treatment with nirmatrelvir/ritonavir and restarting tacrolimus with its baseline regimen (day 6), increased levels were observed, so the dose was reduced again (4 mg) for two days and then returned to the baseline regime (6 mg).

- In patient 3, tacrolimus levels remained stable throughout treatment with nirmatrelvir/ritonavir. No analytical determinations were performed from day 6 to day 20, so no elevation of tacrolimus levels could be observed after restarting it, as in the other two cases. In fact, there was a marked decrease in tacrolimus levels compared with the last determination before starting nirmatrelvir/ritonavir, as this patient started with elevated baseline levels.

- The detailed evolution of the tacrolimus blood concentrations and the administration regimen of the three patients can be seen in the online supplemental figure.

- The tacrolimus levels elevation did not have repercussions in the serum creatinine concentration, which remained stable in the three patients throughout the study. It is important to emphasise that none of the patients required hospitalisation during the study, nor did they show signs of graft rejection.
Even as a short course treatment, nirmatrelvir/ritonavir can cause significant DDIs, particularly for drugs that are predominantly metabolised by CYP3A4 and/or have a narrow therapeutic window. Recommendations on these DDIs are challenging, as they need to balance the benefit of nirmatrelvir/ritonavir in preventing serious COVID-19 disease against the risk of having a clinically relevant DDI, considering that the risk may be further increased for some drugs owing to limited monitoring options outside the clinical setting.4

Prikis et al6 conclude that the DDI between nirmatrelvir/ritonavir and tacrolimus is strong and leads to high levels of tacrolimus and its metabolites, producing adverse effects and acute kidney injury. This highlights the role of the pharmacist in warning about these interactions and monitoring tacrolimus levels.

There is still no consensus on the management of patients on treatment with these two drugs. Lange et al8 propose interrupting tacrolimus administration before starting treatment with nirmatrelvir/ritonavir and restarting at a dose of 25–75%, depending on the patient’s tacrolimus levels. In the case of Hiremath et al,11 it is not recommended to restart immunosuppressive treatment until two or three days after the end of nirmatrelvir/ritonavir therapy. We agree with withholding tacrolimus during treatment with nirmatrelvir/ritonavir and close monitoring, but in our case, there has been some variability in restarting immunosuppressive treatment, and it has been guided by drug levels.

The main limitation of this study is the variability in the number of tacrolimus blood concentration determinations after finishing nirmatrelvir/ritonavir treatment, as in one patient, concentrations could not be measured from day 6 to 20. However, the experience obtained in our hospital provides further evidence that this interaction should not be a contraindication to treatment with nirmatrelvir/ritonavir and can be managed with close monitoring of tacrolimus levels. Studies with a larger number of patients are necessary to develop a standardised protocol.

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**Contributors** CGC and MSTV have worked together in the design, conduct and realisation of the study, contributing equally in all cases.

**Funding** The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

**Competing interests** None declared.

**Patient consent for publication** Not applicable.

**Ethics approval** Not applicable.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** No data are available.

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**REFERENCES**

Objetivos: El nirmatrelvir/ritonavir puede provocar una interacción medicamentosa (DDI) clínicamente relevante con fármacos inmunosupresores, como el tacrolimus, que puede condicionar su uso en pacientes trasplantados. El presente estudio pretende describir el manejo de esta interacción.

Métodos: Estudio observacional y prospectivo en el que se estudiaron todos los pacientes durante 20 días tras el inicio del tratamiento antiviral. Las principales variables estudiadas para medir esta DDI fueron la concentración sanguínea de tacrolimus y su ajuste de dosis.

Resultados: Se incluyeron tres pacientes que suspendieron el tacrolimus el día anterior al inicio del tratamiento antiviral, y la decisión de reiniciarlo se tomó en función de sus niveles sanguíneos de tacrolimus. Durante el estudio, la elevación de los niveles de tacrolimus no tuvo impacto en la creatinina sérica, que se mantuvo estable en todos los pacientes. Además, ninguno requirió hospitalización ni mostró signos de rechazo.

Conclusiones: Nuestra experiencia aporta una evidencia más de que esta interacción no debe ser una contraindicación para el tratamiento con nirmatrelvir/ritonavir y puede ser manejada con una estrecha vigilancia de los niveles de tacrolimus.