



## Paxlovid-Tacrolimus Drug–Drug Interaction in a 23-Year-Old Female Kidney Transplant Patient with COVID-19

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Kidney transplant patients are at a high risk for adverse severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) infection outcomes in terms of morbidity and mortality. Therefore, these patients are candidates for additional pharmacotherapy. Paxlovid was authorized as such a therapy in December 2021. Because of potential paxlovid drug–drug interactions, transplanted patients receiving calcineurin inhibitors must be monitored. We report on a case of a kidney transplant patient who received paxlovid for SARS-CoV-2 infection who developed a drug–drug interaction with tacrolimus.

A 23-year-old woman was hospitalized on 9 January, 2022 because of a symptomatic coronavirus disease 2019 (COVID-19) infection. The patient had end-stage kidney disease due to interstitial nephritis and had undergone a living-related donor kidney transplant in 2013. Her immunosuppression regimen included: oral prednisone 5 mg/day, oral mycophenolic acid 360 mg  $\times$  2/day, and oral tacrolimus 2 mg  $\times$  2/day. She also took oral vitamin D 1000 U/day. She had received two doses of the messenger RNA BNT162b2 COVID-19 vaccine, completed 8 months before presentation. Upon admission, she had a fever of 39 °C, profound weakness, and muscle aches. She was hemodynamically stable with an O<sub>2</sub> saturation of 99%. Kidney function, liver function, and hematocrit were all within normal ranges. Her clinical status was mild with an elevated risk for progression. On the day after her admission, oral paxlovid was

prescribed as: nirmatrelvir 300 mg combined with ritonavir 100 mg, twice a day. Her immunosuppressive medications were adjusted: prednisone dose was doubled to 10 mg/day, mycophenolic acid was withheld. The tacrolimus dose was halved to 1 mg  $\times$  2/day and then further reduced and stopped 6 days after the first dose of paxlovid. The patient overall took three doses of paxlovid and it was stopped at her request. Consecutive tacrolimus blood concentration was measured daily, but the results were not immediately available. The tacrolimus blood concentration was measured using a chemiluminescent microparticle immunoassay for the quantitative determination of tacrolimus in human whole blood on the ARCHITECT I system (Abbott Laboratories, Abbott Park, IL, USA). The tacrolimus trough blood concentration increased up to 92.4 ng/mL on the fourth day after the first paxlovid dose (2 days after paxlovid was stopped). The patient had no clinical manifestations of a tacrolimus overdose but there was a transient elevation in her creatinine level from 0.9 mg/dL upon admission to 1.3 mg/dL on the fifth day of hospitalization. Her COVID-19 symptoms had not deteriorated, the patient's clinical condition improved, her creatinine level returned to the baseline level, and the patient was discharged from hospital on the seventh day (tacrolimus and paxlovid doses and tacrolimus blood concentration are shown in Table 1).

To estimate the individual pharmacokinetic parameters of the patient for tacrolimus, we used a Bayesian maximum a posteriori probability method [1], using a previously published population pharmacokinetic model for tacrolimus [2], and the “mapbayr” package in R [3] [see Electronic Supplementary Material]. The results show a significant decrease in tacrolimus clearance when administered with paxlovid to a level of approximately 3.9% of the normal population pharmacokinetic value. The intercompartmental flow,  $Q/F$ , was significantly reduced to approximately 2.7% of the standard pharmacokinetic value (Table 2). The results indicate a major drug–drug interaction between tacrolimus and paxlovid.

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**Table 1** Daily doses of tacrolimus and paxlovid, and tacrolimus blood concentration

Date (January 2022)	Tacrolimus daily dose (mg)	Paxlovid dose (mg)	Tacrolimus concentration (ng/mL) [standardized to hematocrit 45%] <sup>a</sup>
Baseline	4		8–10 <sup>b</sup>
10 (admission day)	3		NA
11	1	{ 300 mg/100 mg } × 1/day	10 <sup>c</sup>
12	2	{ 300 mg/100 mg } × 2/day	13.6
13	2		48.5
14	1		92.4
15	0.5		85.8
16 (discharge day)	0.5		62
17	0		NA
18	0		14.9

NA Not assessed

<sup>a</sup>Concentration standardized = (45%/hematocrit) concentration observed

<sup>b</sup>Recommended range for tacrolimus concentration in kidney transplant patients, up to 15 ng/mL

<sup>c</sup>Tacrolimus concentration was taken before first paxlovid tablet, after the morning dose of tacrolimus, and does not represent the trough concentration

**Table 2** PK estimation of tacrolimus, administered concomitantly with paxlovid

Patient body size descriptors	PK parameters	Population PK values	Patient-specific Bayesian MAP estimates	95% Central credibility interval
Weight = 53 kg	$CL/F$ (L/h)	11.83	0.151	0.27–0.79
Height = 155 cm	$V_c/F$ (L)	82.83	70.48	20.72–82.32
FFM = 39.8 kg	$Q/F$ (L/h)	15.8	0.963	0.22–0.83
	$V_p/F$ (L)	422.73	422.73	
	$K_a$ (h <sup>-1</sup> )	1.01	1.01	

$CL/F$  apparent clearance,  $FFM$  fat-free mass,  $MAP$  maximum a posteriori probability,  $PK$  pharmacokinetic,  $Q/F$  inter-compartmental flow,  $VC/F$  volume of central compartment

Kidney transplant patients are at an increased risk for morbidity and mortality because of SARS-CoV-2 infection [4]. In addition, their humoral response to the COVID-19 vaccination is weak [5], and the high morbidity and mortality persist even after vaccination [6]. When infected with COVID-19, kidney transplant patients are at an elevated risk for progression to severe disease. Therefore, they are candidates for further therapeutic interventions against SARS-CoV-2. The efficacy of a specific therapeutic intervention depends on several factors and may change over time with the emergence of new variants of the virus.

Paxlovid is a combination of nirmatrelvir, a 3CL protease inhibitor of SARS-CoV-2 and ritonavir, which is a pharmacokinetic enhancer. Paxlovid is highly effective in symptomatic COVID-19 infection by reducing the risk of progression to severe disease, hospitalizations, and mortality [7]. On December 2021, the US Food and Drug Administration granted an Emergency Use Authorization for paxlovid

in patients with COVID-19. It was recommended by the National Institutes of Health at the time our patient was hospitalized [8]. Ritonavir is a cytochrome P450 3A inhibitor and a P-glycoprotein inhibitor and may increase the plasma concentration of tacrolimus and other medications that are substrates of cytochrome P450 3A and P-glycoprotein enzymatic systems. Tacrolimus metabolism via the cytochrome P450 3A pathway is associated with multiple drug–drug interactions. A drug–drug interaction with paxlovid is expected, but the concomitant use of paxlovid and tacrolimus is not contraindicated. Tacrolimus blood concentrations may also be affected by numerous other factors such as diarrhea or hemolysis. We did not identify any such additional factor in our patient.

The case we report demonstrates the strong and prolonged interaction between tacrolimus and the ritonavir component of paxlovid with resulting extremely reduced tacrolimus clearance. Recently, there have been guidelines

and recommendations suggested for diminishing the possible adverse outcomes of this interaction. The recommendations include withholding or reducing tacrolimus doses and blood concentration monitoring while receiving paxlovid treatment [9]. We suggest, after our experience with our patient, that tacrolimus should be withheld if paxlovid is administered and should be resumed when blood concentration is within the therapeutic range. In addition, other therapeutic options against SARS-CoV-2 must be sought and considered in organ transplanted patients who take tacrolimus.

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## Declarations

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**Conflicts of interest** Noa Berar Yanay, Ido Bogner, Khader Saker, and Elias Tannous have no conflicts of interest that are directly relevant to the content of this case report.

**Ethics approval** Institutional review board approval was exempted because of the de-identified personal information in a case report.

**Consent to participate** Not applicable.

**Consent for publication** The patient provided her consent for the publication of this case report.

**Availability of data and material** Not applicable.

**Code availability** The code used for this analysis is included in the Electronic Supplementary Material.

**Authors' contributions** Concept and design: NBY; case management during hospitalization: IB and KS; acquisition of data and pharmacokinetic analysis: ET; drafting the manuscript: NBY; and critical revision of the manuscript: all authors.

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