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# Paxlovid (Nirmatrelvir/Ritonavir) and Tacrolimus Drug-Drug Interaction in a Kidney Transplant Patient with SARS-2-CoV infection: A Case Report

Marios Prikis\*, and Alexandra Cameron

Division of Nephrology and Transplantation, Department of Medicine, University of Vermont Medical Center, Burlington, Vermont, USA

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## ABSTRACT

The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has had a significant impact on communities and health systems. New antiviral medications against this disease have not been properly tested yet, and their efficiency, side effects, and drug–drug interactions are not entirely known. Organ transplant recipients receive immunosuppressive medications such as tacrolimus to prevent graft rejection. Tacrolimus is metabolized by the cytochrome P450 3A4 enzyme system. Many medications can either induce or inhibit this enzyme and affect the level. Awareness of possible drug–drug interactions is vital because tacrolimus levels should be kept within a specific narrow range determined by the recipient’s immunologic risk. Underexposure increases the risk of graft rejection, whereas overexposure may lead to adverse effects. Paxlovid, a novel antiviral medication approved for emergency use to treat SARS-CoV-2, is a combination of nirmatrelvir and ritonavir, a cytochrome P450 3A4 inhibitor. In this case report, we present a case of a kidney transplant patient receiving tacrolimus treated with Paxlovid, leading to an abruptly high tacrolimus level, significant symptoms, treatment interruption, and acute kidney injury. We conclude that the drug–drug interaction between Paxlovid and tacrolimus is indeed robust and noteworthy and leads to high tacrolimus levels and its metabolites, adverse effects, and acute kidney injury. Physicians managing immunocompromised patients receiving tacrolimus should be aware of this significant drug–drug interaction and consider other options or reduction of daily tacrolimus dose during treatment in addition to timely monitoring of both tacrolimus levels and serum creatinine. Consulting with the transplant pharmacist is foremost in alerting for these interactions.

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**T**HE current novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has had significant effects on local, national, and global communities, economies, and health systems. The scientific community has been attempting to develop new antiviral medications that can control the morbidity and mortality resulting from infection by SARS-CoV-2. These medications may not have been tested in proper clinical trials and they may be hesitantly used for the general population. Immunocompromised recipients of solid organ transplants are at high risk for progressing to severe disease when contracting SARS-CoV-2 and therefore are strong candidates for treatment with these antiviral medications. Nevertheless, awareness of potential drug–drug interactions is important when these agents will be used for these patients because some of the immunosuppressive medications may interact with the new agents, resulting in unwelcome outcomes. Advice by a

transplant pharmacist with knowledge of these new agents and their interactions will help guide management and reduce the risk to the graft or adverse effects to the patient.

We present a case of a patient with a kidney transplant receiving maintenance immunosuppression with tacrolimus (FK506), mycophenolate mofetil, and prednisone who was treated with the recently approved antiviral medication Paxlovid (a combination of nirmatrelvir and ritonavir; Pfizer, New York, NY, USA) against SARS-CoV-2 infection. This led to abruptly high tacrolimus levels, as detected by a microparticle enzyme immunoassay at our institution from a whole blood specimen because

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\*Address correspondence to Marios Prikis, Division of Nephrology and Transplantation, Department of Medicine, University of Vermont Medical Center, 1 South Prospect Street, Rehab 2nd Floor, UHC, Burlington, VT 05401. Tel: (+1) 802-847-4774; Fax: (+1) 802-847-3619. E-mail: [marios.prikis@uvmhealth.org](mailto:marios.prikis@uvmhealth.org)

of drug–drug interaction between tacrolimus and Paxlovid. The patient developed significant symptoms resulting in interruption of treatment and also acute kidney injury most likely due to toxicity by either the parent FK506 compound and/or its metabolites.

### CASE PRESENTATION

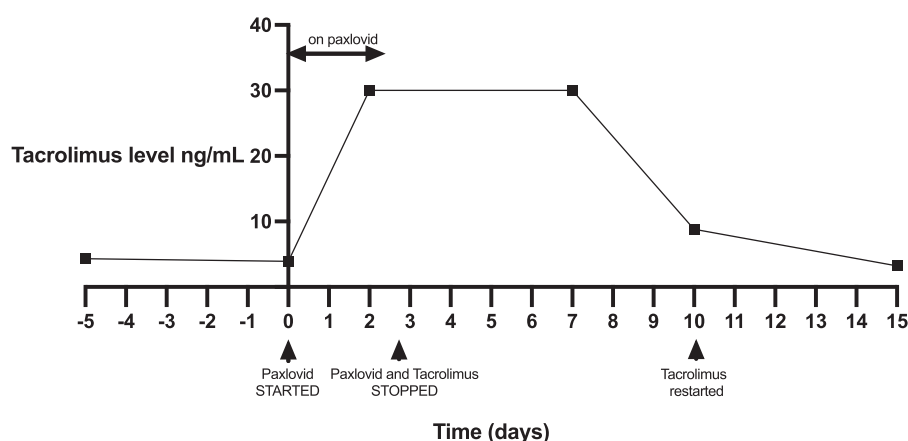
Our patient is a 34-year-old man with end-stage renal disease secondary to focal segmental glomerulosclerosis. He underwent a successful living related kidney transplant at the age of 25. Post-transplant complications included BK viremia treated with reduction of immunosuppression and recurrent focal segmental glomerulosclerosis verified with allograft biopsy. Other significant medical history is notable for hypertension and hyperglycemia managed with lifestyle modifications. His baseline serum creatinine had been stable at about 1.2–1.5 mg/dL over the past 2 years.

Current immunosuppression included short-acting tacrolimus 2.0 mg every 12 h (goal level range 4–6 ng/mL), leflunomide 20 mg once daily and prednisone 5 mg once daily. Other medications were amlodipine, lisinopril, omeprazole, calcitriol, cholecalciferol, and magnesium oxide. There were no recent dose changes in any of the above medications recently and no new medications administered.

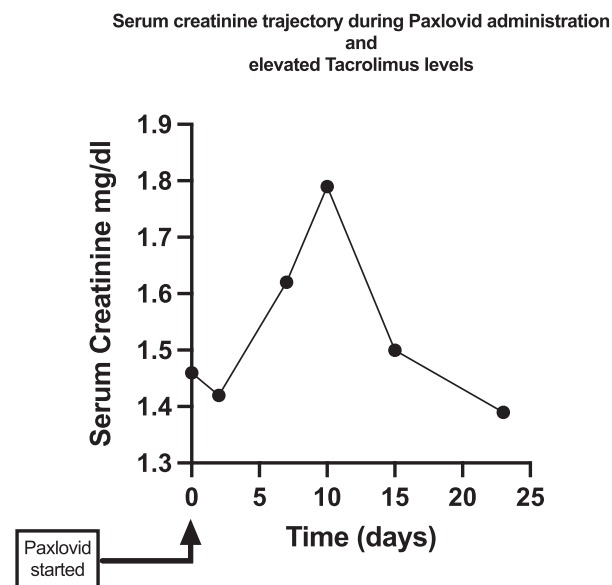
The patient was in his usual state of health when he reported that, over the previous 2 days, he had intermittent fever, running nose, headaches, significant muscle aches, and mild shortness of breath. He denied chest pain, diarrhea, nausea, or vomiting. He was hemodynamically stable. The patient was unvaccinated against SARS-CoV-2. Because of the progression of his symptoms and the fact that he was unvaccinated and thus at high risk of progressing to more severe disease, treatment against SARS-CoV-2 was considered. After discussion between the patient and his primary care team, transplant team, and transplant pharmacist, it was decided that he should be treated with the new oral antiviral medication Paxlovid (a combination of the

antiviral compounds nirmatrelvir and ritonavir) recently authorized in the United States as treatment against the novel coronavirus SARS-CoV-2 for emergency use only [1]. Because of his reduced glomerular filtration rate (GFR) of 55–60 mL/min/1.73 m<sup>2</sup> (chronic kidney disease stage 3a), and based on the US Food and Drug Administration manufacturer’s guidelines for health care providers [2], he was prescribed a reduced dose of Paxlovid, nirmatrelvir 150 mg with ritonavir 100 mg twice daily for a total of 5 days (adult dose for GFR >60 mL/min/1.73 m<sup>2</sup> is 300 mg of nirmatrelvir with 100 mg ritonavir twice daily for 5 days). The patient took both doses on day 1 and day 2 without complaints of side effects. Laboratory test samples, including a basic metabolic panel with electrolytes and whole blood tacrolimus level, were drawn on day 2 and became available on day 3, showing a tacrolimus level of more than 30 ng/mL, well above the goal range of 4–6 ng/dL. (Tacrolimus levels at our institution are assayed using Abbott chemiluminescence technology, a microparticle enzyme immunoassay, from a whole blood specimen.) His serum creatinine was at his baseline (1.42 mg/dL). On day 3, he received only the morning dose, but then he reported nausea and vomiting and wanted to stop taking the medication. As soon as the measured tacrolimus level (drawn on day 2) was reported to be extremely high, and because his symptoms were not improving, Paxlovid was withdrawn on day 3, and tacrolimus was held. Tacrolimus levels were checked again on day 7 (level reported more than 30 ng/dL again) and on day 10 (8.8 ng/dL). Serum creatinine was noted to be elevated above his baseline at 1.62 mg/dL on day 7 and even further above at 1.79 mg/dL on day 10. The patient’s symptoms improved 1 day after he stopped taking Paxlovid and resolved completely by day 7. Because the level dropped below 10 ng/dL, tacrolimus was readministered at 2.0 mg every 12 h (the dose before Paxlovid), and levels were monitored weekly until stabilized at a goal range of 4–6 ng/dL (Fig 1). The patient’s serum creatinine improved to 1.50 mg/dL and 1.39 on day 15 and day 23, respectively, coinciding with the drop in tacrolimus levels, and they have remained at baseline (Fig 2).

Changes in Tacrolimus level



**Fig 1.** Change in tacrolimus level with Paxlovid treatment over time. Increase in whole blood tacrolimus levels shown after initiation of Paxlovid treatment and subsequent return to the goal range after holding tacrolimus.



**Fig 2.** Change in serum creatinine during treatment with Paxlovid treatment. Increase in serum creatinine consistent with acute kidney injury is shown after Paxlovid was given and tacrolimus level increased. Subsequently, serum creatinine improved with decreasing tacrolimus level.

## DISCUSSION

In 1990, tacrolimus (or FK506), a calcineurin inhibitor was introduced in the field of organ transplantation. Since then, it has been the mainstay of most immunosuppressive regimens currently used globally. It has been associated with improved graft outcomes, a lower incidence of rejection, and fewer side effects. However, following a successful organ transplantation, tacrolimus level monitoring remains complicated. Levels need to be kept within specific narrow ranges because underexposure increases the risk of graft rejection and the appearance of donor specific antibodies, whereas overexposure may lead to adverse effects such as nephrotoxicity, neurotoxicity, infections, malignancies, diabetes, and gastrointestinal complaints [3]. Goal level range depends mainly on the recipient's immunologic risk. Acutely, high tacrolimus levels may result in elevation of serum creatinine and acute kidney injury. This occurs because of reduction in the effective renal blood flow and GFR without structural damage (functional toxicity). However, it may also cause toxic tubulopathy (through isometric vacuolization of tubules with dysmorphic nuclei and microcalcifications), thrombotic microangiopathy (acute arteriopathy), and electrolyte imbalances and hypertension. Chronic toxicity may include nodular hyaline arteriopathy and linear interstitial fibrosis and tubular atrophy and eventual graft loss [4]. These factors have led to the consensus that therapeutic drug monitoring of steady-state whole blood trough tacrolimus levels is beneficial for the optimization of tacrolimus therapy. High-pressure liquid chromatography–tandem mass spectrometry (HPLC-MS/MS)-

based assays have been viewed as the gold standard for accurate monitoring of whole blood FK506 levels. Nevertheless, most commercially available methodologies for the routine monitoring of tacrolimus have been immunoassay based, using an anti-FK506 monoclonal antibody such as cloned enzyme donor immunoassay and microparticle enzyme immunoassay, because HPLC-MS/MS-based assays are more time- and labor-intensive. These antibody-based assays may make rapid assays possible as part of the immunoassay modules on standard combined chemistry/immunoassay instruments but have been shown to overestimate tacrolimus levels because of cross-reactivity with tacrolimus metabolites. FK506 is extensively metabolized by the cytochrome P450 isoenzyme CYP3A4 and, to a lesser extent, by CYP3A5 in the liver and small intestine, resulting in the formation of several metabolites. These metabolites are variably recognized by anti-FK506 antibodies, few of them as efficiently as the parent compound. Consequently, a microparticle enzyme immunoassay, such as the one used at our institution, that employs nonspecific antibodies is likely to overestimate the true concentration of parent FK506 compound relative to HPLC-MS/MS [5–9].

Numerous other drugs can induce or inhibit the cytochrome P450 enzyme system; therefore, vigilance is required to avoid potential drug interactions between tacrolimus and commonly prescribed medications.

Paxlovid is a novel medication very recently approved for emergency use to treat infection with SARS-CoV-2, the cause of the novel and severe COVID-19. It is a copackaged combination of nirmatrelvir, a second-generation protease inhibitor, and ritonavir, a pharmacologic enhancer. Nirmatrelvir disrupts the proteolysis stage of viral replication, thus reducing the viral load, whereas ritonavir is a cytochrome P450(CYP) 3A4 inhibitor that slows down its metabolism, thus allowing the compound to remain active for a prolonged time [1].

Paxlovid is given orally for 5 days in patients early in the course of infection and reduces hospital admissions and deaths among people with COVID-19 who are at high risk of severe illness when compared with placebo, as Pfizer reported [10]. It has not been linked to serum aminotransferase elevations or to clinically apparent liver injury [11].

Our patient was prescribed Paxlovid because he was being immunocompromised and unvaccinated and thus at high risk for progression to severe disease. Because of reduced GFR (<60 mL/min), his nirmatrelvir dose was reduced. The patient was receiving tacrolimus, and because ritonavir is a CYP3A4 inhibitor, there were significant concerns that tacrolimus levels would be increased. Nevertheless, Paxlovid is a new medication that has not yet been used extensively, and certainly experience in patients with organ transplantation receiving tacrolimus is very minimal. Even though a drug–drug interaction may be expected, it has been unclear how significant the effect on tacrolimus is. It is unknown how strong the interaction is, how fast the levels may change, and whether it will affect graft function or lead to severe side effects. We therefore did not reduce the tacrolimus dose before administering Paxlovid but chose to monitor frequent whole blood tacrolimus levels and serum creatinine starting early in the treatment course. This approach was

selected because it was unclear how strong this drug–drug interaction is. The patient developed significant adverse effects by day 2 (nausea, vomiting), eventually leading to cessation of Paxlovid on day 3. Tacrolimus levels were higher than 30 ng/dL as quickly as the second day and remained elevated until at least the seventh day after the first dose of Paxlovid was given, despite holding tacrolimus. On day 10, the levels finally dropped to below 8 ng/dL (Fig 1). The patient's symptoms improved 1 day after cessation of Paxlovid and holding tacrolimus and completely resolved by day 7. Furthermore, it was noted that as tacrolimus levels increased because of this drug–drug interaction, the patient's serum creatinine increased, too. Serum creatinine peaked at 1.79 mg/dL and then returned to baseline levels when tacrolimus levels dropped (Fig 2). This is most likely a functional toxicity caused by a sudden reduction in effective renal blood flow. Additionally, some degree of acute tubular necrosis or other tubular toxicity cannot be excluded and could have an impact on the graft's long-term survival.

As mentioned earlier, FK506 levels at our institution are measured in whole blood specimens using a microparticle enzyme immunoassay instead of HPLC-MS/MS-based assay, and therefore tacrolimus levels may have been overestimated because of the presence of metabolites. Thus, we cannot claim with certainty that the patient's symptoms, adverse effects, and renal toxicity are exclusively caused by high levels of the parent FK506 compound or that there was a contribution by any of its metabolites.

Finally, this case and its unfolding stress the importance of discussing the plan to use any novel antiviral medications promptly with a transplant pharmacist, whose knowledge of these new agents and their interactions will alert the physicians and enable timely dose adjustments, a monitoring plan, and thus avoidance of possibly adverse effects or risk of harm to the allograft.

## CONCLUSIONS

We conclude that the drug–drug interaction between Paxlovid and tacrolimus is robust and noteworthy and can lead to abruptly high tacrolimus levels. This increase may lead to adverse effects by the parent FK506 compound and/or its metabolites, requiring cessation of the treatment, acute kidney injury of the graft, and potentially other acute and chronic effects on the allograft. Patients with organ transplants are at high risk for severe COVID-19, especially if they are unvaccinated. Novel antiviral agents such as Paxlovid are vital tools against this disease and should certainly be considered for use.

Even so, all physicians involved in the care of immunocompromised patients receiving tacrolimus or other calcineurin inhibitors should be aware of this significant drug–drug interaction and consider other options if possible. The role of the transplant pharmacist is foremost in alerting for these interactions and subsequently advising about dose adjustments, close monitoring, and side effects.

If Paxlovid is to be used, we recommend reduction of daily tacrolimus dose during treatment and additionally early and frequent monitoring of both whole blood tacrolimus levels and serum creatinine so that adjustments may be made if needed to prevent complications.

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