

Supratherapeutic Tacrolimus Concentrations With Nirmatrelvir/Ritonavir in Solid Organ Transplant Recipients Requiring Hospitalization: A Case Series Using Rifampin for Reversal

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Nirmatrelvir/ritonavir was recently granted emergency use authorization for mild to moderate coronavirus disease 2019. Drug–drug interactions between ritonavir and tacrolimus are underappreciated by nontransplant providers. We describe 2 solid organ transplant recipients prescribed nirmatrelvir/ritonavir for outpatient use who developed tacrolimus toxicity requiring hospitalization and were managed with rifampin for toxicity reversal.

Keywords. COVID-19; drug interactions; nirmatrelvir/ritonavir; tacrolimus.

Coronavirus disease 2019 (COVID-19) is responsible for >900 000 deaths in the United States (US) [1]. In December 2021, the US Food and Drug Administration issued an emergency use authorization (EUA) for nirmatrelvir/ritonavir (NIM-RTV), an agent that disrupts replication of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), for outpatient treatment in individuals at high risk of disease progression [2].

Immunocompromised solid organ transplant recipients (SOTRs) are at risk of severe COVID-19 disease, making them ideal candidates for NIM-RTV. Ritonavir, a strong cytochrome P450 3A (CYP3A) inhibitor, “boosts” concentrations of nirmatrelvir targeting SARS-CoV-2, while also raising concentrations of other CYP3A-metabolized medications [2].

We describe complications in 2 cases of NIM-RTV and tacrolimus coadministration. Clarity regarding the magnitude of this interaction is important to guide decision-making for SOTRs diagnosed with COVID-19. We detail the hospital clinical course and management of these patients.

Patient 1

A 40-year-old man with a history of pancreas-kidney transplant 7 years earlier presented to the emergency department with worsening fatigue and “gnawing” back and abdominal pain. The patient saw his outpatient nephrologist (who is unaffiliated with our transplant center) 4 days prior with a complaint of fatigue and cough and was diagnosed with COVID-19. The patient was started on renally dose-adjusted NIM-RTV at 150/100 mg twice daily for a serum creatinine (SCr) level of 1.2 mg/dL and corresponding Cockcroft-Gault estimated creatinine clearance (eCRCL) of 55 mL/minute from November. His nephrologist preemptively reduced tacrolimus to 3 mg AM/ 2 mg PM over concerns of drug–drug interactions (DDIs) with NIM-RTV and held his mycophenolic acid-sodium (MPS). He previously had stable allograft functions and no rejections. Table 1 lists pertinent baseline laboratory tests and demographics. His maintenance immunosuppressants included tacrolimus 6 mg AM and 5 mg PM (goal concentrations: 4–7 ng/mL) and MPS 180 mg twice daily. Historic therapeutic monitoring of tacrolimus troughs was unavailable and recent medication changes were not reported. He completed 4 of 10 doses of NIM-RTV with the reduced tacrolimus dose prior to presenting to our health system.

On admission, the patient was hypotensive with a blood pressure 79/46 mm Hg, tachypneic with a respiratory rate of 22 breaths/minute, and on 3 L of oxygen saturating at 94%. Vitals normalized rapidly after a liter of normal saline. No additional COVID-19 therapies were administered in hospital. Initial laboratory results were unremarkable except a SCr of

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Table 1. Patient Characteristics

Variable	Patient 1	Patient 2
Baseline demographics and immunosuppression		
Age, y	40	58
Sex	Male	Female
Underlying diagnosis	Diabetes mellitus type 1	Pulmonary fibrosis
Transplanted organ(s)	Pancreas-kidney	Bilateral lung
Time posttransplantation, y	7	6
Immunosuppression, drug/dose	Tacrolimus 6 mg (AM), 5 mg (PM) Enteric-coated MPS 180 mg twice daily	Tacrolimus 2.5 mg (AM/PM) Prednisone 10 mg daily
Tacrolimus goals, ng/mL	4–7	5–7
SCr, mg/dL (eCRCL, mL/min)	1–1.4 (75–105)	1 (50)
COVID-19 vaccine type (month of receipt)	mRNA (Apr, May 2021)	mRNA (Jun, Jul, Sept 2021)
NIM-RTV regimen prior to hospitalization	150/100 mg × 4 doses ^a	300/100 × 6 doses
Admission chief complaint	Gnawing back pain, abdominal pain, fatigue	Gnawing back pain, abdominal pain, somnolence
COVID-19 treatment course		
NIM-RTV, mg (No. of doses)	150/100 (4)	300/100 (6)
ED/inpatient treatment	None	ED: casirivimab/imdevimab × 1; Inpatient: remdesivir 200 mg × 1, 100 mg × 4; dexamethasone 6 mg × 8 d

Abbreviations: COVID-19, coronavirus disease 2019; eCRCL, estimated creatinine clearance; ED, emergency department; MPS, mycophenolate acid-sodium; mRNA, messenger RNA; NIM-RTV, nirmatrelvir/ritonavir; SCr, serum creatinine.

^aRenally dose adjusted for eCRCL 40 mL/minute (SCr, 2.4 mg/dL).

2.9 mg/dL (baseline: 1–1.4 mg/dL) and eCRCL 30 mL/minute with normal urinalysis. Physical examination of abdomen and pelvic imaging were unremarkable. There were no additional symptoms or signs of tacrolimus toxicity.

Tacrolimus was immediately lowered to 1 mg twice daily upon admission. On day 2, his creatinine peaked at 3.8 mg/dL and tacrolimus was held secondary to concerns regarding toxicity, which was confirmed when levels returned at ≥ 60 ng/mL later that day. In an effort to reverse acute kidney injury (AKI) and mitigate further sequela of tacrolimus toxicity, oral rifampin 600 mg was initiated on the evening of day 3. Two additional doses of rifampin 600 mg were administered on day 4. On day 5, after 3 consecutive days of tacrolimus concentrations ≥ 60 ng/mL, concentrations decreased to 33 ng/mL, and SCr was 1.7 mg/mL (Figure 1A). On day 6, he developed transaminitis with aspartate aminotransferase (AST)/alanine aminotransferase (ALT) peaking at 200/167 units/L (baseline: 16/26 units/L); however, these laboratory results were down-trending at discharge (AST/ALT: 151/165 units/L). Follow-up laboratory tests after discharge are unavailable. Tacrolimus 1 mg twice daily and MPS were restarted prior to discharge per our transplant physicians on day 7 and 8 since concentrations returned to goal range. He made an otherwise uneventful recovery from his COVID-19 infection.

Patient 2

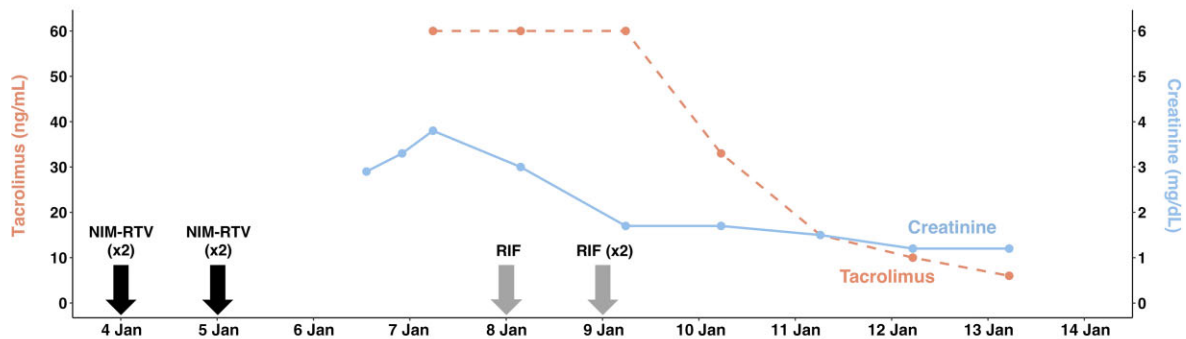
A 58-year-old bilateral lung transplant recipient presented to our emergency department with 1 day of fever 38.1°C, epigastric pain, and an otherwise unremarkable examination. Her baseline SCr was 1 mg/dL with a corresponding eCRCL

50 mL/minute. Table 1 lists pertinent baseline laboratory tests and demographics. Her maintenance immunosuppressant agents included prednisone 10 mg daily and tacrolimus 2.5 mg twice daily (goal concentrations: 5–7 ng/mL). Historic therapeutic monitoring of tacrolimus was unavailable (managed by an unaffiliated lung transplant team) with no recent medication changes. Her SARS-CoV-2 rapid polymerase chain reaction tested positive, prompting an infusion of casirivimab/imdevimab. She was prescribed NIM-RTV 300 mg/100 mg twice daily, despite an eCRCL < 60 mL/minute warranting a dose reduction, and discharged from the emergency room. No internal guidance documents, aside from the EUA NIM-RTV fact sheet, had been developed at our center.

Three days later, after 6 of 10 doses of NIM-RTV with her maintenance tacrolimus regimen, she returned with severe “gnawing” abdominal pain, nausea and vomiting, and somnolence. There were no additional complaints suggestive of tacrolimus toxicity. Intravenous fluids, dexamethasone, remdesivir, vancomycin, and ceftriaxone were administered empirically for increasing oxygen requirements with chest radiographic findings consistent with presumptive pneumonia. Initial laboratory tests were significant for an elevated creatinine from baseline at 1.7 mg/dL and a tacrolimus concentration ≥ 60 ng/mL on admission. Tacrolimus and NIM-RTV were discontinued. Oral rifampin 300 mg was started that evening to lower tacrolimus concentrations in the setting of concomitant AKI. Two doses of rifampin 300 mg were administered on day 2 and an additional dose on day 3. Serum tacrolimus concentrations decreased from ≥ 60 ng/mL on day 2 to 35 ng/mL on day 3 (Figure 1B). SCr returned to baseline by day 3 and our

A

Hospital Days Dates	4–5 Jan	5–6 Jan	Day 1 6–7 Jan (Admit)	Day 2 7–8 Jan	Day 3 8–9 Jan	Day 4 9–10 Jan	Day 5 10–11 Jan	Day 6 11–12 Jan	Day 7 12–13 Jan	Day 8 13–14 Jan (Discharge)
Tacrolimus Levels (ng/mL)	-	-	-	>60	>60	>60	33	15	10	6
Creatinine (mg/dL)	-	-	2.9 (13:25) 3.3 (21:58)	3.8	3.0	1.7	1.7	1.5	1.2	1.2
Nirmatrelvir-ritonavir (mg)	150/100 (AM) 150/100 (PM)	150/100 (AM) 150/100 (PM)	-	-	-	-	-	-	-	-
Rifampin (mg)	-	-	-	-	600	600 (11:57) 600 (20:15)	-	-	-	-
Tacrolimus (mg)	3 (AM) 2 (PM)	3 (AM) 2 (PM)	1	1	-	-	-	-	1	1 (05:19) 1 (11:51)



B

Hospital Days Dates	6–7 Jan	7–8 Jan	8–9 Jan	Day 1 9–10 Jan (Admit)	Day 2 10–11 Jan	Day 3 11–12 Jan	Day 4 12–13 Jan	Day 5 13–14 Jan	Day 6 14–15 Jan	Day 7 15–16 Jan	Day 8 16–17 Jan (Discharge)
Tacrolimus Levels (ng/mL)	-	-	-	>60	>60	35	20	6	4	4	11
Creatinine (mg/dL)	1.0 (Baseline)	-	-	1.7 (08:04) 1.2 (21:30)	0.9	0.8	1.1	1.1	1.1	1.1	1.2
Nirmatrelvir-ritonavir (mg)	300/100	300/100 (AM) 300/100 (PM)	300/100 (AM) 300/100 (PM)	300/100	-	-	-	-	-	-	-
Rifampin (mg)	-	-	-	300	300 (08:37) 300 (21:44)	300	-	-	-	-	-
Tacrolimus (mg)	2.5 (AM) 2.5 (PM)	2.5 (AM) 2.5 (PM)	2.5 (AM) 2.5 (PM)	-	-	-	-	0.5	1.5 (08:30) 1.5 (17:39)	1.5 (08:35) 0.5 (16:59) 2.0 (17:55)	-

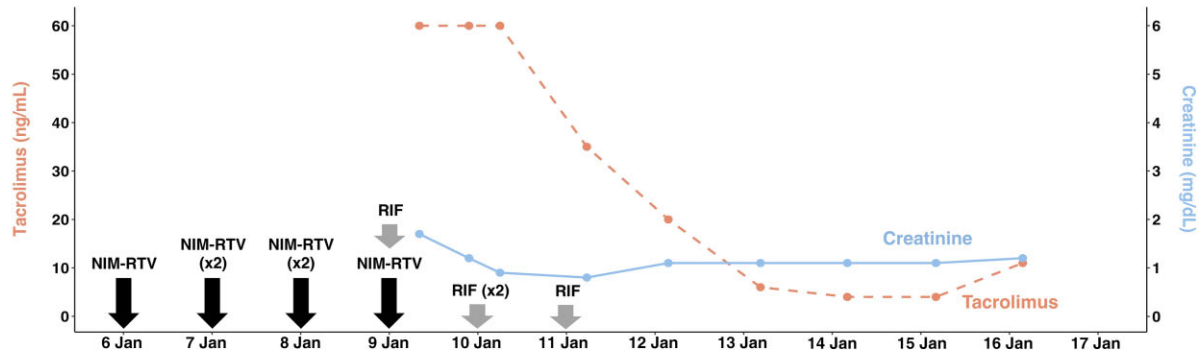


Figure 1. Time course of medication interactions and tacrolimus and serum creatinine trends. Serum trough tacrolimus and creatinine levels over hospital course for patient 1 (A) and patient 2 (B). The respective tables and graph detail the serum trough tacrolimus (dashed line) and creatinine (solid line) levels in relation to the dose and timing of nirmatrelvir/ritonavir (NIM-RTV), rifampin (RIF), and tacrolimus administration.

transplant team reinitiated tacrolimus at 1.5 mg twice daily on hospital day 5. She completed a 5-day course of remdesivir and ceftriaxone. Her abdominal pain and enteritis, attributed to tacrolimus toxicity, had completely resolved at the time of discharge. She returned to baseline oxygen requirements and had an otherwise uneventful recovery from COVID-19.

DISCUSSION

To our knowledge, we describe the first clinical descriptions of tacrolimus toxicity in conjunction with NIM-RTV, and the use of rifampin as an antidote. DDIs between NIM-RTV and calcineurin inhibitors due to irreversible CYP3A inhibition by ritonavir result in suppressed metabolism and supratherapeutic

levels of tacrolimus [3, 4]. Coadministered ritonavir increases tacrolimus exposure by 57-fold [3]. Furthermore, CYP3A enzymatic inhibition peaks shortly after exposure to an inhibiting agent. This is demonstrated by ritonavir's rapid reduction of midazolam clearance (another CYP3A substrate) to 8.4% of baseline within 48 hours of exposure [5]. A review on CYP-associated inhibition and induction on tacrolimus metabolism is available elsewhere [6]. No other drug interactions were identified in our patients.

Early pandemic experience with ritonavir and tacrolimus bore a worrisome harbinger. In lung transplant recipients with COVID-19, 71.4% experienced elevated tacrolimus concentrations (mean, 28.5 ng/mL) despite lowering/discontinuing tacrolimus upon lopinavir/ritonavir initiation [7]. Patients also developed AKI with a mean eGFR of 16 mL/minute/1.73 m². In another case, a renal transplant patient developed AKI on darunavir/ritonavir despite a 50% tacrolimus dose reduction [8], with levels peaking at 49.4 ng/mL despite drug discontinuation, and tacrolimus concentration only normalized after 10 days. After discontinuing lopinavir/ritonavir, CYP3A inhibition decreases profoundly by 46%–61% in the first 24 hours and 70%–90% by days 2–5, but complete recovery of functional enzymes may take 3 weeks [9]. This is not unexpected following the discontinuation of an irreversible inhibitor (as opposed to reversible inhibition, which can be overcome by higher substrate concentrations); as the half-life of CYP3A enzyme is approximately 2 days, one would not anticipate full recovery for several days to allow regeneration of new enzymatic activity.

Potent CYP3A inducers (phenytoin, rifampin, and phenobarbital) can act as antidotes, quickly reducing concentrations [10–12]. Hebert et al demonstrated that rifampin increased clearance of tacrolimus by 2-fold [10]. Chenhsu et al described a kidney transplant recipient whose tacrolimus concentration went from 15.5 to 1.5 ng/mL after several doses of rifampin given for tuberculosis. This patient ultimately experienced graft failure related to subtherapeutic concentrations [11]. Naylor and Robichaud also reported tacrolimus level reductions after 4 days of rifampin [12].

Our decision to initiate rifampin to rapidly lower supratherapeutic tacrolimus levels in both patients was borne of a concern for adverse events (eg, seizures, encephalopathy, optic neuropathy with visual loss, AKI) due to prolonged exposure to toxic concentrations. Rifampin was specifically chosen for its short half-life (3–5 hours) compared to phenytoin or phenobarbital (half-lives of 7–42 and 79 hours, respectively). This short half-life allowed for quicker restoration of therapeutic tacrolimus concentration upon rifampin discontinuation. This was important as persistent enzymatic induction causing prolonged subtherapeutic tacrolimus concentrations has been associated with allograft rejections [11]. Most literature reporting rifampin as an inducer of tacrolimus metabolism

happens without concurrent noncompetitive CYP3A inhibitors like ritonavir, which would simultaneously inhibit tacrolimus metabolism. Rifampin reduces ritonavir exposure by up to 35% and likely reduced both tacrolimus and ritonavir exposure in our patients [13]. Of note, nirmatrelvir is not anticipated to contribute to these interactions as it has no activity on CYP enzymes. We cannot ascertain the exact contribution of rifampin, but the effect of spontaneous CYP3A activity recovery on tacrolimus clearance was not likely significant in the absence of rifampin initiation given the sustained supratherapeutic tacrolimus concentration with NIM-RTV discontinuation alone.

As healthcare providers gain experience navigating this DDI with tacrolimus and NIM-RTV over the last 3 months, additional guidance regarding its management has been developed. In early 2022; however, specific recommendations were unavailable. The EUA fact sheet and University of Liverpool COVID-19 Drug Interactions database suggested a possible interaction, but providers without practical experience prescribing ritonavir in the setting of human immunodeficiency virus could easily miss these warnings [14, 15]. In mid-January, the University of Liverpool COVID-19 Drug Interactions database (covid19-druginteractions.org) strengthened this recommendation, stating “do not coadminister” [15]. Shortly thereafter, 2 publications reiterated this recommendation to hold tacrolimus for the 5-day duration of NIM-RTV, with reinitiation dependent on therapeutic drug monitoring [16, 17]. Finally, in late February, the National Institutes of Health COVID-19 treatment guidelines recommended contacting the patient's specialist provider prior to prescribing NIM-RTV to ensure close monitoring of tacrolimus or to use an alternative COVID-19 therapy when this is not feasible [18]. Currently, therapeutic drug monitoring of tacrolimus 1–3 days after NIM-RTV is recommended to guide reinitiation [16–18].

Based on the cumulative data coupled with our cases, we recommend (1) holding tacrolimus during the 5-day NIM-RTV course; (2) checking tacrolimus concentrations on day 2–3 of therapy (transplant centers could implement mobile phlebotomy services that avoid violating Centers for Disease Control and Prevention quarantine guidance); and (3) implementing biweekly therapeutic drug monitoring following tacrolimus reinitiation, as residual CYP3A inhibition could last ≥ 3 –7 days despite NIM-RTV discontinuation. Early data in 25 adult SOTRs suggests that this strategy does not compromise patient safety and that the majority can restart 82% of their daily baseline tacrolimus dose 3 days after NIM-RTV completion [19]. Importantly, 4 patients in this cohort experienced supratherapeutic concentrations after restarting, supporting an individualized, frequent monitoring plan. Even more conservative management (ie, holding tacrolimus for 1–2 days pre-NIM-RTV) may be necessary in high-risk recipients. Unfortunately, this approach could reduce efficacy by delaying

NIM-RTV therapy and is highly individualized based on the inpatient half-life variability of tacrolimus. This group recognizes that there may be significant barriers to safe NTM-RTV use in SOTRs on tacrolimus and recommends a greater focus on local strategies that allow coordinated access to remdesivir and monoclonal antibodies as first-line therapy in this patient population.

Increased NIM-RTV prescriptions by outpatient providers unfamiliar with immunosuppression could result in serious toxicities. These DDIs extend beyond calcineurin inhibitors, including common therapeutic classes like anticoagulants, antiarrhythmics, antifungals, and antiepileptics. It becomes imperative to urgently educate nontransplant professionals and patients through national and state resources. We believe that a “Boxed Warning” added directly to medication packaging, provider fact sheets, and drug-interaction software in inpatient and outpatient pharmacies prior to EUA approval and nationwide distribution would mitigate the dire consequences of these drug interactions for SOTRs and other patient populations on medications with narrow therapeutic indices.

Though rifampin is not without risks ranging from transaminitis to graft rejection secondary to inducement of subtherapeutic concentrations of immunosuppressants, it could greatly improve the calculus in cases of tacrolimus toxicity. The decision to initiate rifampin for reversal should be carefully balanced with these risks against severe or worsening symptomatology (eg, neurological, cardiac, renal toxicity) of tacrolimus toxicity. Outpatient therapy for COVID-19 is an exciting development; however, the complexities with NIM-RTV coadministration must be cautiously managed by a multidisciplinary partnership between community providers, transplant centers, and specialty pharmacists (eg, transplant, infectious disease).

Notes

Patient consent. This study did not include factors necessitating patient consent. No human subject experiments were related to this case report; therefore, approval by local ethical committees was not indicated.

Potential conflicts of interest. All authors: No reported conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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