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BRIEF REPORT

Elevated tacrolimus levels after treatment with nirmatrelvir/ritonavir (Paxlovid) for COVID-19 infection in a child with a kidney transplant

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Abstract

Background Paxlovid (nirmatrelvir/ritonavir) is a novel drug available under emergency use authorization by the Food and Drug Administration for the treatment of COVID-19 infection. Tacrolimus, a calcineurin inhibitor, is commonly used as an immunosuppressant medication in children with kidney transplants. While tacrolimus is metabolized by the cytochrome P450 system (CYP3A4), ritonavir is a potent CYP3A4 inhibitor. There is a paucity of data regarding the drug-drug interaction between nirmatrelvir/ritonavir and tacrolimus in children with kidney transplants.

Case-Diagnosis/Treatment This is a case report of a 14-year-old female with a history of a kidney transplant, maintained on tacrolimus and prednisone, who starts nirmatrelvir/ritonavir for a COVID-19 infection. She subsequently develops supratherapeutic tacrolimus levels and an increase in serum creatinine. Her tacrolimus was held, and the nirmatrelvir/ritonavir was stopped. Over time, her kidney function returned to baseline, her tacrolimus levels returned to the therapeutic goal, and her tacrolimus was resumed.

Conclusions Our case report highlights the strong interaction with concomitant use of tacrolimus and nirmatrelvir/ritonavir in a pediatric kidney transplant recipient and the development of supratherapeutic tacrolimus levels. Providers should therefore be cautious when prescribing nirmatrelvir/ritonavir to a pediatric patient currently on tacrolimus.

Keywords Nirmatrelvir/Ritonavir (Paxlovid) · COVID-19 infection · Child with a kidney transplant

It is recommended to use caution with concurrent administration of both tacrolimus and nirmatrelvir/ritonavir (Paxlovid) since ritonavir exhibits inhibition of P-glycoprotein and strong inhibition of CYP3A4, both of which mediate tacrolimus pharmacokinetics. By inhibiting the transport and enzymatic pathways required for tacrolimus absorption and metabolism, ritonavir has the potential to significantly increase tacrolimus exposure within the systemic circulation, resulting in potential drug-related adverse effects. There are isolated reports of drug-drug interactions between nirmatrelvir/ritonavir and tacrolimus in the adult kidney transplant population [1]. However, there are currently no published reports on the interaction between tacrolimus and nirmatrelvir/ritonavir in the pediatric population. The goal of this paper is to increase published data regarding the profound effect of the drug-drug interaction between nirmatrelvir/ritonavir and tacrolimus in the pediatric kidney transplant population.

Here, we report a 14-year-old, 52-kg female with a history of kidney failure secondary to Henoch-Shonlein Purpura nephritis who underwent living related kidney transplantation at 12 years of age. At the time of presentation, her immunosuppression regimen consisted of prednisone 5 mg PO daily and tacrolimus 2.5 mg PO twice daily with a tacrolimus trough goal range of 3–5 ng/mL. Her immunosuppression regimen had previously been lowered, including discontinuation of mycophenolate mofetil and reduction in tacrolimus trough goal to 3–5 ng/mL, 6 months prior to nirmatrelvir/ritonavir administration due to the development of EBV viremia. She had received three doses of the BNT162b2 mRNA COVID-19 vaccine; the last of which was 6 months prior to presentation. One week before presentation, her serum creatinine was 0.9 mg/dL, tacrolimus trough was 4.8 ng/mL, and her EBV PCR was detected at 520 copies/mL. She presented to an outside hospital with upper

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respiratory tract symptoms, nausea, body aches, and fever to 102.3 F. She did not report decreased PO intake, emesis, or diarrhea. She tested positive for SARS-CoV-2 and was prescribed nirmatrelvir/ritonavir 300 mg/100 mg by mouth twice daily of which she took two doses. Notably, this prescription was sent to an external pharmacy which did not have access to this patient's current list of prescribed medications. Subsequently, the patient contacted her pediatric nephrologists, and in consultation with pediatric pharmacy, the tacrolimus was held and the nirmatrelvir/ritonavir was stopped. Twenty-four hours after her nirmatrelvir/ritonavir was stopped and tacrolimus was held, she presented to the outpatient infusion center where she received SARS-CoV-2 monoclonal antibody infusion (bebtelovimab); her tacrolimus level was supratherapeutic at 54 ng/mL and her serum creatinine increased from her baseline of 0.9 to 1.1 mg/dL. Besides upper respiratory tract symptoms, she had no neurologic symptoms, no electrolyte derangements, and an EKG ruled out QTc prolongation. A repeat tacrolimus level 1 and 3 days later showed a decline to 49 ng/mL (54 h following last tacrolimus dose) and 13 ng/mL (103 h following last tacrolimus dose), respectively, and a serum creatinine back at her baseline of 0.9 mg/dL. The following morning, after consulting with our pediatric pharmacist, she received a tacrolimus dose of 1 mg (123 h or 5 days after holding the tacrolimus) and subsequently resumed her tacrolimus dose of 2.5 mg PO twice daily starting that evening. However, her tacrolimus trough level remained supratherapeutic at 9.5 ng/mL upon re-check 3 days later. Her tacrolimus dose was then decreased to 2.5 mg/2 mg for a total daily dose of 4.5 mg per day with a subsequent trough level of 6.1 ng/mL 4 days following the dose change. All subsequent tacrolimus trough levels remained in therapeutic range. She was seen in clinic 2 weeks after her tacrolimus had been restarted and by that time all of her COVID-19 symptoms including fever, nausea, and upper respiratory tract symptoms had completely resolved.

Nirmatrelvir/ritonavir is a medication authorized under emergency use authorization by the FDA for the treatment of mild to moderate COVID-19 infection in adults and children 12 years of age and older, weighing at least 40 kg. [2]. Nirmatrelvir is a SARS-CoV-2 main protease inhibitor [3]. Ritonavir is an HIV-1 protease inhibitor and CYP3A4 inhibitor [3]. Without the co-administration of ritonavir, nirmatrelvir would not be able to reach plasma levels required to have a therapeutic effect [3]. Tacrolimus is a calcineurin inhibitor that is primarily metabolized by the cytochrome P450 system (CYP3A4) [4]. While authorized by the FDA for emergency use, nirmatrelvir/ritonavir is an investigational drug that is still being studied and there is limited information regarding overall safety and efficacy [2].

In this child with a kidney transplant who received concomitant administration of nirmatrelvir/ritonavir and tacrolimus there is a clear temporal relationship between starting nirmatrelvir/ritonavir and the development of supratherapeutic tacrolimus levels. She also developed an increase in serum creatinine, although it was unclear if this was due to high tacrolimus levels, COVID-19 infection, or a combination of high tacrolimus levels and COVID-19 infection. This case also highlights the risks of using multiple pharmacies in patients with complex medical histories receiving multiple medications given the potential for unidentifiable drug-drug interactions.

Additional research needs to be conducted regarding the drug-drug interaction profile between tacrolimus and nirmatrelvir/ritonavir and recommendations for empiric dose adjustments. In the interim, alternative treatments should be considered for patients who are taking tacrolimus or other medications that rely on CYP3A metabolism and who are diagnosed with COVID-19. If nirmatrelvir/ritonavir is prescribed to any patient taking tacrolimus, tacrolimus trough levels should be closely monitored, strong consideration should be given to reducing tacrolimus dose, and a pediatric pharmacist should be consulted.

Declarations

Conflict of interest The authors declare no competing interests.

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