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Tacrolimus toxicity in a liver-kidney transplant patient receiving Nirmatrelvir/Ritonavir for COVID-19

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ABSTRACT

Due to the rapid approval of some of the newer therapies for COVID-19 infection, there are several pharmacologic aspects of these therapies that are not fully known, including drug-drug interactions. Transplant recipients face notable risks in relation to these interactions. This article outlines complications arising from the concurrent administration of nirmatrelvir/ritonavir and tacrolimus in a patient with history of combined kidney and liver transplantation. Additionally, it highlights the effective utilization of phenytoin as an inducer to correct the supratherapeutic levels of tacrolimus.

Keywords: drug interaction, tacrolimus, COVID-19, renal transplant, phenytoin

INTRODUCTION

Transplant patients on immunosuppressive treatment face an elevated risk of experiencing severe COVID-19 disease, making them candidates for early intervention in the course of the illness. Nirmatrelvir-ritonavir, also known as ritonavir-boosted nirmatrelvir (manufactured in the United States under the brand name Paxlovid), can be administered orally and was granted emergency use authorization in 2021 by the US Food and Drug Administration (FDA) for mild to moderate COVID-19 disease. It has been shown to significantly reduce the risk of developing severe disease [1]. Demonstrating an 89% decrease in severe cases compared to the placebo [2]. Ritonavir, a robust inhibitor of cytochrome P450 3A (CYP3A), enhances the concentrations of nirmatrelvir, which is directed against SARS-CoV-2, while concurrently elevating the concentrations of other medications metabolized by CYP3A [3].

The rapid approval of newer therapies for COVID-19 infection has left various pharmacologic aspects of these medications not fully understood, including potential drug-drug interactions. Transplant patients may be at significant risk related to drug interactions with the ritonavir component [4]. This case describes complications related to the coadministration of nirmatrelvir/ritonavir and tacrolimus in a combined kidney and liver transplant patient. Phenytoin was employed for its CYP3A inducing properties to address the supratherapeutic levels of tacrolimus.

CASE PRESENTATION

This case describes a 70-year-old female with a history of end-stage renal disease (ESRD) secondary to hypertension and type 2 diabetes mellitus, in addition to end-stage liver disease (ESLD) from non-alcoholic fatty liver disease. She had undergone a combined kidney and liver transplantation at 68 years of age, for which she was on immunosuppression with tacrolimus 2 mg twice daily (with target trough concentrations of 6–8 ng/mL), prednisone 5 mg daily, and mycophenolate 360 mg twice daily. She was diagnosed with COVID-19 when she had a low-grade fever and a non-productive cough three days prior and was started on nirmatrelvir/ritonavir 300 mg/100 mg orally twice daily in the outpatient setting. Following the absence of improvement and some new symptoms, the patient presented to the emergency room with nausea, vomiting, diarrhea, and lethargy persisting for 6 hours. Initial laboratory results were remarkable for a creatinine of

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3.58 mg/dL, increased from her baseline of 0.9 mg/dL. She was diagnosed with acute kidney injury (AKI) stage 3. The working diagnosis was AKI due to vomiting, diarrhea, and poor fluid intake prior to admission, for which she received intravenous (IV) hydration. A chest radiograph was remarkable for bilateral lower-lobe opacities. She was not a candidate for remdesivir due to her reduced glomerular filtration rate (GFR).

The morning after admission, her tacrolimus trough level was found to be supratherapeutic at 108 ng/mL. Further tacrolimus doses were held, and after 24 hours, levels had decreased but were still elevated at 75 ng/mL. To enhance the metabolism of tacrolimus, IV phenytoin was given for its CYP3A-inducing properties. Tacrolimus levels normalized three days later to 6.5 ng/mL. After normalization of levels, tacrolimus was restarted at a lower dose. Her renal functions were also gradually improving. Later, during her hospital course, she experienced hypoxia related to the COVID-19 infection. By this time, her GFR had improved to allow for the safe administration of remdesivir. She improved and was discharged on hospital day 10 with her kidney function at baseline. Tacrolimus levels were closely followed by the transplant team following discharge.

DISCUSSION

Tacrolimus, a calcineurin inhibitor, has been pivotal in the majority of immunosuppressive protocols for solid organ transplant recipients. Its application has demonstrated enhanced graft survival, a reduced occurrence of rejection, and improved drug tolerance, presenting fewer side effects in comparison to cyclosporine [5].

Tacrolimus undergoes primary metabolism via CYP3A and serves as a substrate for P-glycoprotein, making it susceptible to a variety of drug-drug interactions [6]. Levels need to be kept within specific, narrow ranges due to their narrow therapeutic index. Lower drug levels increase the risk of graft rejection and the appearance of donor-specific antibodies. In contrast, excessive exposure can result in various negative effects, such as nephrotoxicity, neurotoxicity, susceptibility to infections, and gastrointestinal issues [7].

Nirmatrelvir-ritonavir is a novel oral antiviral drug for use against COVID-19, given for 5 consecutive days to patients with mild to moderate disease. Nirmatrelvir/ritonavir is comprised of nirmatrelvir, a novel inhibitor of the SARS-CoV-2 main protease, and ritonavir, which functions as an inhibitor of CYP3A. This inhibition serves to reduce the metabolism of nirmatrelvir, consequently elevating its serum levels [8]. Although granted emergency use authorization by the FDA, nirmatrelvir/ritonavir is an investigational drug currently under study, and there is limited available information regarding its comprehensive safety and effectiveness [8].

Nirmatrelvir/ritonavir has demonstrated a substantial increase in tacrolimus exposure, reaching up to 40-fold, primarily due to CYP3A inhibition properties from the ritonavir component [9]. To minimize the likelihood of drug-drug interactions, it is imperative to address two crucial phases. The first involves either discontinuation or empirical adjustments to CNI dosages when initiating nirmatrelvir/ritonavir. The second phase entails either the reintroduction of CNIs or adjustment of their doses after completion of nirmatrelvir/ritonavir treatment [10].

Tang Y et al. [10] compared patients who discontinued tacrolimus while undergoing nirmatrelvir/ritonavir treatment to those who either continued or reduced their dosage. The first group exhibited lower rates of hospitalization (13.3% vs 89.9%) and tacrolimus toxicity (4% vs 78%) during the follow-up period. Despite some patients in the tacrolimus-holding group having low tacrolimus though levels throughout the 5-day treatment period, no instances of acute rejection were reported. Consequently, withholding tacrolimus at the initiation of nirmatrelvir/ritonavir treatment appears to be a straightforward and secure strategy to prevent excessive exposure.

While there are recommendations regarding the dosage of nirmatrelvir/ritonavir based on creatinine clearance (CrCl), with a caution against administration in cases with a CrCl less than 30, there are no established guidelines on the duration for which tacrolimus should be withheld or its dosage reduced. Ceasing nirmatrelvir/ritonavir results in a reduction of CYP3A inhibition, decreasing by up to 60% within the initial 24 hours and up to 90% by day 5 [11]. In a recent Letter to the Editor published in the American Journal of Transplantation, a proposed strategy was outlined, suggesting the cessation of tacrolimus for a period of 5 days during the administration of nirmatrelvir/ritonavir [12].

There have been cases documented in the literature where patients, initially prescribed nirmatrelvir/ritonavir as outpatients without discontinuing tacrolimus, later necessitated hospitalization due to adverse reactions or a significant increase in tacrolimus concentrations [13-15].

Although there is still limited data on the management of tacrolimus toxicity, there are case reports describing the utility of phenytoin and rifampin to accelerate tacrolimus metabolism and excretion, leading to a substantial decrease in tacrolimus levels [3,17,18]. Rifampin and phenytoin promote the metabolism of tacrolimus by their CYP3A and P-glycoprotein-inducing properties [17-18]. Hence, providers should take into account these medications in transplant patients hospitalized due tacrolimus toxicity resulting from

nirmatrelvir/ritonavir administration. Our case illustrates the efficacy of IV phenytoin in normalizing tacrolimus levels, which had remained elevated despite discontinuation of tacrolimus on admission.

CONCLUSION

In conclusion, this case highlights the importance of increased awareness of potential adverse interactions when prescribing new medications to patients on immunosuppressive therapy. Consideration may be given to employing nirmatrelvir/ritonavir in transplant patients using tacrolimus, provided there is a proactive strategy in place to mitigate the risk of toxicity. Similarly, for hospitalized transplant patients, prompt recognition of possible drug-drug interactions is crucial. A multidisciplinary approach involving transplant teams and pharmacists is essential to guiding management and minimizing the risk of additional organ damage. Our case further adds evidence to the literature about the practicality and efficacy of "inducers" like phenytoin and rifampin, which enhance the metabolism of tacrolimus in the context of toxicity.

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