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Drug Interaction Between Tacrolimus and Paxlovid (Nirmatrelvir/Ritonavir) in an Adolescent with Inflammatory Bowel Disease

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Abstract: The coronavirus disease of 2019 (COVID-19) led to a worldwide pandemic. The emergency use of a combination of nirmatrelvir/ritonavir (paxlovid) was approved for high-risk individuals (such as immunocompromised) testing positive for the disease. We present a patient with ulcerative colitis being treated with tacrolimus, as well as ustekinumab, who was diagnosed with COVID-19 and placed on paxlovid due to her immunosuppressed state. She stopped her tacrolimus while on paxlovid and did well clinically. Tacrolimus was restarted 12 hours after completion of paxlovid, but she became symptomatic with vomiting, headache, and malaise and was found to have a toxic tacrolimus level. Tacrolimus was stopped and symptoms resolved, but levels remained elevated for a prolonged period. There is a paucity of literature on this drug–drug interaction, and with the resurgence of COVID-19, it is important to be cognizant of the potential for adverse effects and toxicity.

Key Words: COVID-19, inflammatory bowel disease, paxlovid, tacrolimus

INTRODUCTION

The SARS-COV-2 virus, which causes the coronavirus disease of 2019 (COVID-19), has resulted in a global pandemic. As a result of the pandemic, an investigational medicine called paxlovid was granted emergency authorization for adults and children (aged 12 years and above) who tested positive for COVID-19 and were at high risk for severe infection (1).

Inflammatory bowel disease (IBD) is a chronic condition that causes inflammation in the gastrointestinal tract. The management of this disease involves the use of immunosuppressive medications such as corticosteroids and biologics. We present a case of an adolescent female on combination therapy of tacrolimus and ustekinumab for her ulcerative colitis (UC) who was started on paxlovid after testing positive for COVID-19. The patient was brought to the emergency department (ED) with suspected tacrolimus toxicity.

CASE REPORT

A 13-year-old female whose UC was in remission presented to the ED with vomiting and fatigue following the completion of paxlovid (administered 2 times a day for 5 days) treatment for COVID-19. Her UC regimen included tacrolimus (5 mg twice a day) and ustekinumab (90 mg every 8 weeks). She was on no other medications.

Tacrolimus was held with the initiation of antiviral treatment due to the previously reported risk of drug–drug interaction in the transplant literature (2–4). The patient had stable tacrolimus levels (ranging from 6 to 10.9 ng/mL) for the 5 months she was on combination therapy with ustekinumab before contracting COVID-19. Normal range of tacrolimus levels in UC is 5–10 ng/mL. Her tacrolimus trough was 10.9 ng/mL immediately before initiation of paxlovid therapy. She was restarted on tacrolimus (5 mg twice a day) 12 hours after the completion of paxlovid therapy. She had no worsening of her gastrointestinal symptoms while her tacrolimus was being held. Two days later, the patient was brought to the ED for acute symptoms which included vomiting, fatigue, headaches, and myalgia. Lab results obtained revealed a toxic tacrolimus level of >60 ng/mL. Electrolytes, creatinine, Blood Urea Nitrogen, and urinalysis were within normal ranges, illustrating no renal toxicity. In addition, her hemoglobin was stable at 12.9 g/dl (normal: 12.5–16.1 g/dl) and her hematocrit was 33.8% (normal: 36–47%). After consulting with toxicology, the observed level of tacrolimus was deemed toxic due to the drug–drug interaction between paxlovid and tacrolimus. The patient was advised to discontinue the tacrolimus, allow 48 hours for washout, and obtain repeat levels. Three days later, her symptoms resolved, yet the level remained elevated at 15.8 ng/mL without evidence of renal dysfunction. Repeat tacrolimus trough after 6 days revealed a level of 2.9 ng/ml. At this point, it was decided to restart tacrolimus.

DISCUSSION

Tacrolimus is an immunosuppressant commonly used for the management of organ transplant patients. Studies have shown that tacrolimus is also an effective treatment for IBD and has been used as a bridge to biological therapy (5). Tacrolimus can result in significant adverse effects necessitating constant monitoring of its levels. At abnormally high levels, it can lead to acute or chronic kidney disease (6). The normal range of tacrolimus is referenced between 5 and 15 ng/mL (7).

Due to the rapid escalation of the COVID-19 pandemic, the antiviral medication paxlovid was approved for emergency use in high-risk patients, including those on immunosuppressant medication. Paxlovid is administered as a 5-day oral course of a combination of nirmatrelvir and ritonavir tablets twice a day (1).

This patient, who was considered high risk due to being on dual immunosuppression, was prescribed paxlovid and instructed to discontinue tacrolimus during the treatment course. This is due to reports in the transplant literature of the potential for toxicity. Tacrolimus is metabolized in the small intestine by cytochrome P450 3A4 (CYP3A4) (8). This enzyme is involved in the oxidative metabolism of molecules including many drugs (9). Ritonavir is a CYP3A enzyme inhibitor and can significantly increase the

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plasma concentration of the drugs metabolized by this enzyme (10). She restarted her tacrolimus treatment 12 hours after her last dose of paxlovid. Two days later, she arrived at the ED complaining of vomiting, fatigue, recurrent headaches, and muscle aches. Lab tests revealed her tacrolimus level was >60 ng/mL. This toxic level was concluded to be a result of the drug-to-drug interaction with paxlovid. The patient immediately stopped the tacrolimus. After 3 days, her symptoms resolved; however, repeat lab tests still revealed an elevated level of 15.8 ng/mL. After an additional 3 days, the tacrolimus level was 2.9 ng/mL and she was instructed to restart tacrolimus therapy.

This case demonstrates the importance of performing close drug monitoring of tacrolimus when combined with therapies that may induce toxicity, such as paxlovid. The perceived reason for close monitoring is related to how drug clearance time may be impacted by the addition of paxlovid. Other factors that may contribute to the length of clearance time are unknown (eg, Body Mass Index, kidney function/disease) or may vary from patient to patient. This case suggests discontinuation for a longer period than the completion of the antiviral drug course. The transplant literature supports withholding tacrolimus during paxlovid treatment (2–4). The case report by Young, et al (2) of tacrolimus toxicity in a kidney transplant patient showed prolonged elevation of tacrolimus levels for a week after stopping the antiviral. The drug-to-drug interactions between these 2 treatments may cause significant side effects with a further risk of renal toxicity. We, therefore, recommend monitoring tacrolimus levels once the paxlovid course is completed to determine the optimal time to restart, which, based on our case and the literature, may be prolonged. In addition, monitoring of renal function should be performed to ensure no evidence of nephrotoxicity when the combination is being used.

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