CLINICAL VIGNETTE

Paxlovid-induced Tacrolimus Toxicity in a Renal Transplant Recipient

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Introduction

COVID-19 is the disease caused by infection with the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which was first detected in late 2019. This virus quickly spread globally, leading the WHO to declare a pandemic in March 2020.[1] The resulting pandemic has affected humanity in countless ways, including successful deployment of new messenger RNA (mRNA) vaccine technology as well as new medications to treat the disease. Immunosuppressed patients are at particular risk for infections in general and additionally are at higher risk for potential drug-drug interactions due to multiple medications. This renal transplant recipient on maintenance tacrolimus received nirmatrelvir with ritonavir (brand name Paxlovid) for symptomatic COVID-19 infection. She was hospitalized for gastrointestinal symptoms from acute tacrolimus toxicity.

Case

A 37-year-old female with ESRD due to IgA nephropathy status post living related donor renal transplant six years prior presented to our emergency department with nausea, emesis, diarrhea, and mild tremor. She had recently travelled outside of the Los Angeles area to attend a wedding. While away, she developed fevers, chills, cough, congestion, and sore throat, four days prior to coming to our emergency department. She was initially seen three days prior to admission at a non-UCLA urgent care clinic and found to be COVID-19 positive. She was not hypoxic in clinic and was prescribed nirmatrelvir : ritonavir (Paxlovid) which she started that evening and returned to Los Angeles. She continued to have fatigue and fever and presented to UCLA immediate care for further evaluation of persistent symptoms. Nirmatrelvir : ritonavir was stopped due to potential drug-drug interaction with her tacrolimus, and she was prescribed molnupiravir (brand name Lagevrio) as an alternative treatment. She remained non-hypoxic without gastrointestinal symptoms during this visit. Labs showed a creatinine of 0.82 (around her baseline renal function with Cr 0.9-1.0), but a tacrolimus level was not drawn. Later that evening she developed diarrhea and progressive nausea and was unable to start the molnuparivir. She had difficulty taking her home immunosuppressive regimen of tacrolimus and prednisone, and could not keep liquids down, prompting her to present to our emergency department for evaluation.

Upon presentation, her fever, congestion, cough and sore throat had resolved, but she reported ongoing fatigue, severe nausea and diarrhea. Vital signs were only significant for mild tachycardia to the 90s, but physical exam also revealed a new mild tremor. Labs included WBC of 9.72 and Cr of 1.0. A non-trough tacrolimus level was also obtained with initial labs that afternoon. She was admitted to the general medicine service for her nausea and PO intolerance with transplant nephrology and infectious disease consults and was treated with IVF hydration and received remdesivir (brand name Veklury) for a three-day course as per the infectious disease consult team given her immunosuppressed state and elevated risk for disease progression. The following morning (hospital day one), her Cr was 0.9 and a tacrolimus level returned elevated at 74.3; over the day her diarrhea and fatigue resolved, and her nausea improved. By hospital day two, her nausea had also resolved, the tremor was nearly resolved, and her Cr was 1.07 with tacrolimus level 32.2. On hospital day three, her tremor and symptoms completely resolved, Cr was 1.01, and tacrolimus trough was down to 17.5. She was discharged home off tacrolimus and had repeat outpatient labs the following day (post discharge day one) with further decrease of the tacrolimus level to 9.6 leading to resumption of her prior tacrolimus dose the following day (post discharge day two).

Discussion

The spectrum of COVID-19 illness ranges from completely asymptomatic to critically ill. While many organ systems and symptoms may be involved, severity of COVID-19 illness is classified by respiratory symptoms: mild illness being symptomatic but without SOB, dyspnea, or abnormal chest imaging; moderate illness involving lower respiratory disease without hypoxia (O2 sat >94% on room air); and severe illness being respiratory symptoms with hypoxia (O2 sat <94% on room air).[2] Severe illness is an indication for hospitalization. Current guidelines recommend symptom management for all cases, and starting antiviral therapy for those at risk for progression to severe disease.[3] Nirmatrelvir/ritonavir (Paxlovid) is the first line recommended treatment (grade AIIa recommendation) for those not requiring hospitalization, with remedesivir and molnnuparivir as second and third line agents.[3] This patient was not hypoxic, but met criteria for directed treatment given her immunosuppression and risk of progression. However, solid organ transplant recipients require special consideration given their medication regimens and the potential for drug-drug interactions as was the case here.

The calcineurin inhibitors (CNI) such as tacrolimus, everolimus, and sirolimus are key immunosuppressive agents in organ transplantation, but have many drug-drug interactions. CNIs are metabolized by the Cytochrome P 450 (CYP) 3A enzyme system and any addition or alteration of medications which affect this system can impact the CNI drug level. The NIH recommendations specifically caution the use of Paxlovid with many other medications due to its drug-drug interactions as the ritonavir component is a potent inhibitor of the CY3PA enzyme system, greatly reducing the metabolism of CNIs and boosting their blood level (see Figure 1).[4,5] CNIs are dosed to targeted therapeutic levels requiring close monitoring to prevent graft rejection as well as prevent infections and acute toxic effects of supratherapeutic levels such as acute renal failure, gastrointestinal symptoms, and neurotoxicity.

The patient's goal tacrolimus trough (taken about 1 hour prior to morning dose) was between 5-8 ng/dL. The initial random tacrolimus level sent at presentation never officially resulted as was thought to be erroneous by the lab. The following morning level was 74 ng/dL, prompting the medicine team to inquire about the initial sample. They were told that the level was >120 ng/dL even after serial dilutions (120 ng/dL was the upper limit that the lab could quantify). Figure 2 presents the time course of the patient's symptoms and tacrolimus levels. This patient took the extended release formulation of tacrolimus (brand name Astagraf XL), which is taken once a day versus the standard formulation of Prograf taken twice per day. The extended release formulation's slower metabolism likely contributed to the extremely high level related to the drug-drug interaction with Paxlovid. Although not necessary in this case given the quick resolution and relatively mild symptoms without impairment of her renal graft function, CY3PA inducers such as rifampin, phenytoin, or phenobarbital could be considered to help speed the metabolism of tacrolimus by inducing the CY3PA enzyme system.[5]

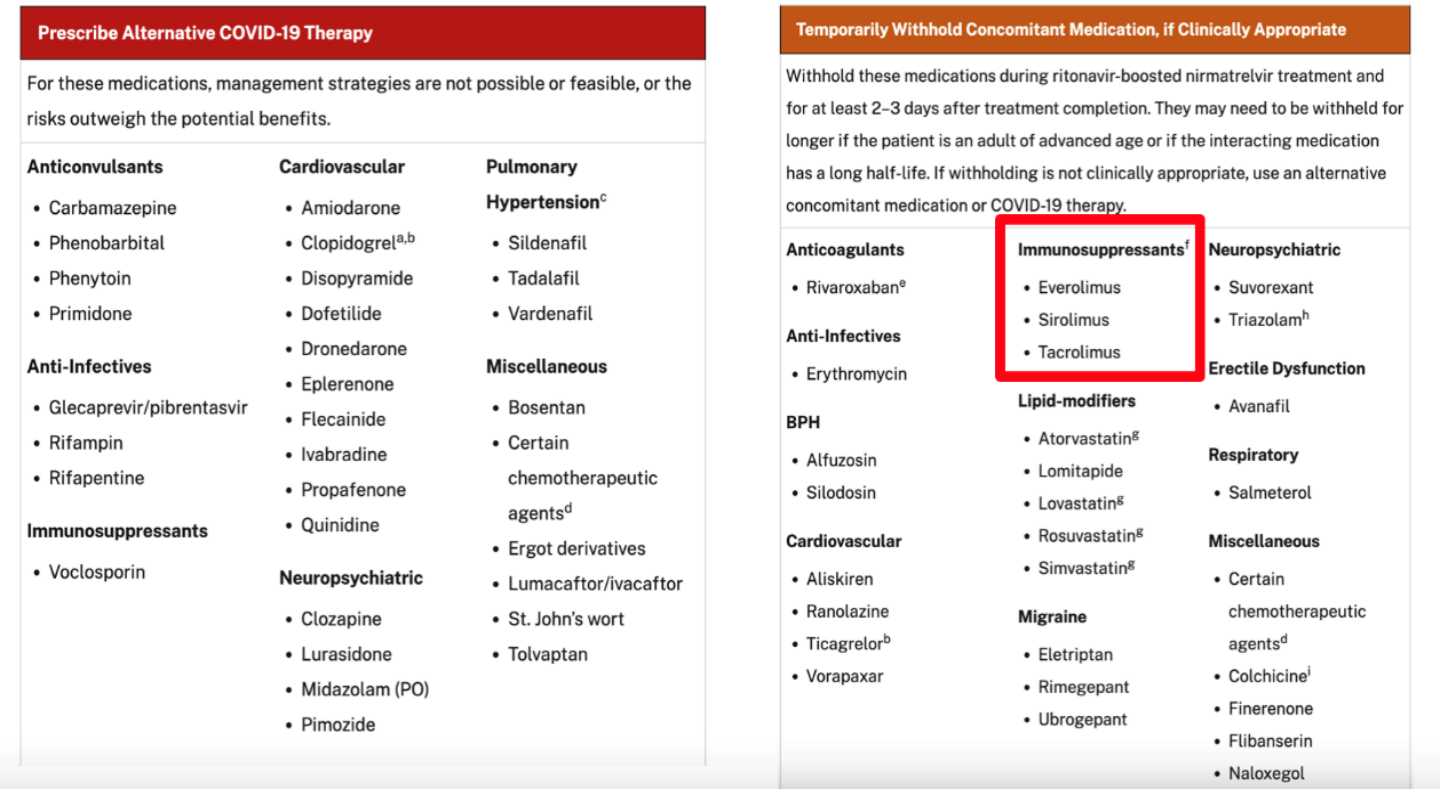

Figure 1: Paxlovid drug-drug interactions noted in NIH prescribing guidelines

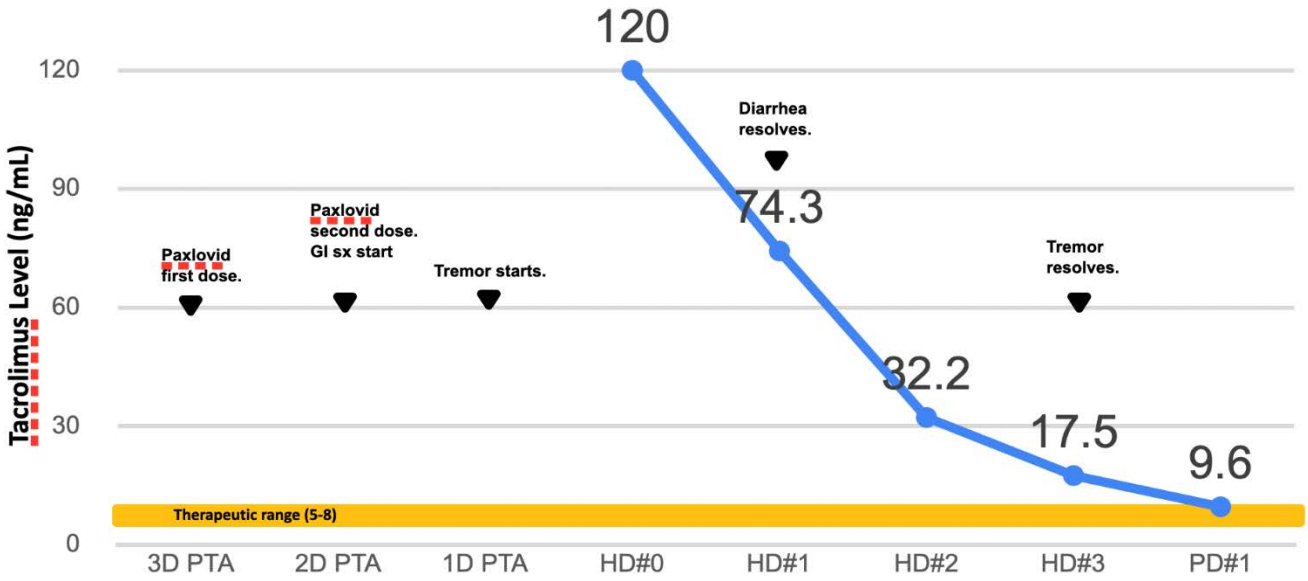

Figure 2: Clinical time course with tacrolimus levels and associated symptoms

Conclusion

As COVID-19 has evolved from pandemic to endemic, the general severity of illness has decreased, and effective therapies have been developed and deployed. Paxlovid, the current first line therapy to prevent severe disease, has many drug-drug interactions. Our patient highlights the need to always assess the risk for drug-drug interactions when prescribing or adjusting medications. While this patient was a renal transplant recipient, it is vital that all providers, not only providers familiar with the care of transplant patients, be aware of the possibility and the risk of drug-drug interactions.

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