Nirmatrelvir-ritonivir, COVID-19, and possible adverse cutaneous reactions

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Abstract

Nirmatrelvir-ritonivir (Paxlovid) recently received emergency use authorization for the treatment of coronavirus disease 2019 (COVID-19). Literature has linked numerous cutaneous adverse effects to nirmatrelvir and ritonavir, the copackaged tablets within Paxlovid. A review and comparison of these adverse effects to the common cutaneous manifestations of COVID-19 is provided. Numerous drug-to-drug interactions exist between nirmatrelvir-ritonivir and commonly-used medications within dermatology.

Keywords: COVID-19, cutaneous, drug reactions, nirmatrelvir-ritonivir, paxlovid, protease inhibitors

Introduction

Until recently, effective oral treatment of coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus two (SARS-CoV-2), has remained elusive. On December 22, 2021, the U.S. Food and Drug Administration (FDA) issued an emergency use authorization (EUA) for copackaged nirmatrelvir and ritonavir tablets for patients over the age of 12 and weighing more than 40kg [1]. This is the first oral therapy approved for home use to prevent COVID-19-related hospitalization. As nirmatrelvir-ritonivir use becomes more common, dermatologists must distinguish between disease manifestations and medication side effects. Although cutaneous adverse effects were not commonly seen during nirmatrelvir-ritonivir's clinical trials, nirmatrelvir and ritonavir themselves have numerous documented cutaneous adverse effects.

Discussion

Nirmatrelvir inhibits a novel SARS-CoV-2 protease (Mpro), [1]. Ritonavir, also a protease inhibitor, is used as a pharmacokinetic enhancer. Ritonavir's inhibition of CYP3A metabolism results in increased concentrations of nirmatrelvir [1,2]. Recommended use is to be started within five days of symptom onset for a duration of five days [1].

Protease inhibitors have been employed in the treatment of human immunodeficiency virus (HIV) and hepatitis C. Cutaneous side effects are well documented in early generation medications, with an incidence of adverse skin events ranging from 2-28% [2]. Although, as next generation medications are developed, adverse effects are becoming less

Table 1. *Commonly prescribed dermatology medications affected by nirmatrelvir-ritonivir [1].*

Therapeutic Class	Drug Name	Comments
Oral Antibiotics	Erythromycin	Increased drug concentration.
	Clarithromycin	
Systemic Immunosuppressant	Cyclosporin	Increased drug concentration. Therapeutic concentration monitoring of immunosuppressant is recommended.
	Tacrolimus	
	Sirolimus	Avoid concomitant use with Paxlovid.
Systemic Steroids	Betamethasone	Increased drug concentration. Increased risk for Cushing's syndrome and adrenal suppression. Consider using alternatives such as beclomethasone and prednisolone in patients using Paxlovid.
	Budesonide	
	Dexamethasone	
	Methylprednisolone	
	Prednisone	
Oral Antifungal	Voriconazole	Avoid concomitant use with Paxlovid.
	Ketoconazole	Increased drug concentration.
	Isavuconazonium sulfate	
	Itraconazole	

common [3]. Despite patients requiring 8-12 weeks of treatment for hepatitis C and lifelong maintenance for HIV, adverse skin events are more likely to present within days of treatment initiation [4].

Most protease inhibitor cutaneous side effects are reported to be mild, yet Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug rash with eosinophilia and systemic symptoms (DRESS), and erythema multiforme have been observed [3]. Per the drug label, nirmatrelvir-ritonivir is contraindicated in patients with a significant history of hypersensitivity reactions (TEN or SJS) to either active ingredients or components of the drug formulation [1].

Ritonavir itself has been reported to cause circumoral paresthesia in up to one-third of patients, yet it has few observed cutaneous side effects [2]. Critical to a dermatologist's practice is an awareness of potential drug-drug interactions. Commonly prescribed agents impacted by nirmatrelvir-ritonivir drug interactions include, but are not limited to, antifungals, antibiotics, immunosuppressants, and systemic corticosteroids (**Table 1**).

As new medications emerge, the healthcare field will rely on dermatologists to differentiate cutaneous COVID-19 manifestations and adverse reactions of treatment [5]. **Table 2** compares the presentation of common skin complaints from COVID-19 to protease inhibitors.

Table 2. *Common cutaneous manifestations of COVID-19 in comparison with protease inhibitors, similar to nirmatrelvir-ritonivir.*

COVID-19	Protease inhibitors
Maculopapular/ morbilliform eruptions [4,5]	Stevens-Johnson Syndrome [3]
Acral pseudo-chilblain lesions [4,5]	Toxic epidermal necrolysis [3]
Urticaria [4,5]	Drug rash with eosinophilia and systemic symptoms [3]
Papulovesicular rash [4,5]	Maculopapular/morbilliform eruption [2-4]
Livedo [4,5]	Urticaria [2,4]
Petechiae, purpura [4,5]	Erythema multiforme [3]
	Pruritis [3]
	Circumoral paresthesia [2]
	Lipodystrophy [2,4]
	Oral mucosal lesions [4]
	Leg edema [4]
	Alopecia [4]
	Lichenoid eruptions [4]
	Xeroderma [4]
	Vesicular rash [4]

Conclusion

Nirmatrelvir-ritonivir is the latest therapeutic addition in the ongoing battle against COVID-19. With a new protease inhibitor introduced into mainstream treatment, dermatologists must be aware of potential adverse effects and drug-drug interactions and should document any observed cutaneous manifestations suspected to be a result of therapy.

Potential conflicts of interest

Dr. Dellavalle receives editorial stipends (*Journal of Investigative Dermatology, Journal of Medical Internet Research*), royalties (UpToDate®), and expense reimbursement from Cochrane Skin.

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