

Drug interactions between common dermatological medications and the oral anti-COVID-19 agents nirmatrelvir-ritonavir and molnupiravir

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ABSTRACT

Introduction: The oral antiviral agents nirmatrelvir-ritonavir (NMV/r) and molnupiravir are used to treat mild-to-moderate COVID-19 infection in outpatients. However, the use of NMV/r is complicated by significant drug-drug interactions (DDIs) with frequently prescribed medications. Healthcare professionals should be aware of the possible risk of DDIs, given the emergence of COVID-19 variants and the widespread use of oral COVID-19 treatments. We reviewed available data on DDIs between NMV/r, molnupiravir and common dermatological medications; summarised the potential side effects; and suggest strategies for safe COVID-19 treatment.

Method: A systematic review using PubMed was conducted on data published from inception to 18 July 2022 to find clinical outcomes of DDIs between NMV/r, molnupiravir and dermatological medications. We also searched the Lexicomp, Micromedex, Liverpool COVID-19 Drug Interactions database and the National Institutes of Health COVID-19 Treatment Guidelines for interactions between NMV/r and molnupiravir, and commonly used dermatological medications.

Results: NMV/r containing the cytochrome P-450 (CYP) 3A4 inhibitor ritonavir has DDIs with other medications similarly dependent on CYP3A4 metabolism. Dermatological medications that have DDIs with NMV/r include rifampicin, clofazimine, clarithromycin, erythromycin, clindamycin, itraconazole, ketoconazole, fluconazole, bilastine, rupatadine, dutasteride, ciclosporin, cyclophosphamide, tofacitinib, upadacitinib, colchicine and systemic glucocorticoids. With no potential DDI identified yet in in vitro studies, molnupiravir may be an alternative COVID-19 therapy in patients taking medications that have complicated interactions with NMV/r, which cannot be stopped or dose adjusted.

Conclusion: NMV/r has significant DDIs with many common dermatological medications, which may require temporary discontinuation, dosage adjustment or substitution with other anti-COVID-19 agents such as molnupiravir.

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INTRODUCTION

In December 2021, an Emergency Use Authorisation was issued by the U.S. Food and Drug Administration (FDA) for the use of the orally active antiviral medications nirmatrelvir-ritonavir (NMV/r, PAXLOVID) and molnupiravir (LAGEVRIO) in the treatment of patients with mild COVID-19, who are at risk of developing severe disease resulting in hospital admission or mortality.^{1,2}

Unfortunately, the use of oral COVID-19 therapies is complicated by their significant drug-drug interactions (DDIs) with many medications. With the emergence of highly transmissible dominant variants such as the Omicron strain and its new subvariants BA.2.12.1, BA.4 and BA.5, coupled with the increasing use of oral COVID-19 therapies and the widespread use of dermatological medications by patients, it is crucial for physicians to recognise DDIs involving the most widely

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CLINICAL IMPACT

What is New

- To our knowledge, this is currently the most comprehensive and in-depth review on drug-drug interactions (DDIs) between the 2 current oral anti-COVID-19 agents—nirmatrelvir-ritonavir (NMV/r) and molnupiravir—and dermatological medications.

Clinical Implications

- Physicians should be aware of and cautious about possible DDIs when prescribing NMV/r in patients taking concomitant medications, including dermatological drugs.
- Molnupiravir may be a suitable substitute anti-COVID-19 agent for NMV/r, particularly when potential complicated DDIs have been identified between NMV/r and medications.

used COVID-19 oral agent, NMV/r, and dermatological medications. This can help to support safe decision-making and initiation of COVID-19 treatment as soon as possible after diagnosis, preferably within 5 days of symptom onset.

We aimed to consolidate and review available data on DDIs between NMV/r, molnupiravir and dermatological medications. We also aimed to provide a summary of potential adverse events, details of the expected duration of the *CYP3A4* gene-related inhibitory effect of ritonavir; and to suggest an appropriate management of co-medications that can potentially interact with NMV/r and molnupiravir.

METHOD

A systematic review (protocol registered with PROSPERO, CRD 42022346065) was conducted to identify the clinical outcomes of DDIs between NMV/r, molnupiravir and dermatological medications, using PubMed from inception to 18 July 2022. The search terms used were: dermatology* AND (nirmatrelvir OR ritonavir OR molnupiravir OR Paxlovid OR Lagevrio). Clinical studies reporting DDI between dermatological drugs and NMV/r or molnupiravir were included in the review. Articles without mention of DDI in the title or abstract were excluded. Conference articles, clinical images/photographic quizzes, as well as pharmacokinetic investigations without clinical outcomes were also excluded. Two authors independently reviewed the titles

and abstracts, and the relevant papers were then selected for full-text review. Any disagreement was resolved by discussion with a third author.

The Lexicomp, Micromedex, Liverpool COVID-19 Drug Interactions database, and the National Institutes of Health COVID-19 Treatment Guidelines were also searched for DDIs between NMV/r and molnupiravir with commonly used dermatological medications from the time of inception to 18 July 2022. Lexicomp and Micromedex were selected as the drug interaction resources because of their completeness, accuracy and ease of use.^{3,4} The Liverpool COVID-19 Drug Interactions⁵ checker is a user-friendly and leading database for DDI with anti-COVID-19 drugs. Apart from their extensive DDI databases, these sources also conduct regular surveillance of ongoing pharmacovigilance and pharmaceutical publications, as well as announcements on new drug developments. In view of the inconsistency among drug interaction resources, we used more than one drug interaction resource.⁶

To predict potential drug interactions with NMV/r or molnupiravir concerning drugs without information in all 4 drug interaction resources, we referred to the pertinent drug monograph to determine whether the drug is an inhibitor, inducer, or substrate of the drug-metabolising enzymes (expressed by the following genes: *CYP3A4*, *CYP2D6*, *CYP2B6*, *CYP2C19*, *CYP2C9* and *CYP1A2*) and the P-glycoprotein. P-glycoprotein—also known as multidrug resistance protein 1, adenosine triphosphate (ATP)-binding cassette subfamily B member 1, and cluster of differentiation 243—is an important ATP-dependent efflux pump with broad substrate specificity, which transports many foreign substances out of the cells.

For drugs identified independently by 2 authors to have clinically significant interactions with NMV/r or molnupiravir, the individual drug prescribing information was reviewed for recommended actions, including the need for withdrawal, dosage reduction or continued use with close monitoring. Any disagreement was resolved by discussion, and further issues were escalated to a third author.

RESULTS

A total of 54 studies were screened, but none of the studies was relevant to be included in the systematic review. The published drug interaction resources, however, generated sufficient data to support our analysis, based on the drug monographs associated with NMV/r and molnupiravir, and on inferences from studies on ritonavir and other CYP450 3A4 enzyme inhibitors.

DISCUSSION

Nirmatrelvir-ritonavir (NMV/r)

Nirmatrelvir is an orally effective SARS-CoV-2 3-chymotrypsin-like protease inhibitor involved in the prevention of viral replication in COVID-19 and other coronavirus infections. It is co-administered with ritonavir, a pharmacoenhancer and strong CYP450 3A4 enzyme inhibitor, to inhibit the metabolism of nirmatrelvir, a CYP3A4 substrate, to maintain the plasma drug concentration at therapeutic levels.⁷

NMV/r is currently the most effective oral antiviral therapy for COVID-19.⁸ However, NMV/r might not be suitable for all patients due to its potential for significant DDIs with co-administered medications.

Drug-drug interactions

The main target molecules of DDIs of NMV/r include other CYP3A4 substrates, with ritonavir-mediated CYP3A4 inhibition, maximal within 48 hours from the first dose of NMV/r, producing an increase in drug plasma concentration, and in the risk of concentration-dependent toxicity.⁹ The concomitant administration of NMV/r with CYP3A4 inhibitors raises the risk of adverse effects from NMV/r. In contrast, CYP3A4 inducers cause a significant reduction of antiviral therapeutic effect, with a potential for the development of viral resistance.

As ritonavir is an irreversible CYP3A4 inhibitor, these DDIs persist even after its discontinuation because time is required for the reduction in CYP3A4 inhibition through synthesis of new CYP3A4 enzyme in the microsomes of liver cells. A significant 80% resolution of CYP3A4 inhibition occurs by 48 hours and 72 hours after the last dose of NMV/r, in adults aged 20–50 years and >60 years, respectively.¹⁰ Hence, in most individuals, a 3-day rule can effectively guide the management of DDI with NMV/r, since medications that interact with NMV/r may be safely restarted, or alternatively restored to their original dose, 3 days after the last dose of NMV/r.¹⁰

As the duration of NMV/r treatment for COVID-19 is only 5 days, many long-term dermatological medications with known drug interactions may be withdrawn or dose adjusted, where clinically appropriate, for a short 8 days to allow for safe treatment with NMV/r. Since NMV/r is currently the only highly effective oral antiviral therapy against COVID-19, DDI should be managed where feasible to allow its use.⁸

Systemic glucocorticoids

Short courses of oral glucocorticoids are used to treat severe acute exacerbations of atopic dermatitis. Many

commonly used glucocorticoids, such as prednisolone and prednisone, are dependent on CYP3A4-mediated metabolism. Thus, co-administration with NMV/r can increase systemic glucocorticoid exposure and the risk of adverse effects, such as hyperglycaemia, adrenal suppression and Cushing's syndrome.¹¹ Recommendations include careful monitoring for the adverse effects.

Systemic immunomodulators

Cyclosporin is a calcineurin inhibitor used to prevent organ rejection. It is also used to treat severe resistant atopic dermatitis and psoriasis. As cyclosporin is primarily metabolised by hepatic and intestinal CYP3A4 enzymes, ritonavir-mediated CYP3A4 inhibition during concomitant administration will greatly elevate its plasma concentrations, with a significantly increased risk of cyclosporin toxicity, including nephrotoxicity, systemic hypertension and hepatotoxicity.¹² Vogel et al. demonstrated the interaction between ritonavir-boosted antiretroviral therapy and cyclosporin in liver transplant human immunodeficiency virus-infected patients.¹³ They were observed to have flattening of absorption/elimination curves with little changes in plasma levels of cyclosporin over 12 hours and an increase of terminal half-life from 4–6 hours up to 38 hours.¹³ Even though cyclosporin doses in liver-transplant patients are much higher than those for dermatology patients, elevated cyclosporin levels due to slower clearance is expected with dermatological use of cyclosporin. In view of a significantly increased risk of cyclosporin toxicity during concomitant administration with NMV/r, it is recommended to discontinue cyclosporin during NMV/r treatment, and resume it 3 days after the last dose of NMV/r.

Cyclophosphamide, an alkylating agent, is used in cytotoxic chemotherapy for cutaneous T-cell lymphomas and in the treatment of severe, refractory autoimmune skin conditions.¹⁴ It is administered as a prodrug requiring activation by hepatic CYP450 enzymes, including CYP2B6 and to a lesser extent, CYP3A4. As ritonavir is a CYP2B6 inducer, the concomitant use of cyclophosphamide with NMV/r results in increased risk for toxic effects such as oral mucositis and neutropaenia, for which patients must be monitored carefully.¹⁵ Patients with genetic variants associated with reduced CYP2B6 function may be less affected than those with increased CYP2B6 function.¹⁶

Janus kinase (JAK) inhibitors are a relatively new treatment for autoimmune diseases such as psoriatic arthritis, for which tofacitinib and upadacitinib have both been approved for use—the latter recently approved by FDA for atopic dermatitis as well.^{17,18}

The metabolism of both tofacitinib and upadacitinib is mediated primarily by hepatic CYP3A4, hence elevated plasma concentrations of the active drugs occur in co-administration with NMV/r via ritonavir-mediated CYP3A4 inhibition. For tofacitinib, a maximum of 5mg once-daily dosing of the immediate-release formulation is recommended.¹⁷ For upadacitinib, a maximum daily dose of 15mg is recommended.¹⁸ Dose reductions should be carried out throughout the NMV/r treatment and for another 3 days from completion of the last NMV/r dose.

Abrocitinib, another JAK inhibitor recently approved for use in atopic dermatitis, is less dependent on CYP3A4 metabolism. Although elevated plasma concentrations are expected in co-administration of abrocitinib with NMV/r, their interaction has not been identified as clinically significant and there are no recommendations for dose adjustments or additional monitoring.¹⁹

Acitretin, apremilast, azathioprine, dimethyl fumarate, methotrexate, mycophenolate mofetil and sulfasalazine may be safely co-administered with NMV/r without expected clinically significant interaction. However, the risk of immunosuppressants such as azathioprine, methotrexate and mycophenolate mofetil exacerbating the COVID-19 infection should be weighed against the risk of a flare-up of the dermatological condition, before deciding whether to continue immunosuppressants during the COVID-19 infection.²⁰

Biologicals

Treatment with biologicals (Table 1) may be safely continued during treatment with NMV/r, without dose adjustment or additional clinical monitoring, if the patient is clinically indicated to continue biologicals during the COVID-19 infection.

Antibacterial drugs

Macrolides such as clarithromycin and erythromycin are indicated for use in acne, rosacea, and staphylococcal skin infections. When co-administered with NMV/r, the CYP3A4-mediated metabolism of clarithromycin and erythromycin is inhibited by ritonavir, and the raised plasma concentration of these macrolides increases the risk of side effects (e.g. hepatotoxicity and QT-interval prolongation).^{21,22} For erythromycin, it is recommended to stop use and replace it with other antibacterial drugs with less interaction with NMV/r. Examples include replacing erythromycin with tetracycline-class drugs for acne and rosacea, and penicillins or cephalosporins for staphylococcal skin infections, barring any drug hypersensitivity. For clarithromycin, which is less

Table 1. Preferred systemic dermatologic medications during nirmatrelvir-ritonavir use^a

Immunomodulators	Anti-acne agents
Acitretin	Isotretinoin
Apremilast	Spironolactone
Azathioprine	
Baricitinib	Hair agents
Dimethyl fumarate	Finasteride
Methotrexate	Minoxidil
Mycophenolate mofetil	
Sulfasalazine	Antibiotics
	Azithromycin
Biologicals	Cephalosporins
Adalimumab	Dapsone
Anakinra	Isoniazid
Certolizumab	Metronidazole
Dupilumab	Penicillins
Etanercept	Pyrazinamide
Guselkumab	Sulfonamides
Infliximab	Tetracyclines
Ixekizumab	Tinidazole
Omalizumab	
Risankizumab	Antifungals
Rituximab	Griseofulvin
Secukinumab	Nystatin
Spesolimab	Terbinafine
Tildrakizumab	
Ustekinumab	Antivirals
	Aciclovir
Antihistamines	Valaciclovir
Buclicine	
Chlorpheniramine	Antiscabetic agent
Desloratadine	Ivermectin
Diphenhydramine	
Loratadine	Miscellaneous: Statins
	Fluvastatin
	Pravastatin

^a Consult the Liverpool COVID-19 Drug Interactions website⁵ for updated drugs

Superscript number: refer to REFERENCES

dependent on CYP3A4 metabolism than erythromycin, careful monitoring for adverse effects is suggested, with dose reduction required only in patients with renal impairment (Kidney Disease Improving Global Outcomes stage ≥ 3 , with creatinine clearance [CrCl] ≤ 60 mL/min). Clarithromycin prescribing information suggests dose reduction by 50% and 75% in patients with CrCl 30–60 mL/min and <30 mL/min, respectively.²²

However, on use of clarithromycin in non-tuberculous mycobacterial infections, replacement by another antibiotic is recommended. Although co-administration of clarithromycin and ritonavir in NMV/r increases the plasma concentration of clarithromycin, there is a reduction in plasma concentration of the active metabolite 14-OH-clarithromycin. The efficacy of clarithromycin treatment might thus be compromised, and the physician should consider replacement with other antibiotics as appropriate.²²

Clindamycin and clofazimine are 2 other antibacterials that depend on CYP3A4 metabolism, and therefore require careful monitoring for adverse effects.

Rifampicin, an anti-tuberculosis agent, is also used in patients with hidradenitis suppurativa, as well as in staphylococcal and non-tuberculous mycobacterial infections.²³ As a potent CYP3A4 inducer, the co-administration of rifampicin with NMV/r would produce decreased plasma concentrations of ritonavir, a CYP3A4 substrate. This can significantly decrease the therapeutic effect of NMV/r, leading to poor treatment outcomes and promoting the development of viral resistance to NMV/r.²⁴ Also, as the induction of CYP3A4 by rifampicin persists for a long time after discontinuation, it is not sufficient to stop rifampicin use before starting NMV/r therapy.⁷ Therefore, it is recommended to consider an alternative COVID-19 treatment, such as molnupiravir, for patients on rifampicin.

Table 1 shows antibacterial drugs often used in skin disorders. The drugs lack an expected interaction with NMV/r, and may be safely continued during NMV/r treatment without dose adjustments or additional monitoring.

Antifungal agents

Systemic azoles, including fluconazole, itraconazole and ketoconazole, are commonly prescribed as oral treatment in extensive or resistant dermatophyte infections, pityriasis versicolor, and other cutaneous fungal infections. All the 3 azoles have significant DDIs with NMV/r as they inhibit CYP3A4 and would produce both raised plasma concentrations of NMV/r, and an increased risk of NMV/r adverse effects. Moreover, itraconazole and ketoconazole are also substrates of CYP3A4, and ritonavir-mediated CYP3A4 inhibition increases the bioavailability and plasma concentrations of these 2 azoles. This raises the risk of side effects, including gastrointestinal symptoms, transaminitis and QT-interval prolongation due to ketoconazole.

The recommendations for fluconazole include careful electrocardiogram (ECG) monitoring, as both fluconazole and ritonavir are known to prolong the QT interval; their concomitant use therefore increases the risk of an additive effect.²⁵ For itraconazole and ketoconazole, dose reduction to a maximum of 200mg daily is suggested, on top of monitoring for side effects.^{26,27}

Antiparasitic agents

The antihelminthic agent albendazole, when co-administered with ritonavir, decreases the plasma albendazole concentration.²⁸ Thus, monitoring for a

reduced clinical response to albendazole therapy is proposed in co-administration with NMV/r.

Antihistamines

Antihistamines are one of the most commonly prescribed drugs in dermatology, ranging from use in pruritic skin dermatoses to cutaneous hypersensitivity reactions, such as urticaria and angioedema.

Hydroxyzine is dependent on hepatic CYP3A4 metabolism; co-administration with the CYP3A4-inhibitor ritonavir will result in elevated hydroxyzine plasma concentrations, increasing the risk of adverse effects, such as QT-interval prolongation.²⁹ Recommendations include close ECG monitoring for a prolonged QT interval.

Bilastine and rupatadine are second-generation antihistamines with significant drug interactions with NMV/r, as they are dependent on P-glycoprotein-mediated efflux and CYP3A4 metabolism, respectively—both processes which are inhibited by ritonavir. The resultant increase in plasma concentrations of these antihistamines increases the risk of side effects like QT-interval prolongation. The Lexicomp Drug Interactions resource lists both bilastine and rupatadine as contraindicated for concomitant use during ritonavir administration.^{30,31} Discontinuation of these antihistamines during the NMV/r treatment course and for an additional 3 days after the last dose of NMV/r is recommended.

Other second-generation antihistamines, such as cetirizine, fexofenadine and loratadine are also dependent on P-glycoprotein-mediated efflux and CYP3A4 metabolism. Drug interaction with ritonavir may result in increased central antihistaminic effects, including drowsiness and prolonged reaction times, but with a minimal risk of severe adverse effects such as QT-interval prolongation. As such, no dosage adjustment or additional monitoring is suggested.

The preferred choices of antihistamines during NMV/r treatment include desloratadine, chlorpheniramine, diphenhydramine and buclizine, for which no clinically significant interactions are expected.

Anti-acne agents

Oral contraceptives with anti-androgenic properties are widely used in treating acne and hirsutism, and in polycystic ovarian syndrome with underlying hyperandrogenism and adult female acne. The synthetic oestrogen ethinylloestradiol is contained in combined oral contraceptive pills (COCPs) with various progestogens (progestins). In co-administration with

ritonavir, the bioavailability and plasma concentration of ethinyloestradiol decrease, probably via ritonavir-mediated induction of CYP2C9 and CYP1A2. On the other hand, progestogen is primarily metabolised by CYP3A4, and elevated plasma progestogen results from the drug interaction with ritonavir, thus raising the risk of side effects, including irregular menstrual bleeding and venous thrombosis. Other side effects with certain progestogens include the risk of hyperkalaemia with drospirenone, as well as hepatotoxicity and hot flashes with cyproterone acetate. Recommendations for co-administration of progestogen-only pills or COCPs with NMV/r include careful monitoring for adverse effects. Patients taking COCPs should be advised to consider additional non-hormonal (i.e. barrier) contraceptives for the prevention of pregnancy during and up to 1 menstrual cycle after completing the course of NMV/r,⁷ although a clinically significant reduction in contraceptive efficacy is unlikely to result from a decreased plasma concentration of ethinyloestradiol during the standard short course of NMV/r.

Hair agents

Dutasteride and finasteride have been shown to be effective in the treatment of male androgenetic alopecia via the inhibition of dihydrotestosterone production. Of these 2 medications, dutasteride depends on CYP3A4 metabolism; drug interaction with the CYP3A4 inhibitor ritonavir elevates the plasma dutasteride concentration, and increases the risk of side effects, including erectile dysfunction and libido reduction. Close monitoring for the adverse effects is suggested for dutasteride, if used concomitantly with NMV/r.³² For finasteride, no additional monitoring is needed.

Topical and oral minoxidil are also used in the treatment of androgenetic alopecia. Minoxidil is not expected to have DDI with NMV/r, and systemic treatment may be safely continued without dosage adjustment or additional monitoring.

Other drugs commonly prescribed for dermatology patients

Colchicine is an anti-gout agent, and also used in treating skin disorders (e.g. leukocytoclastic and urticarial vasculitis, and neutrophilic dermatoses, including Sweet's syndrome). Colchicine is primarily dependent on hepatic CYP3A4 metabolism; co-administration with the potent CYP3A4 inhibitor ritonavir greatly increases plasma colchicine concentrations, thereby risking potentially life-threatening acute colchicine toxicity, which encompasses severe gastrointestinal symptoms,

seizures, bone marrow suppression and multiorgan failure.³³ The use of colchicine during NMV/r treatment is therefore contraindicated. If colchicine therapy is required in a patient who is taking or has taken NMV/r within the last 14 days, and there are no appropriate alternatives, dose reduction of colchicine is recommended (Table 2).³⁴

Dyslipidaemia is common in the general population. In dermatology, abnormal plasma lipoproteins occur particularly in patients with psoriasis and hidradenitis suppurativa, which are conditions linked to the metabolic syndrome; and in patients receiving medications such as retinoids (e.g. isotretinoin and acitretin) and ciclosporin, which predispose to dyslipidaemia.³⁵ As the 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors lovastatin, simvastatin and to a lesser degree, atorvastatin, primarily depend on CYP3A4 metabolism, their co-administration with the CYP3A4-inhibitor ritonavir can increase risks of statin-related myopathy and rhabdomyolysis. Lovastatin and simvastatin intake should cease at least 12 hours before the first dose of NMV/r, during NMV/r treatment, and for another 3 days after the last NMV/r dose.³⁶ For atorvastatin, brief cessation, or dose reduction to 10mg daily with resumption of its usual dose 3 days after completing NMV/r treatment, is recommended. Rosuvastatin is known to have an elevated plasma concentration when co-administered with ritonavir.³⁶ Thus, recommendations for rosuvastatin are similarly to stop temporarily or reduce dose to 10mg daily until 3 days after completing NMV/r treatment. Neither pravastatin nor fluvastatin are expected to have clinically significant interactions with NMV/r.

Molnupiravir

As of December 2022, the use of molnupiravir is still under Emergency Use Authorisation by FDA.³⁷ Molnupiravir has yet to be authorised for use in the European Union.³⁸ In Singapore, molnupiravir (LAGEVRIO) has been granted interim authorisation for the treatment of mild to moderate COVID-19 in patients aged ≥ 18 years, and are at risk of progression to severe COVID-19 and/or hospitalisation, as well as in cases when alternative COVID-19 treatment cannot be used.³⁹

Molnupiravir is administered as a prodrug, subsequently converted to the active metabolite β -D-N⁴-hydroxycytidine (NHC), phosphorylated, and incorporated by viral ribonucleic acid (RNA) polymerase into viral RNA, thereby inhibiting viral replication.⁴⁰ Further studies are needed to explore any potential long-term mutagenic effects of molnupiravir to the host.⁴¹

Table 2. Summary of drug interactions between nirmatrelvir-ritonavir (NMV/r) and dermatologic medications^a

Drugs	Common indications	Expected interaction with NMV/r/effect on plasma drug concentration	Potential adverse effects	Recommended action
Systemic corticosteroids				
Dexamethasone	Vitiligo	↑ Dexamethasone (Dependent on CYP3A4 metabolism)	Systemic glucocorticoid effects (hyperglycaemia, Cushing's syndrome, adrenal suppression)	Careful monitoring for adverse effects. (Lexicomp Risk Rating C, Micromedex Severity: Major)
Hydrocortisone	Angioedema Anaphylaxis	↑ Hydrocortisone (Dependent on CYP3A4 metabolism)		Careful monitoring for adverse effects. (Lexicomp Risk Rating C) Micromedex Drug Reference indicates no drug interactions.
Methylprednisolone	Pemphigus	↑ Methylprednisolone (Dependent on CYP3A4 metabolism)		Careful monitoring for adverse effects. (Lexicomp Risk Rating C, Micromedex Severity: Major)
Prednisolone	Allergic contact dermatitis Atopic dermatitis Bullous pemphigoid Pemphigus Urticaria Vitiligo	↑ Prednisolone (Dependent on CYP3A4 metabolism)		Careful monitoring for adverse effects. (Lexicomp Risk Rating C) Micromedex Drug Reference indicates no drug interactions.
Prednisone	Allergic contact dermatitis Angioedema Urticaria	↑ Prednisone (Dependent on CYP3A4 metabolism)		Careful monitoring for adverse effects. (Lexicomp Risk Rating C, Micromedex Severity: Major)
Immunomodulators				
Abrocitinib	Atopic dermatitis	↑ Abrocitinib (Dependent on CYP3A4 metabolism)		No dose adjustment or additional monitoring necessary.
Ciclosporin	Atopic dermatitis Psoriasis	↑ Ciclosporin (Dependent on CYP3A4 metabolism)	Renal impairment Hypertension	Stop use of ciclosporin during treatment and resume 3 days after last dose of NMV/r. If unable to stop ciclosporin, consider alternative COVID-19 treatment. (Liverpool Drug Interactions checker) (Lexicomp Risk Rating D, Micromedex Severity: Major)
Cyclophosphamide	Autoimmune diseases Dermatomyositis Mycosis fungoides	↑ Cyclophosphamide (Dependent on CYP3A4 and CYP2B6 metabolism)	Oral mucositis Neutropenia Infection	Careful monitoring for adverse effects. (Lexicomp Risk Rating C, Micromedex Severity: Major)
Tofacitinib	Psoriatic arthritis	↑ Tofacitinib (Dependent on CYP3A4 metabolism)	Transaminitis Neutropenia Infection	Dose reduction to 5mg once daily. Avoid tofacitinib XR and replace with immediate-release tofacitinib. ¹⁷ (Lexicomp Risk Rating D, Micromedex Severity: Moderate)

Table 2. Summary of drug interactions between nirmatrelvir-ritonavir (NMV/r) and dermatologic medications^a (Cont'd)

Drugs	Common indications	Expected interaction with NMV/r/effect on plasma drug concentration	Potential adverse effects	Recommended action
Upadacitinib	Atopic dermatitis Psoriatic arthritis	↑ Upadacitinib (Dependent on CYP3A4 metabolism)	Infection Thrombosis	Careful monitoring for adverse effects at upadacitinib 15mg/day dosing. ¹⁸ Avoid higher doses of upadacitinib during NMV/r treatment and 3 days after completion of NMV/r treatment. (Lexicomp Risk Rating D)
Antibiotics				
Clarithromycin	Acne Rosacea Staphylococcal skin infections Nontuberculous mycobacterium infections	↑ Clarithromycin but ↓ clarithromycin active metabolites (Dependent on CYP3A4 metabolism)	Hepatotoxicity QT-interval prolongation	Consider alternative antibiotics for mycobacterial infections as efficacy may be compromised. (Micromedex, Lexicomp) Careful monitoring for adverse effects especially in patients with renal impairment. No dose adjustment necessary in patients with normal renal function. Avoid clarithromycin doses greater than 1,000mg/day. Dosage should be reduced by 50% and 75% in patients with CrCl 30–60mL/min and <30mL/min, respectively. ²² (Lexicomp Risk Rating D, Micromedex Severity: Major)
Clindamycin	Hidradenitis suppurativa Staphylococcal skin infections	↑ Clindamycin (Dependent on CYP3A4 metabolism)	Gastrointestinal symptoms Nephrotoxicity	Careful monitoring for adverse effects. (Lexicomp Risk Rating C; however, Micromedex states no drug interactions)
Clofazimine	Leprosy	↑ Clofazimine (Dependent on CYP3A4 metabolism)	QT-interval prolongation	Careful monitoring for adverse effects, including ECG monitoring. (Lexicomp Risk Rating C, Micromedex Severity: Major)
Erythromycin	Acne Rosacea Staphylococcal skin infections	↑ Erythromycin (Dependent on CYP3A4 metabolism)	Gastrointestinal symptoms Hepatotoxicity QT-interval prolongation	Stop and replace with another antibiotic that has less interaction with NMV/r. Alternatively, carefully monitor for adverse effects and consider dose reduction. (Lexicomp Risk Rating C, Micromedex Severity: Major)
Rifampicin	Hidradenitis suppurativa Staphylococcal skin infections Nontuberculous mycobacterium infections	↓ NMV/r (rifampicin is a CYP3A4 inducer)	Reduced therapeutic effects of NMV/r Risk of loss of virological response	Concomitant use of rifampicin is contraindicated. Consider alternative COVID-19 treatment or antimycobacterial therapy (e.g. rifabutin) or alternative treatment for hidradenitis suppurativa. (Lexicomp Risk Rating X, Micromedex Severity: Contraindicated)
Antifungals				
Fluconazole	Dermatophyte infections Pityriasis versicolor Candidiasis	↑ NMV/r (fluconazole is a CYP3A4 inhibitor)	Gastrointestinal symptoms Transaminitis QT-interval prolongation	Careful monitoring for adverse effects, including ECG monitoring. (Lexicomp Risk Rating C, Micromedex Severity: Contraindicated)

Table 2. Summary of drug interactions between nirmatrelvir-ritonavir (NMV/r) and dermatologic medications^a (Cont'd)

Drugs	Common indications	Expected interaction with NMV/r/effect on plasma drug concentration	Potential adverse effects	Recommended action
Itraconazole	Dermatophyte infections Onychomycosis Pityriasis versicolor	↑ Itraconazole (Dependent on CYP3A4 metabolism) ↑ NMV/r (itraconazole is an CYP3A4 inhibitor)	Gastrointestinal symptoms Transaminitis QT-interval prolongation	Avoid high doses (>200mg/day) of itraconazole and carefully monitor for adverse effects. ²⁶ (Lexicomp Risk Rating D, Micromedex Severity: Moderate)
Ketoconazole	Dermatophyte infections Pityriasis versicolor	↑ Ketoconazole (Dependent on CYP3A4 metabolism) ↑ NMV/r (ketoconazole is an CYP3A4 inhibitor)	Gastrointestinal symptoms Transaminitis QT-interval prolongation	Avoid high doses (>200mg/day) of ketoconazole and carefully monitor for adverse effects. ²⁷ (Lexicomp Risk Rating D, Micromedex Severity: Major)
Antiparasitics				
Albendazole	Parasitic worm infections	↓ Albendazole (ritonavir is an inducer of hepatic metabolism of albendazole)		Monitor for reduced clinical response to albendazole therapy. (Lexicomp Risk Rating C)
Antihistamines				
Bilastine	Angioedema and other allergic dermatological reactions Atopic dermatitis Urticaria Pruritus	↑ Bilastine (Dependent on P-glycoprotein efflux)	QT-interval prolongation	Stop use of bilastine during NMV/r treatment, especially in patients with moderate-severe renal impairment, and resume 3 days after last dose of NMV/r. (Lexicomp Risk Rating X)
Hydroxyzine		↑ Hydroxyzine (Dependent on CYP3A4 metabolism)	QT-interval prolongation Torsades de pointes	Consider close ECG monitoring for QT-interval prolongation. (Micromedex Severity: Major)
Rupatadine fumarate		↑ Rupatadine fumarate (Dependent on CYP3A4 metabolism)	QT-interval prolongation Torsades de pointes	Concomitant use of rupatadine with NMV/r is contraindicated. ³¹ Stop use during treatment and resume 3 days after last dose of NMV/r. (Lexicomp Risk Rating X)
Cetirizine Fexofenadine Levocetirizine		↑ Cetirizine ↑ Fexofenadine ↑ Levocetirizine (Dependent on P-glycoprotein efflux and CYP3A4 metabolism)	Greater central antihistamine effects (reduced alertness, longer reaction times) (Lexicomp)	No dose adjustment or additional monitoring necessary. (Lexicomp Risk Rating B)

Table 2. Summary of drug interactions between nirmatrelvir-ritonavir (NMV/r) and dermatologic medications^a (Cont'd)

Drugs	Common indications	Expected interaction with NMV/r effect on plasma drug concentration	Potential adverse effects	Recommended action
Acne agents				
Oral contraceptives	Acne	↓ Ethinyloestradiol (Probable CYP2C9 and CYP1A2 metabolism)	Irregular bleeding Venous thrombosis Dyslipidaemia Hyperkalaemia (drospirenone) Hepatotoxicity (cyproterone) Hot flashes (cyproterone)	Careful monitoring for adverse effects. Reduction in contraceptive efficacy is unlikely to be clinically significant given the short course of NMV/r. However, patients on oestrogen-containing hormonal contraception are advised to consider additional non-hormonal method of contraception during and up to 1 menstrual cycle after completing the course of NMV/r. ⁷
Oestradiol	Prevention of pregnancy			
Ethinylloestradiol				
Hair agents				
Progestogen (progestin)		↑ Chlormadinone acetate ↑ Dienogest ↑ Levonorgestrel ↑ Norethindrone ↑ Norgestimate ↑ Norgestrel ↑ Drospirenone ↑ Cyproterone acetate (Dependent on CYP3A4 metabolism)		
Chlormadinone acetate				
Dienogest				
Levonorgestrel				
Norethindrone				
Norgestimate				
Norgestrel				
Drospirenone				
Cyproterone acetate				
Dutasteride	Androgenetic alopecia	↑ Dutasteride (Dependent on CYP3A4 metabolism)	Erectile dysfunction Decreased libido	Careful monitoring for adverse effects. (Lexicomp Risk Rating C)
Other commonly encountered drugs in dermatology patients				
Colchicine	Leukoerythrocytic vasculitis Neutrophilic dermatoses Sweet's syndrome Urticarial vasculitis	↑ Colchicine (Dependent on CYP3A4 metabolism) Risk of serious toxicity	Acute colchicine toxicity (gastrointestinal symptoms, seizures, bone marrow suppression, multiorgan failure)	Concomitant use of colchicine with NMV/r is contraindicated. ⁷ Stop use during NMV/r treatment if possible. A colchicine dose adjustment is required in patients who are taking or have taken NMV/r within the past 14 days. Recommendations on dose adjustment for dermatologic indications are not available but can be inferred from dose adjustment for other indications. For the treatment of a gout flare-up with concomitant use of NMV/r, the adjusted dose of colchicine is 0.6mg once, then 0.3mg 1 hour later (repeated no earlier than every 3 days). For the prophylaxis of gout flare, if the original dose is 0.6mg 2 times daily, the adjusted dose is 0.3mg once daily. If the original dose is 0.6mg once daily, the adjusted dose is 0.3mg every other day. In patients with familial Mediterranean fever with concomitant use of NMV/r, the maximum daily dose of colchicine is 0.6mg (may be given as 0.3mg twice daily). ³⁴

Table 2. Summary of drug interactions between nirmatrelvir-ritonavir (NMV/r) and dermatologic medications^a (Cont'd)

Drugs	Common indications	Expected interaction with NMV/r/effect on plasma drug concentration	Potential adverse effects	Recommended action
HMG-CoA reductase inhibitors Atorvastatin Rosuvastatin	Dyslipidaemia E.g. in acne patients taking isotretinoin or psoriasis patients taking acitretin	↑ Atorvastatin ↑ Rosuvastatin (Less dependent on CYP3A4 metabolism than simvastatin or lovastatin)	Myopathy Rhabdomyolysis	Consider stopping use during treatment and resuming 3 days after last dose of NMV/r. If concomitant intake of atorvastatin and NMV/r is required, atorvastatin dose should be reduced to 10mg daily and resume the usual dose 3 days after completion of NMV/r. (Liverpool Drug Interactions checker) If concomitant intake of rosuvastatin and NMV/r is required, maximum rosuvastatin dose should be 10mg daily and resume the usual dose 3 days after completion of NMV/r. (Liverpool Drug Interactions checker) Monitor carefully for adverse effects. (Micromedex Severity: Major; Lexicomp Risk Rating D and C for atorvastatin and rosuvastatin, respectively)
Simvastatin Lovastatin		↑ Simvastatin ↑ Lovastatin (Dependent on CYP3A4 metabolism)		Concomitant use of simvastatin or lovastatin with NMV/r is contraindicated. ⁷ Stop use at least 12 hours before first dose of NMV/r and resume 3 days after last NMV/r dose. (Lexicomp Risk Rating X, Micromedex Severity: Contraindicated)

CYP: cytochrome; ECG: electrocardiogram; HMG-CoA: 3-hydroxy-3-methylglutaryl coenzyme A; ↑: increased plasma drug concentration; ↓: decreased plasma drug concentration
^aConsult the Liverpool COVID-19 Drug Interactions⁵ checker for updated drugs. If a drug is not listed here, co-administration cannot be automatically assumed to be safe.

Superscript numbers: refer to REFERENCES

Currently, no DDIs involving molnupiravir have been identified. In vitro studies show that molnupiravir and its metabolite NHC are not substrates, inhibitors or inducers of major drug metabolising CYP450 enzymes. Also, they are not substrates of P-glycoprotein or breast cancer resistance protein efflux transporters, which are important mediators of intestinal absorption and subsequent excretion of drugs.³⁷ Therefore, molnupiravir can be an option for alternative COVID-19 therapy in patients who are clinically indicated for oral COVID-19 antiviral therapy, but are contraindicated for NMV/r. Molnupiravir is contraindicated during pregnancy, and men and women of childbearing potential should practise contraception for 3 months after the last dose.

Limitations

This present review has 4 main limitations. First, the list of drugs reviewed within this article is not exhaustive, and might not include newer drugs still pending approval by the European Medicines Agency and FDA. To the best of our knowledge, this is the most comprehensive and in-depth review of drug interactions between dermatological medications and the 2 current oral COVID-19 medications. Second, some of the drugs were not listed on the Liverpool COVID-19 Drug Interactions checker at the time of our literature search, and cannot be assumed to be safe to co-administer with NMV/r, although we attempted to corroborate with the individual product monographs. Third, given that NMV/r interacts with many medications, the focus on dermatological medications may be too specialised for generalists and other specialists. However, as patients in the community often present with comorbidities including dermatological conditions, information on DDIs between NMV/r and dermatological agents can be useful for physicians. Moreover, some of the medications discussed here are frequently prescribed by generalists and/or specialists (e.g. systemic glucocorticosteroids, antibiotics, statins, immunomodulators and biologicals). Lastly, information contained within our review is based on our literature search ending on 18 July 2022—recommendations and practices may vary between regions and with time.

CONCLUSION

Clinically significant DDIs exist between NMV/r and numerous dermatological medications, mostly due to CYP3A4 inhibition caused by ritonavir. Genetic variations in the *CYP450* genes encoding the drug metabolising enzymes may also influence the extent of drug interaction between NMV/r and concomitant

medication. Long-term dermatological medications linked to potential drug interactions should be withdrawn or dose-adjusted as appropriate, for 8 days to enable safe and timely access to treatment with NMV/r. Molnupiravir may be considered as an alternative COVID-19 therapy for patients who take medications that have complicated drug interactions with NMV/r, and are not suitable for temporary cessation or dose reduction.

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HH Oon is a speaker, advisory board member and researcher for Galderma, Janssen and Novartis. She has also been a clinical investigator for Pfizer, as well as a speaker and advisory board member for AbbVie and Eli Lilly.

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