

Pharmacokinetic and pharmacogenomic considerations in managing use of nirmatrelvir-ritonavir and molnupiravir and dermatological treatments

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The COVID-19 pandemic has been unprecedented in its impact on global health, economic, financial, psychosocial and political systems. The World Health Organization estimates approximately 627 million confirmed cases and 6.5 million deaths reported globally.¹ In Singapore, the swift and prompt public health response of the government during the early days of the pandemic led to a relatively low cumulative fatality count of 1,709 deaths as of mid-December 2022.²

The SARS-CoV-2 is a ribonucleic acid (RNA) virus belonging to the genus betacoronavirus and it is constantly evolving through random mutations. The viral spike glycoprotein binds to the angiotensin-converting enzyme 2 receptor on the plasma membrane of the host cell to facilitate host cell invasion. The spectrum of presentation due to SARS-CoV-2 infection may vary from mild upper respiratory tract infection that is usually accompanied by fever, muscle pain and fatigue, to a severe infectious state characterised by a hyperinflammatory response, vasculopathy, microangiopathy and widespread thrombosis. Mortality increases in patients of advanced age and with underlying comorbidities.

With a better understanding of the structure of the SARS-CoV-2 virus and its mechanism of replication, several therapeutic agents such as corticosteroids, antivirals, immunomodulatory agents, antimalarial agents and therapeutic antibodies have been investigated in its clinical management. The choice of drugs depends on the presenting clinical conditions of the patients and is particularly challenging, when dealing with those who have severe infections. Current therapeutic interventions are generally based on the following approaches: (1) targeting host cell entry of SARS-CoV-2, (2) inhibiting viral genome replication, (3) priming of immune system via memory T cell production and (4) inhibition of pro-inflammatory markers that manifest as viral-induced cytokine storms.³

Two new oral antivirals, nirmatrelvir-ritonavir (NMV/r) and molnupiravir are approved for emergency outpatient

use in adult and paediatric patients who are considered to be at high risk for progression to severe COVID-19.^{4,5} Nirmatrelvir is a protease inhibitor targeting the Mpro protease of SARS-CoV-2, resulting in inhibition of viral replication. Hammond et al.⁴ reported that nirmatrelvir plus ritonavir, administered twice daily for 5 days at a respective oral dose of 300mg and 100mg was effective in reducing the risk of COVID-19-associated 30-day mortality by 89% compared with placebo when treatment was started within 3 days of onset of COVID-19 symptoms.⁴

Molnupiravir was authorised for emergency use by the U.S. Food and Drug Authority (FDA) for individuals ≥ 18 years in the event that alternative COVID-19 treatments authorised by FDA are unavailable, among other usage parameters.⁵ On 19 April 2022, the Singapore Health Sciences Authority granted interim authorisation for molnupiravir (LAGEVRIO) to treat mild-to-moderate COVID-19 for those ≥ 18 years and at risk of developing severe COVID-19, among other usage parameters.⁶ As a prodrug of ribonucleoside β -D-N⁴-hydroxycytidine (NHC) that is incorporated by viral RNA polymerase to induce viral mutations and lethal mutagenesis, molnupiravir is metabolised via the pyrimidine metabolic pathways, and renal or hepatic elimination of NHC is not meaningful or expected routes, respectively.⁷

Nirmatrelvir undergoes rapid clearance in the body due to extensive metabolism by hepatic cytochrome P-450 (CYP) 3A4. It is thus co-administered with ritonavir, a potent irreversible CYP3A4 inhibitor, which acts as a pharmacokinetic enhancer to prolong its half-life.⁸ Significant drug-drug interactions (DDIs) associated with NMV/r result from the strong inhibitory effect of ritonavir on CYP450 enzyme (e.g. CYP3A4) and drug transporters (such as P-glycoprotein, and organic anion transporting polypeptides 1B1 and 1B3).

Ritonavir's inhibitory effect on CYP3A4 is rapid and maximal at a dose of 100mg.⁸ It can therefore potentially result in elevated plasma concentrations

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of co-medications that are metabolised primarily by CYP3A enzymes, and/or have a narrow therapeutic index (e.g. ciclosporin and tacrolimus), and/or are substrates or P-glycoprotein (e.g. digoxin). Pharmacokinetic modelling suggests that approximately 80% of CYP3A4 inhibition is reversed by 72 hours following cessation of ritonavir in young and elderly adults. On the other hand, ritonavir can also induce other CYP450 enzymes such as CYP1A2, CYP2B6, CYP2C9, CYP2C19 and uridine diphosphate glucuronosyltransferases. However, as opposed to ritonavir's inhibitory effect on CYP3A4/5, its inductive effect on other CYP450 enzymes is unlikely to be clinically relevant with NMV/r as the maximal effect is unlikely to be reached during the short treatment course of 5 days. Due to its significant DDIs, the use of NMV/r may not be feasible in patients with severe comorbidities. To date, DDIs with molnupiravir have not been identified due to a lack of supporting studies.

In this issue of the *Annals*, the systematic review by Quah et al.⁹ is timely and summarises several potential DDIs of NMV/r with commonly used dermatological medications. Immunosuppressants such as ciclosporin, are often prescribed for autoimmune diseases and severe atopic dermatitis, while tofacitinib, another immunosuppressant, is prescribed for severe alopecia areata and psoriatic arthritis. Both these drugs undergo CYP3A4/5-mediated hepatic metabolism and their concomitant use with NMV/r may exacerbate concentration-dependent toxicities by elevating nirmatrelvir concentrations, which may induce renal impairment and transaminitis. It is recommended that ciclosporin administration be stopped and resumed 3 days after the last NMV/r dose has been administered, whereas dose reduction is recommended for tofacitinib.¹⁰ In situations where immunosuppressants such as ciclosporin cannot be temporarily withheld, such as for solid organ transplantation, it may be advisable to consider alternative treatments such as molnupiravir. Similarly, as a strong inducer of CYP3A4, rifampicin is contraindicated with nirmatrelvir-ritonavir, whereby the therapeutic concentrations of nirmatrelvir could be reduced to subtherapeutic levels that may compromise its antiviral activity. Rifampicin is also a potent inducer of P-glycoprotein, which may affect the bioavailability of ritonavir.

The potential for severe DDIs in the elderly population presenting with COVID-19 infection should not be overlooked. The practice of polypharmacy is rife in this population, and with their underlying comorbidities, they

are often prescribed multiple drugs that are metabolised via the CYP3A4/5 pathway. Extreme precaution should be taken when NMV/r is prescribed in this particular patient population. Also, systemic bioavailability of topical agents that are CYP3A4 substrates may vary depending on their physicochemical and pharmacokinetic properties, which may culminate in potential DDIs when administered with NMV/r. This pharmacokinetic interaction may be important in patients with severe COVID-19 infection whereby the release of inflammatory cytokines has been shown to cause suppression of hepatic CYP450-mediated metabolic functions.¹¹

A limitation of the systemic review by Quah et al.⁹ is the lack of information on the pharmacogenomic impact of functional variants in the genes encoding the various CYP450 enzymes that can significantly affect a particular phenotypic outcome. Genetic polymorphisms are most prevalent in 5 CYP isozymes, namely, CYP2A6, CYP2C9, CYP2C19, CYP2D6 and CYP3A4—the latter 2 being the most important of all CYP isozymes. The pharmacogenetics of some of these isozymes are complex, and contributes greatly to the wide variation in drug response and toxicity within a population, as well as between populations of different ethnic origins.¹² Although CYP3A4 metabolises approximately 60% of drugs in the human body, it shares similar substrate specificity with CYP3A5. Also, pharmacogenetic variability in CYP3A4 is less common in Asians but less so for CYP3A5. The latter is highly polymorphic in Asians and the frequency of the defective *CYP3A5**3/*3 genotype varies from 30% in Malays and Indians, to 60% in Chinese.¹³ The *CYP3A5**3 allele results in a truncated protein with resultant loss of hepatic CYP3A5 expression and decreased catalytic activity. Thus, dermatologic agents that are CYP3A4 substrates may also undergo CYP3A5-mediated metabolism in the liver. An understanding of the pharmacogenetic impact of CYP3A4/5 variants on the pharmacokinetics of candidate drugs when administered concomitantly with ritonavir would be crucial to alleviate the risk of serious DDIs. Such considerations are particularly important when patients on NMV/r are also prescribed drugs with low therapeutic indices such as immunosuppressive agents.

Thus, given the complexity in the multiplicity of drug metabolising enzymes and transporters involved in the disposition of dermatologic agents when co-administered with NMV/r to COVID-19 patients, it is imperative that special precautions be taken to avoid serious DDIs.

Safe management of DDIs are possible if healthcare professionals are aware of their presence. Apart from pharmacokinetics-based interactions, the impact of pharmacogenomics factors should also be considered in the dose optimisation strategies of NMV/r when prescribing with dermatologic agents or other co-medications.

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