PERSPECTIVE

Managing Potential Drug Interactions of Nirmatrelvir/Ritonavir in COVID-19 Patients: A Perspective from an Israeli Cross-Sector Collaboration

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In this perspective, we highlight major clinical pharmacology-related issues encountered since the rapid introduction of nirmatrelvir/ritonavir in Israel. We describe the rationale for the practical recommendations issued by an *ad hoc*, cross-sector team of clinical pharmacologists and clinical pharmacists and provide examples of adaptations made by the team. The aim of this paper is to raise awareness of gaps in knowledge and stimulate discussion as to the best clinical practice with nirmatrelvir/ritonavir.

Nirmatrelvir/ritonavir was approved by the Israeli Ministry of Health (MOH) on December 26, 2021, for treating patients with mild-to-moderate coronavirus disease 2019 (COVID-19), as described in its US Food and Drug Administration (FDA) Emergency Use Authorization. It became available for use 1 week later. The emergency authorization and the situation in Israel of being in the midst of the fifth COVID-19 wave, with nirmatrelvir/ritonavir as the only then-available option for preventing severe disease and mortality, called for maximizing the number of patients eligible for this treatment. Nirmatrelvir, a severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) protease inhibitor, is co-packaged with ritonavir to inhibit CYP3A-mediated nirmatrelvir's metabolism, bringing nirmatrelvir plasma concentrations to levels anticipated to inhibit SARS-CoV-2 replication. Two tablets of nirmatrelvir (300 mg) together with one tablet of ritonavir (100 mg) are administered twice daily for 5 days.[1]

In face of the multiple drug interactions expected due to the ritonavir component, and the short treatment duration (5 days), a guidance document for clinicians was rapidly compiled. The document suggests medications which could be temporarily withheld, those that could be continued despite the potential interaction, or medications which should not be combined with nirmatrelvir/ritonavir or their dose may be reduced. The document was based on the nirmatrelvir/ritonavir fact sheet, labels of interacting medications, and a literature review. It was published on the MOH website (https://www.gov.il/BlobFolder/policy/medical-treatment/he/files_regulation_pfizer_medical_treatment_PAXLOVID_TABLE-OF-RECOMENDATIONS.pdf). Separate documents were prepared by the Maccabi Health Maintenance Organization and the Israeli Chapter of the International League against Epilepsy.[2] Simultaneously, an *ad hoc* forum consisting of clinical pharmacologists and pharmacists from the MOH, hospitals, Health Maintenance Organizations, and academia was established to address emerging issues related to clinical pharmacology and periodically update the recommendations.

Here, we describe major challenges related to the use of nirmatrelvir/ritonavir and the principles that guided the recommendations issued in Israel, with examples (**Table S1**).

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POTENTIAL DRUG-INTERACTIONS OF NIRMATRELVIR/RITONAVIR

Ritonavir is primarily metabolized by cytochrome P450 (CYP) 3A4, with a minor contribution of CYP2D6. It is a strong CYP3A4 inhibitor and a weak inhibitor of CYP2D6. Ritonavir inhibition of CYP3A4 is time-dependent, although it may also involve a reversible component.[3] In healthy subjects, 20 mg of daily ritonavir at steady-state reduced the CYP3A-mediated clearance of midazolam by 66%. Near-maximal CYP3A4 inhibition was achieved at 100 mg/day.[4] The daily ritonavir dose in the combined preparation likely affects both the bioavailability and the systemic clearance of sensitive CYP3A4 substrate drugs[3,4] and is sufficient to inhibit the CYP3A4-mediated metabolism of nirmatrelvir.[1] Ritonavir additionally inhibits multidrug resistance protein 1 (P-glycoprotein) and the OATPs 1B1 and 1B3.[5] It induces UGTs[1] and is a weak-to-moderate inducer of several CYP isoenzymes.[5] The effect of enzyme induction by the short nirmatrelvir/ritonavir treatment course is likely to be delayed and temporary, and its clinical significance has yet to be established.

Nirmatrelvir/ritonavir is contraindicated with certain medications, including narrow therapeutic index drugs that are highly dependent on CYP3A for clearance and with drugs that are strong CYP3A inducers. It cannot be started immediately after discontinuation of strong inducers, although a safe time interval is not defined.[1] The drug's fact sheet lists established and other potentially significant drug interactions with clinical comments, mostly replicated from the labels of ritonavir-containing preparations for long-term treatment. With this information as a starting point, our recommendations had to be practical and relevant to patients in isolation in the community who are monitored only remotely. We weighted the effect of comedication (occasionally polypharmacy) with nirmatrelvir/ritonavir against withholding chronic drugs or avoiding nirmatrelvir/ritonavir use. Important considerations included safety, efficacy, and pharmacokinetic parameters, in light of the medical background of patients who use potentially interacting medications. The following sections depict major principles that guided the recommendations issued in Israel in the absence of data relating to the clinical significance of interactions during short-term nirmatrelvir/ritonavir use.

PRIMUM NON NOCERE (FIRST, DO NOT HARM)

Concentration-related toxicities of potentially interacting drugs had to be weighed against depriving patients of a drug that may save their lives, or undertreating them with their chronic medications. The latter two can lead to loss of control of underlying conditions or, worse, disease exacerbation. For some diseases (e.g., epilepsy), maintaining treatment continuity was prioritized with some exceptions, to avoid risks, such as status epilepticus and sudden unexplained death of epilepsy, CYP3A4 is not a major route of elimination for many antiseizure medications, some CYP3A4 substrate drugs are expected to accumulate slowly due to their extended half-lives, and many concentration-dependent short-term adverse effects of antiseizure medications are not life-threatening. Another example of medications that cannot be temporarily withheld is immunosuppressant's, such as cyclosporine, due to the risk of organ rejection. Here, we recommended that if drug levels could not be monitored daily (due to patient isolation at home), other COVID-19 treatments should be preferred (molnupiravir was introduced in Israel after nirmatrelvir/ritonavir). As our recommendations could not be personalized, we suggested that the treating physician considers the patient's condition when deciding how to adjust their treatment. For instance, some medications can be stopped temporarily without harming the patient, such as statins for primary or secondary prevention in stable patients. Another case is patients with diabetes mellitus, in whom the recommendation was for monitoring only, given the mild-to-modest changes in glucose levels generally expected with the addition of nirmatrelvir/ritonavir treatment. Apixaban dose should be reduced or its administration may be temporarily halted in patients with low-risk atrial fibrillation. Yet, in high-risk patients with atrial fibrillation, or in those with recent venous thromboembolism, low molecular weight heparin may substitute apixaban. The latter recommendation requires patient training if they have no previous experience with the use of prefilled syringes. Some recommendations were related to the timing of the interaction. For example, we suggested delaying the administration of the antibody-drug conjugate trastuzumab emtansine until after the nirmatrelvir/ritonavir treatment is over. This is because the small molecule warhead of trastuzumab emtansine might exert significant toxicities in the presence of CYP3A4 inhibitors (**Table S1**).

KEEP IT SIMPLE

Keeping recommendations simple is of crucial importance when it comes to the provision of drugs in the community by a large number of physicians who need to clearly convey treatment instructions to their patients by virtual means. Under these circumstances, simplicity can reduce the medication error risk. One generalization related to the washout period before re-administration of chronic medications at their usual doses. Initial studies found either near-complete or incomplete recovery of CYP3A4 activity 3 days after ritonavir discontinuation (400 or 300–600 mg/day, respectively).[3] Simulations predicted mean 61% (95% confidence interval (CI) 17–80), 51% (95% CI 9–78), 50% (95% CI 8–76), and 46% (95% CI 8–80) recovery of hepatic and intestinal CYP3A activity 1 day post-discontinuation in people aged 20–50, 60–69, 70–79, and 80–89 years, respectively. The mean values for 2 days ranged between 80% and 71% for the youngest and oldest patients, respectively.[6] Based on the limited evidence, the default recommendation for medications with long half-lives was for a washout period of 24 hours after the last nirmatrelvir/ritonavir dose, considering the time to CYP3A4 recovery and to accumulation of the victim drug after treatment onset or dose escalation (**Table S1**). Longer washout periods were suggested for sensitive CYP3A4 substrate drugs with short half-lives (a few hours), such as vardenafil (**Table S1**). We recommended a washout period of 72 hours before emergency treatment with buccal midazolam (with rectal diazepam as an alternative).

CONSIDER THE EFFECTIVE CONCENTRATION (AND ITS SAFETY MARGINS)

Decisions relating to concomitant use of weak-to-moderate CYP3A4 inducers considered the predicted total plasma concentrations of nirmatrelvir (co-administered with ritonavir) which are generally ~ 5-6-fold above the *in vitro* total antiviral effective concentration 90% of 292 ng/mL.[7] The comparative reference was rifabutin, which was suggested by the manufacturer as an alternative to rifampin.[1] In clinical studies with oral midazolam, the midazolam AUC decreased by 69% with rifabutin compared with > 80% with rifampin[8] and 79% with another contraindicated drug, carbamazepine.[9] Accordingly, a 70% decrease in the area under the curve (AUC) of sensitive CYP3A4 substrates was used as a general cutoff value for moderate CYP3A4 inducers which cannot be substituted. This allowed the administration of nirmatrelvir/ritonavir to patients treated with drugs such as dipyrone (metamizole; **Table S1**). In patients treated with strong inducers, nirmatrelvir/ritonavir was contraindicated. The recommended time from their discontinuation to onset of nirmatrelvir/ritonavir treatment was set at 2 weeks, based on CYP3A4 degradation turnover and a published simulation for carbamazepine.[10]

CONCLUSIONS

This perspective provides an example of cross-sector collaboration between clinical pharmacologists and clinical pharmacists aimed to overcome knowledge gaps affecting daily practice. Nirmatrelvir/ritonavir has been administered to thousands of patients in Israel, with no unexpected safety signals although real-world data of efficacy, or impact of our recommendations is still being collected and has not been published. Given the paucity of clinical evidence, some clinical decisions have to rely on assumptions. We hope that further data on the safety, efficacy, and pharmacokinetics of the new drug (and other upcoming COVID-19 medications) will soon be published to increase the quality of quantitative pharmacology models. This could help optimize the use of such medications based on patient characteristics and expand the spectrum of patients eligible for pharmacological COVID-19 treatments.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

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