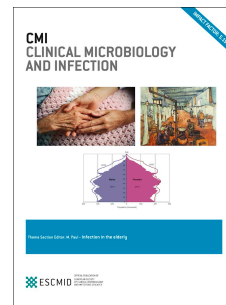


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Evaluating the risk of drug-drug interactions with pharmacokinetic boosters: the case of ritonavir-enhanced nirmatrelvir to prevent severe COVID-19.

Drug-drug interactions and ritonavir-enhanced nirmatrelvir

François Girardin,^{1,2} Oriol Manuel,³ Catia Marzolini,^{4,5} Thierry Buclin¹

¹Division of clinical Pharmacology, Department of Laboratory Medicine and Pathology, Lausanne University Hospital, Faculty of Medicine, University of Lausanne, Lausanne, Switzerland

²Division of clinical Pharmacology and Toxicology, Department of Anesthesiology, Clinical Pharmacology, Intensive Care and Emergency Medicine, Geneva University Hospitals, Geneva, Switzerland

³Infectious Diseases Service and Transplantation Centre, Lausanne, Lausanne University Hospital, Faculty of Medicine, University of Lausanne, Lausanne, Switzerland

⁴Division of Infectious Diseases and Hospital Epidemiology, Departments of Medicine and Clinical Research, University Hospital of Basel and University of Basel, Basel, Switzerland

⁵Department of Molecular and Clinical Pharmacology, University of Liverpool, United Kingdom

Address for correspondence:

Prof. François Girardin, MD, MSc, eMBA

Division of clinical Pharmacology, Department of Laboratory Medicine and Pathology

Lausanne University Hospital (CHUV) and University of Lausanne

Rue du Bugnon 17

CH-1011 Lausanne, Switzerland

Email: francois.girardin@chuv.ch

Phone: +41 22 314 42 76

Fax: +41 22 314 42 66

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COMMENTARY

The concept of pharmacokinetic enhancement can be traced back to the 1940s when probenecid was added to extend penicillin exposure. It revived in the 1990s with the advent of HIV combined antiretroviral therapies, when ritonavir was shown to markedly increase the circulating concentrations of saquinavir and other HIV protease inhibitors. Along with cobicistat, ritonavir remains widely used as a booster to leverage the effectiveness of co-administered antiretrovirals: both substances are potent cytochrome P450 inhibitors that reduce metabolic activity, extend drug half-lives, and improve the bioavailability of a wide range of concomitant drugs at sustained plasma concentrations. At 100 mg twice daily, ritonavir causes a strong inhibition of intestinal and hepatic CYP3A4 and p-glycoprotein (P-gp).

Nirmatrelvir (PF-07321332), a CYP3A4 substrate, is a new peptidomimetic inhibitor of SARS-CoV-2 main protease (Mpro), which blocks the polyprotein precursors and prevents viral replication:[1] nirmatrelvir (NMV) combined with ritonavir (NMV/r) is assessed in phase 3 trials as an early therapeutic agent for patients at risk for COVID-19-related complications. Data supporting the emergency use authorization for NMV/r (Paxlovid™) are from EPIC-HR, a randomized, double-blind, placebo-controlled clinical trial in non-hospitalized symptomatic adults with a diagnosis of SARS-CoV-2 infection. NMV/r administered within three days of symptom onset reduced the risk of COVID-19 related hospitalization and death from any cause by 88%, compared to placebo. [2]

Issues with pharmacokinetic boosters

NMV 300 mg and ritonavir 100 mg (Paxlovid™), in two separate tablets, are administered twice daily for five days in patients with mild to moderate COVID-19 to prevent progression to severe disease. The boosting effect of ritonavir causes strong inhibition of the key drug metabolizing enzyme, CYP3A4. NMV/r has the potential to cause detrimental drug-drug interactions (DDI) notably with sensitive CYP3A4 or P-gp substrates or narrow therapeutic index drugs.[3] [4] Ritonavir is, already at low dose, a strong inhibitor of CYP3A4/5 and P-gp, and, to a lesser extent, of CYP2D6.[5] By contrast, ritonavir induces CYP1A2, CYP2B6, CYP2C9, and CYP2C19, as well as UDP-glucuronyl transferases. [3] However, since induction occurs slowly (i.e. generally 10-15 days after initiation of inducer), NMV/r is not anticipated to cause significant DDIs as an inducer, due to its short treatment course.

On the other hand, NMV/r can be impacted by strong CYP P450 inducers (i.e. St. John's wort, anti-tuberculosis drugs (rifampicin, rifapentine), and anticonvulsants (carbamazepine, phenobarbital, phenytoin). Importantly, DDI with strong inducers cannot be avoided by pausing inducers due to the persisting inducing effect (i.e. approximately two weeks) after stopping a strong inducer. Thus,

patients on strong inducers would not qualify for NMV/r treatment. Alternative COVID-19 treatments should be considered in this situation, such as sotrovimab, remdesivir or molnupiravir.

DDI with MNV/r: medications of concern

NMV/r is used for a short time (five days), primarily in outpatients as post-exposure or therapeutic treatment of mild to moderate COVID-19. In spite of the short treatment duration, the propensity for DDI is clinically significant due to the rapid onset of cytochromes inhibition by ritonavir (i.e. reaching maximal inhibition 48 hours after ritonavir initiation). By contrast, the induction of enzymatic activity develops progressively and more slowly than inhibition due to nuclear receptor-mediated transcriptional regulatory processes. The most clinically relevant DDI with MNV/r will be with medications predominantly metabolized by CYP3A4 (i.e. sensitive CYP3A4 substrates with narrow therapeutic index) and with sensitive substrates of P-gp.

Drug classes of particular concern are those prone to concentration-dependent toxicities or lack of efficacy (Type A adverse drug events), including immunosuppressant drugs, such as mTOR inhibitors (everolimus, sirolimus) and calcineurine inhibitors (tacrolimus, cyclosporine),[6] oral anticoagulants (rivaroxaban, apixaban), antiplatelets (clopidogrel, ticagrelor), amiodarone, some statins (simvastatin, lovastatin), atypical antipsychotics (quetiapine, aripiprazole), benzodiazepines (midazolam, triazolam, diazepam), antimigraine agents, sildenafil, herbal (St. John's wort), and recreational drugs (amphetamines, ecstasy). Further interactions may affect hospitalized patients (e.g. opioids, anesthetics, anticancer treatments, such as vinca alkaloids or taxol derivatives), and some anti-tuberculosis agents. All these drugs are often prescribed to patients susceptible to be at risk of complications from SARS-CoV-2 infection, and thus candidate to receive a course of NMV/r over their usual treatment.[7]

Reconstituting the medication history can be difficult and time consuming in patients with polypharmacy. Some patients might not readily acknowledge their reliance on psychotropic agents, erectile function enhancers or complementary medicines.

We expect that NMV/r will be essentially given to outpatients but also to hospitalized patients: pre-emptive measures to contain DDI could be particularly challenging to implement, given the need to manage dosing adjustment/monitoring quickly and for a short time period.[8] Medication reconciliation and DDI screening using specialized resources or expert consultation is advised before prescribing NMV/r. Up-to-date interaction checkers such as the online tool COVID-19 DDIs checker by the Liverpool Drug Interaction Group are of utmost usefulness for this task.[9]

For drugs requiring impractical dosing adjustment/monitoring, the DDI concerns associated with ritonavir will need to take into account the risk-benefit of prescribing NMV/r to prevent severe COVID-19. If some medications have to be stopped during NMV/r treatment, prescribers should be

aware that CYP3A4 inhibition takes a few days to resolve.[10] According to updated DDI recommendations, paused medications can be resumed three days following the last dose of NMV/r.[9]

Practical recommendations

We would strongly recommend utmost caution with the wide scale prescription of NMV/r, given its high potential to cause DDI: straightforward and easily understandable warnings on drug categories should be mandatory to facilitate pre-emptive and thorough evaluation of any co-administered medication. Readily access to comprehensive patient treatments with treatment reconciliation will facilitate DDI screening using specialized resources.

Step 1: establish the complete list with all current medications, including over-the counter drugs, herbal products, and recreational substances.

Step 2: identify potential DDIs using specialized resources (e.g. www.covid19-druginteractions.org).

Step 3: assess the risk/benefit of NMV/r treatment in presence of an interacting medication (**Table 1**). This assessment should take into account the risk of a given patient to develop a complicated COVID-19 course (risk is higher in immunocompromised patients elderly, see NIH COVID19 treatment website for other risky conditions). The following strategies should be considered when managing DDIs with NMV/r: i) pausing the comedication if it is clinically appropriate to do so; ii) monitoring or dose adjustment of the comedication (challenging to implement given the short treatment course of NMV/r); iii) switch comedication; iv) patient counselling about potential DDIs with advice to withhold temporarily a comedication if feeling unwell or v) use of alternative COVID-19 therapy (sotrovimab, remdesivir, molnupiravir) [8].

Neglecting these precautions could raise concerns and therapeutic promise of nirmatrelvir might be outweighed by the risk associated with its pharmacokinetic booster once this antiviral agent will be prescribed to patients in the real world.

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Classification of DDI risk	Recommendation for DDI management	Examples of medications (list is not exhaustive)
Deleterious DDI	Sensitive CYP3A4 and/or P-gp drugs and/or narrow therapeutic index drugs with a long elimination half-life. DDI is not manageable → choose alternative anti-Covid-19 drug	Amiodarone, bepridil, bosentan, clorazepate, diazepam, pimozide
	Strong inducers are expected to reduce NMV/r efficacy. Given the persisting enzymatic induction upon discontinuation of inducer, DDI is not manageable → choose alternative anti-Covid-19 drug	Carbamazepine, enzulatamide, phenobarbital, phenytoin, primidone, rifampicine, rifapentine, St. John's wort
	Sensitive CYP3A4 and/or P-gp substrates and/or narrow therapeutic index drugs. NMV/r use only possible if comedication is paused. If paused, drug can be resumed 72 h after completing NMV/r treatment. TDM is advised for calcineurine inhibitors and mTOR inhibitors → conditional use of NMV/r	Alfuzosin, apixaban, calcineurine inhibitors (tacrolimus, cyclosporine), clopidogrel (recently stented patient), domperidone, lovastatin, midazolam, mTOR inhibitors (everolimus, sirolimus), rivaroxaban, simvastatin, ticagrelor
Potential DDI manageable by dose adjustment/monitoring (and for some medications by patient counselling)	Drugs requiring dosage adjustment and/or specific monitoring (e.g. INR, TDM,) → evaluate risk/benefit of prescribing NMV/r	Aripiprazole, haloperidol, risperidone, cancer drugs (CYP3A4/P-gp substrates), digoxin, warfarin
	Patient counselling about potential DDI with advice to pause temporarily the medication if feeling unwell or informed to be aware of side effects → use of NMV/r possible	Amlodipine, diltiazem, indapamide, verapamil, zolpidem, zopiclone
DDI of weak clinical relevance	Drugs for which a weak magnitude DDI is expected or with a low risk of adverse event from DDI → safe use of NMV/r	Bupropion, codeine, desipramine, ezetimibe, mirtazapine, methadone, mycophenolate
No expected DDI	→ safe use of NMV/r	β-blockers, ACE-inhibitors, lamotrigine; drugs not undergoing CYP3A4 metabolism and/or not transported by P-gp

Table 1: Risk of drug-drug interactions with nirmatrelvir/ritonavir and recommended drug-drug interaction. Note that the inhibitory effect of ritonavir needs 72 h after discontinuation to resolve. The classification of the drug-drug interactions refers to the University of Liverpool COVID19 drug interaction resource: www.covid19-druginteractions.org.

DDI= drug-drug interactions; NMV/r: nirmatrelvir-ritonavir; P-gp: p-glycoprotein