Clinical Microbiology and Infection 28 (2022) 1044–1046

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Commentary

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

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ARTICLE INFO

Article history:
Received 27 January 2022
Received in revised form
4 March 2022
Accepted 7 March 2022
Available online 28 March 2022

Editor: L. Leibovici

Keywords:
Antivirals
COVID-19
Drug safety
Drug-drug interactions
Nirmatrelvir
Ritonavir
Pharmacokinetic boosters

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 severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) main protease, 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 Evaluation of Protease Inhibition for Covid-19 in High-Risk Patients (EPIC-HR), a randomized, double-blind, placebo-controlled clinical trial in nonhospitalized 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

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https://doi.org/10.1016/j.cmi.2022.03.030

is not anticipated to cause significant DDIs as an inducer, because of 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 NMV/r: medications of concern

NMV/r is used for a short time (5 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 NMV/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 calcineurin 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 (e.g. with opioids, anesthetics, anticancer treatments, such as vinca alkaloids or taxol derivatives) may affect hospitalized patients, 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;

Table 1
Risk of drug-drug interactions with nirmatrelvir/ritonavir and recommended drug-drug interaction

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 calcineurin 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**	ß-blockers, ACE-inhibitors, lamotrigine; drugs not undergoing CYP3A4 metabolism and/or not transported by P-gp

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 COVID-19 drug interaction resource: www.covid19-druginteractions.org [9].
DDI, drug-drug interactions; INR,; NMV/r, nirmatrelvir-ritonavir; TDM,; P-gp, p-glycoprotein; INR, international normalized ratio; TDM, therapeutic drug monitoring.

straightforward and easily understandable warnings on drug categories should be mandatory to facilitate pre-emptive and thorough evaluation of any co-administered medication. Ready 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) [9].

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 older patients who are immunocompromised, see NIH COVID19 treatment website for other risky conditions) [11]. The following strategies should be considered when managing DDIs with NMV/r: (a) pausing the comedication if it is clinically appropriate to do so, (b) monitoring or dose adjustment of the comedication (challenging to implement given the short treatment course of NMV/r), (c) switch comedication, (d) patient counselling about potential DDIs with advice to withhold temporarily a comedication if feeling unwell, or (e) use of alternative COVID-19 therapy (sotrovimab, remdesivir, molnupiravir) [8].

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

Funding

No external funding was received.

Author's contributions

All authors wrote the original draft. FG, OM, and CM conceptualized the table. All authors contributed to review and editing.

Transparency declaration

Authors have no conflict of interest. FG is the representative of Swiss hospitals at the Federal Drug Commission (Federal Office of Public Health) and expert for InnoSuisse – the Federal Agency for Innovation (Section Life Sciences). OM received lecture honoraria from MSD and Takeda, CM received lecture honoraria from MSD and ViiV.

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