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PHARMACOKINETICS

Management of drug-drug interactions with nirmatrelvir/ritonavir in patients treated for Covid-19: Guidelines from the French Society of Pharmacology and Therapeutics (SFPT)

Florian Lemaitre[a,b,*], Matthieu Grégoire[c,d], Caroline Monchaud[e,f], Stéphane Bouchet[g], Béatrice Saint-Salvi[h], Elisabeth Polard[a,b], On behalf of the SFPT Therapeutic Drug Monitoring and Treatment Personalization group (STP-PT) of the French Society of Pharmacology and Therapeutics (SFPT) French Pharmacovigilance Network (CRPV) , ANRS-MIE AC-43 Clinical Pharmacology Committee, joint working group , The SFPT Therapeutic Drug Monitoring and Treatment Personalization group (STP-PT) of the French Society of Pharmacology and Therapeutics (SFPT) , French Pharmacovigilance Network (CRPV) , ANRS-MIE AC-43 Clinical Pharmacology Committee, joint working group, Sihem Benaboud[i], Laurent Chouchana[j,k], Jean-Luc Cracowski[l], Milou-Daniel Drici[m], Rodolphe Garraffo[m], Romain Guilhaumou[n], Annie-Pierre Jonville-Bera[o], Mathieu Molimard[u], Patric Muret[p], Gilles Peytavin[q,r], Vincent Richard[s], Caroline Solas[t] ,

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* Corresponding author. Service de pharmacologie CHU de Rennes, hôpital Pontchaillou, 2, rue Henri Le Guilloux, 35033 Rennes, France.
E-mail address: florian.lemaitre@chu-rennes.fr (F. Lemaitre).

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[a] *Université de Rennes, CHU Rennes, Inserm, EHESP, Irset (Institut de recherche en santé, environnement et travail)-UMR_S 1085, 35000 Rennes, France*
[b] *Inserm, centre d'investigation clinique, CIC 1414, 35000 Rennes, France*
[c] *Clinical pharmacology department, Nantes university hospital, 44000 Nantes, France*
[d] *UMR Inserm 1235, The Enteric Nervous System in Gut and Brain Disorders, University of Nantes, 44000 Nantes, France*
[e] *Department of pharmacology, toxicology and centre of pharmacovigilance, CHU de Limoges, 87000 Limoges, France*
[f] *UMR-1248, Inserm, 87000 Limoges, France*
[g] *Laboratoire de pharmacologie et toxicologie, service de pharmacologie médicale, CHU Pellegrin, Inserm U1219, 33000 Bordeaux, France*
[h] *Medical interactions unit, Agence nationale de sécurité du médicaments et des produits de santé, 93200 Saint-Denis, France*
[i] *Université de Paris, 75000 Paris, France*
[j] *Département de pharmacologie, centre régional de pharmacovigilance, hôpital Cochin, 75000 Paris, France*
[k] *Université Paris Descartes, 75000 Paris, France*
[l] *CRPV Grenoble, université Grenoble-Alpes, 38043 Grenoble, France*
[m] *Department of clinical pharmacology, university Côte d'Azur medical center, hôpital Pasteur, 06000 Nice, France*
[n] *Aix-Marseille Univ, AP-HM, service de pharmacologie clinique et pharmacovigilance, institut des neurosciences des systèmes, Inserm UMR, 11600, 13385 Marseille, France*
[o] *Pharmacovigilance and drug information centre, department of pharmacosurveillance, CHU de Tours, 37044 Tours, France*
[p] *Clinical pharmacology department, Minjoz university hospital, 25000 Besançon, France*
[q] *AP—HP, Bichat Claude-Bernard hospital, pharmacology department, 75018 Paris, France*
[r] *Université de Paris, Inserm UMR-1137, IAME, 75018 Paris, France*
[s] *Laboratoire de pharmacologie, Inserm U1096 & RHU STOP-AS, université de Rouen Normandie, 76000 Rouen, France*
[t] *Aix-Marseille Univ, APHM, unité des virus emergents (UVE) IRD 190, Inserm 1207, laboratoire de pharmacocinétique et toxicologie, hôpital La Timone, 13005 Marseille, France*
[u] *Laboratoire de pharmacologie et toxicologie, service de pharmacologie médicale, CHU Pellegrin, Inserm U1219, 33000 Bordeaux, France*

KEYWORDS
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Summary
Objectives. — Nirmatrelvir in association with ritonavir (PAXLOVID™, Pfizer) is an antiviral agent targeting the 3-chymotrypsin—like cysteine protease enzyme (3C-like protease or Mpro) which is a key enzyme of the viral cycle of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This combination with a well-known pharmacokinetic enhancer leads to a high risk for drug-drug interactions in a polymedicated elected population for treatment. The aim of this work was to provide recommendations on behalf of the national French society of pharmacology (French Society of Pharmacology and Therapeutics; SFPT), by suggesting optimal and pragmatic therapeutic strategies if nirmatrelvir/ritonavir is to be given together with drugs commonly used, in order to ensure secured physicians' prescription.
Methods. — Six clinical pharmacologists search the scientific literature to provide a first draft of recommendations. Thereafter, twelve other clinical pharmacologists verified the recommendations and proposed modifications. The final draft was then validated by all 18 participants.
Results. — Five distinct recommendations were issued: i) contra-indications, ii) ''PAXLOVID™ not recommended with the comedication'', iii) ''PAXLOVID™ possible whether the comedication is discontinued'', iv) ''PAXLOVID™ possible only after an expert advice'' and v) ''PAXLOVID™ possible without modification of the associated treatment''. The final document comprises recommendations for 171 drugs/therapeutic classes aiming to secure prescription. In complex situations, clinicians are advised to contact their pharmacology department to obtain specific recommendations on the management of drug-drug interactions with nirmatrelvir/ritonavir.

Conclusion. — These recommendations intend to be a help for clinicians willing to prescribe nirmatrelvir/ritonavir and to prevent drug-drug interactions leading to adverse drug reactions or loss of efficacy. They constitute a guideline for primary care situations. Of course, some complex situations may require expert advices and here, again, clinical pharmacologists are at the forefront in providing therapeutic advice.

Abbreviations

ANSM	Agence nationale de sécurité des medicaments et des produits de santé
BCRP	breast cancer resistance protein
COVID-19	severe coronavirus disease 2019
CYP3A4	cytochrome P450 3A4 isoenzyme
DDI	drug-drug interactions
Pgp	P-glycoprotein
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SFPT	French Society of Pharmacology and Therapeutics
SmPC	summary of products characteristics
UGTs	UDP-glucuronyl transferases

Introduction

Up to recently, no antiviral treatment was available for the severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) infection, particularly during the early phase of infection (i.e the viremic phase) in order to prevent the progression to severe pneumonia (i.e the inflammatory phase). Nirmatrelvir in association with ritonavir (PAXLOVID™, Pfizer) is an antiviral agent targeting the 3-chymotrypsin—like cysteine protease enzyme (3C-like protease or M^{pro}) which is a key enzyme of the viral cycle of the SARS-CoV-2 [1]. The drug pharmacological mechanism prevents the 11 cleavages performed by M^{pro} on the polyprotein produced by the virus and then blocks its replication cycle. Nirmatrelvir has shown a good efficacy in preclinical models (cellular human bronchial epithelial cells Calu-3 and in murine models) with effective concentrations achievable in patients [2,3]. In a randomized controlled trial including symptomatic, unvaccinated, non-hospitalized adults at high risk for progression to severe coronavirus disease 2019 (COVID-19), nirmatrelvir reduced the incidence of COVID-19 related hospitalization or death by 89.1% at day-28. Notably, there was no death in the experimental arm while 13 patients died in the placebo arm [4]. Nirmatrelvir appears, therefore, as a first line option for the treatment of at-risk patients of severe COVID-19 such as elderly patients and those with chronic disease. However, as already observed with HIV-protease inhibitors, nirmatrelvir displays a short half-life, which could result in suboptimal drug exposure and difficulties in achieving efficacy threshold. Indeed, nirmatrelvir is also a substrate of cytochrome P450 3A4 isoenzyme (CYP3A4) and is extensively metabolized through this pathway, which contributes to the important inter-individual pharmacokinetic variability. To circumvent this limitation, nirmatrelvir is combined with ritonavir, a well-known pharmacokinetic enhancer for its potent CYP3A4 inhibiting properties. The approved drug dosage is 300 mg of nirmatrelvir (in two 150 mg tablets) to be administered in combination with ritonavir 100 mg twice daily within 3 to 5 days following the first COVID-19 symptoms and during five consecutive days.

The main concern in case of a broad use of nirmatrelvir is the impact of ritonavir on the clearance of numerous co-administered drugs, which can results in major drug-drug interactions (DDI) leading to potential adverse drug reactions [5]. While numerous studies on ritonavir combined with HIV protease inhibitors are available for, data regarding DDI with nirmatrelvir/ritonavir association are scarce. In this context, the expert opinion of clinical pharmacologists is crucial for a safe use of this drug, which is expected to be prescribed by general practitioners to the at-risk, polymedicated patients.

The aim of this work was to provide recommendations on behalf of the national French society of pharmacology (French Society of Pharmacology and Therapeutics; SFPT), by suggesting optimal and pragmatic therapeutic strategies if nirmatrelvir/ritonavir is to be given together with drugs commonly used, in order to ensure secured physicians' prescription.

Methods

Six clinical pharmacologists, called in the paper the specialists in clinical pharmacology, were in charge of analyzing documents related to potential DDI for drugs expected to be combined with nirmatrelvir/ritonavir in patients. These specialists in clinical pharmacology reviewed the scientific literature on DDI studies between substrates and ritonavir or, whether no study was available with ritonavir, with ketoconazole, an equipotent CYP3A4 inhibitor. These documents were extracted from the Medline database, the summary of products characteristics (SmPC) of the various drugs of interest (see references) and the national handbook for DDI (*Thesaurus des interactions médicamenteuses*) edited by the French national regulatory agency (Agence Nationale de Sécurité du Médicament, ANSM) [6]. The SmPC of the drug

Table 1

Substrate	Nature and magnitude of the effect	Therapeutic strategy	Comments
Anti-platelet agents			
Aspirin	No interaction expected	Paxlovid possible without modification of the associated treatment	
Prasugrel	45% decrease in prasugrel AUC but clinical effect is expected to be maintained	Paxlovid possible without modification of the associated treatment	In case of recent angioplasty (<6 weeks): a cardiologist advice is required
Clopidogrel	Decrease in anti-platelet effect reported but clinical effect is expected to be maintained	Paxlovid possible without modification of the associated treatment	In case of recent angioplasty (<6 weekss): a cardiologist advice is required
Ticagrelor	Increase in ticagrelor exposure and increase in bleeding risk	Paxlovid contra-indicated with the comedication	
Anticoagulants			
Acenocoumarol, Warfarin	Weak interaction expected	Paxlovid possible without modification of the associated treatment	INR monitoring and adjustment of treatment dosage if needed
Apixaban	Increase in apixaban exposure and increase in bleeding risk	Paxlovid not recommended with the comedication	
Dabigatran	Increase in dabigatran exposure (AUC increase by 90%). Increase bleeding risk.	Paxlovid not recommended with the comedication	
Rivaroxaban	Increase in rivaroxaban exposure (AUC and Cmax increased by 153% and 53%, respectively) with increase in bleeding risk.	Paxlovid not recommended with the comedication	
Drugs for angina and heart failure			
Ivabradine, Eplerenone	Risk of heart rythm disorders	Paxlovid contra-indicated with the comedication	
Antiarrhythmic agents			
Amiodarone, Flecainide, Dronedarone, Propafenone, Quinidine	Risk of cardiac arrhythmias	Paxlovid contra-indicated with the comedication	
Digoxine	Digoxine AUC increase expected between 30 and 80%	Paxlovid possible whether the comedication is discontinued	
Antihypertensive drugs			
ACEi/ARBs/Diuretics	No interaction expected	Paxlovid possible without modification of the associated treatment	
Calcium channel blockers - except for Lercanidipine, Verapamil, Diltiazem	Weak interaction expected	Paxlovid possible without modification of the associated treatment	
Lercanidipine, Verapamil, Diltiazem	Higher interaction expected than for other calcium channel blockers	Paxlovid possible whether the comedication is discontinued	
Beta-blockers -(Atenolol, Propranolol, Nebivolol, Carvedilol, Timolol - except for Bisoprolol)	Weak interaction expected for Propranolol, Nebivolol, Carvedilol, Timolol and for Aténolol (which is renally excreted)	Paxlovid possible without modification of the associated treatment	

Table 1 (*Continued*)

Substrate	Nature and magnitude of the effect	Therapeutic strategy	Comments
Bisoprolol	Higher interaction expected	Paxlovid not recommended with the comedication	
Lipid agents			
HMG-CoA reductase inhibitors	Particularly high interaction magnitude expected for simvastatin and lovastatin	Paxlovid possible whether the comedication is discontinued	Lovastatine and Simvastatine contra-indicated in SmPC
Lomitapide	Increase of AUC by a factor 27 expected	Paxlovid contra-indicated with the comedication	
Antipsychotics			
Clozapine	Possible QTc prolongation	Paxlovid contra-indicated with the comedication	
Quetiapine	Quetiapine AUC is increased by a factor 6.5	Paxlovid contra-indicated with the comedication	
Antidepressants			
SSRI/SNRI/Mirtazapine/ Mianserine	Weak interaction expected (10-50%)	Paxlovid possible without modification of the associated treatment	
Tricyclic antidepressants/MAOi		Paxlovid not recommended with the comedication	
Benzodiazepines and related drugs			
Midazolam oral, Diazepam, Clorazepate, Estazolam	Increase in benzodiazepine exposure by a 10 to 25 factor. Risk of respiratory failure.	Paxlovid contra-indicated with the comedication	
Alprazolam	Increase in benzodiazepine exposure by a 2 to 3 factor. Risk of respiratory failure.	Paxlovid not recommended with the comedication	
Zolpidem, Zopiclone	Weak interaction expected	Paxlovid possible without modification of the associated treatment	
Anticonvulsivants			
Carbamazepine	Risk of antiviral treatment failure.	Paxlovid contra-indicated with the comedication	
Phenobarbital	Risk of antiviral treatment failure.	Paxlovid contra-indicated with the comedication	
Phenytoin	Risk of antiviral treatment failure.	Paxlovid contra-indicated with the comedication	
Valproate	Weak interaction expected	Paxlovid possible without modification of the associated treatment	
Lamotrigine	Possible decrease in lamotrigine concentrations but weak magnitude expected.	Paxlovid possible without modification of the associated treatment	
Levetiracetam	No interaction expected	Paxlovid possible without modification of the associated treatment	

Table 1 (*Continued*)

Substrate	Nature and magnitude of the effect	Therapeutic strategy	Comments
Immunosuppressive drugs			
Tacrolimus	Increase in tacrolimus exposure by 40 fold.	Paxlovid possible only after an expert advice	Administer 1/8th of the usual daily dose (DD) on day-1, then stop. Administer 1/2nd of the DD on day-6 then 3/4 on day-7 and restart usual DD on day-8. Alternative for low immunological risk: Start Nirmatrelvir/Ritonavir 12h after the last intake of tacrolimus and restart tacrolimus at usual DD 24h after the last antiviral dose. Dosage with treatment individualization using therapeutic drug monitoring if possible.
Ciclosporine	Increase in ciclosporine exposure by 8 fold.	Paxlovid possible only after an expert advice	Administrer 1/5th of the usual daily dose (DD) every day of Nirmatrelvir/Ritonavir treatment. Administer 1/2nd of the DD on day-6 then 3/4 on day-7 and restart usual DD on day-8. Dosage with treatment individualization using therapeutic drug monitoring if possible
Everolimus	Increase in everolimus exposure by 15 fold	Paxlovid possible only after an expert advice	Administer 1/8th of the usual daily dose (DD) on day-1, day-3 and day-5. Usual DD can be restart on day-7. Dosage with treatment individualization using therapeutic drug monitoring if possible.
Sirolimus	Increase in sirolimus exposure by 11 fold	Paxlovid possible only after an expert advice	Administer 1/8th of the usual daily dose (DD) on day-1, day-3 and day-5. Usual DD can be restart on day-7. Dosage with treatment individualization using therapeutic drug monitoring if possible.
Mycophenolic acid	Weak interaction expected. Possible decrease in mycophenolic acid exposure.	Paxlovid possible only after an expert advice	Whether a treatment with mycophenolic acid is required, the dosage can be maintained.

Table 1 (*Continued*)

Substrate	Nature and magnitude of the effect	Therapeutic strategy	Comments
Prednisone	Weak interaction expected. Possible increase in prednisoneexposure.	Paxlovid possible only after an expert advice	Prednisone dosage can be maintained. If needed, a 1/3 dosage decrease can also be proposed.
Anticancer drugs			
Cytotoxic drugs	According to the substrates, an important interaction can occur. Vincristin, Vinblastin: risk of neutropenia and neurotoxicity.	Paxlovid possible whether the comedication is discontinued, cytotoxic agent treatment should be postponed after the end of antiviral treatment.	
For the following kinase inhibitors: Abemaciclib, Axitinib, Bosutinib, Cobimetinib, Crizotinib, Encorafenib, Erlotinib, Gefitinib, Ibrutinib, Nilotinib, Olaparib, Palbociclib, Pazopanib, Sunitinib...) except for the drug below	Increase in kinase inhibitors, which may be important for some substrates.	Paxlovid possible whether the comedication is discontinued	Therapeutic strategies are proposed in some drugs' SmPCs. An expert advice (Pharmacologist and Oncologist) should be sought to safely adjust the drug dosage.
Venetoclax	Risk of tumor syndrome lysis	Paxlovid contra-indicated with the comedication	
Afatinib, Alectinib, Binimetinib, Cabozantinib, Imatinib, Osimertinib, Sorafenib, Trametinib	Weak exposure increase (AUCs increase from 26 to 40%)	Paxlovid possible without modification of the associated treatment	
Tamoxifen	Weak interaction expected	Paxlovid possible without modification of the associated treatment	
Apalutamide, Enzalutamide	Risk of antiviral treatment failure.	Paxlovid not recommended with the comedication	
Pneumology drugs			
Beta-2 agonists	Exposure increase but weak clinical effect expected	Paxlovid possible without modification of the associated treatment	
Inhaled corticosteroids	Exposure increase but weak clinical effect expected	Paxlovid possible without modification of the associated treatment	
Sildenafil, Tadalafil, Vardenafil, Avanafil	Large increase in substrates' exposure	Paxlovid contra-indicated with the comedication	
Bosentan	Increase in bosentan exposure by a 5 factor.	Paxlovid not recommended with the comedication	
Non opiates analgesics drugs			
Aspirin, Acetaminophen, Ibuprofen, Diclofenac, Naproxen, Ketoprofen	No interaction expected	Paxlovid possible without modification of the associated treatment	
Colchicin	Risk of colchicin accumulation and toxicity	Paxlovid contra-indicated with the comedication	
Opiates			
Codeine, Tramadol, Buprenorphine	Weak interaction expected	Paxlovid possible without modification of the associated treatment	

Table 1 (*Continued*)

Substrate	Nature and magnitude of the effect	Therapeutic strategy	Comments
Fentanyl	Possible increase in fentanyl exposure with risk of respiratory failure	Paxlovid not recommended with the comedication	
Methadone	Possible decrease in methadone exposure	Paxlovid possible without modification of the associated treatment	
Morphine	Possible increase in morphine glucuronide metabolites	Paxlovid possible without modification of the associated treatment	
Oxycodone	Increase in oxycodone exposure by 90%	Paxlovid contra-indicated with the comedication	
Antibacterial agents			
Aminoglycosides	No interaction expected	Paxlovid possible without modification of the associated treatment	
Beta-lactams	No interaction expected	Paxlovid possible without modification of the associated treatment	
Fluoroquinolones	No interaction expected	Paxlovid possible without modification of the associated treatment	
Fosfomycin	No interaction expected	Paxlovid possible without modification of the associated treatment	
Glycopeptides	No interaction expected	Paxlovid possible without modification of the associated treatment	
Oxazolidinones	No interaction expected	Paxlovid possible without modification of the associated treatment	
Polymyxines	No interaction expected	Paxlovid possible without modification of the associated treatment	
Sulfamides	No interaction expected	Paxlovid possible without modification of the associated treatment	
Tetracyclines	No interaction expected	Paxlovid possible without modification of the associated treatment	
Macrolides - except Erythromycin	Increase in macrolides exposure (clarithromycin)	Paxlovid possible without modification of the associated treatment	In patients with QTc prolongation risk, an EKG monitoring is recommended.
Erythromycin	Possible increase in erythromycin exposure and risk of cardiac arrhythmia	Paxlovid not recommended with the comedication	
Antituberculous agents			
Isoniazid, Ethambutol, Pyrazinamide	No interaction expected	Paxlovid possible without modification of the associated treatment	

Table 1 (*Continued*)

Substrate	Nature and magnitude of the effect	Therapeutic strategy	Comments
Rifampicin	Large decrease in NIrmatrelvir/ritonavir exposure	Paxlovid contra-indicated with the comedication	
Rifabutin	Possible decrease in Nirmatrelvir/ritonavir exposure. Increase of rifabutin exposure by a 4 fold factor	Paxlovid not recommended with the comedication	
Antifungal agents			
Echinocandins	No interaction expected	Paxlovid possible without modification of the associated treatment	
Fluconazole, Isavuconazole, Itraconazole, Posaconazole	Moderate increase in Nirmatrelvir/Ritonavir exposure (up to 39% with itraconazole)	Paxlovid possible without modification of the associated treatment	
Voriconazole	Decrease in voriconazole exposure (decrease of AUC of 39%). Mild increase in Nirmatrelvir/ritonavir exposure expected.	Paxlovid not recommended with the comedication	
Antiretrovirals			
Boosted protease inhibitors (Darunavir/r, Atazanavir/r, Lopinavir/r)	Increase in protease inhibitors exposure	Paxlovid possible without modification of the associated treatment	Adverse drug reaction monitoring (digestive disorders for Ritonavir)
Integrase strand inhibitors (Raltegravir, Dolutegravir, Bictegravir, Cabotegravir)	Weak interaction expected	Paxlovid possible without modification of the associated treatment	
Nevirapine, Efavirenz, Etravirine	Possible decrease in Nirmatrelvir/ritonavir exposure. No decrease in substrates exposure is expected/	Paxlovid not recommended with the comedication	
Doravirine	Increase in doravirine exposure by a 3.5 factor.	Paxlovid possible without modification of the associated treatment	
Rilpivirine	Possible increase in rilpivirine exposure and possible risque of QTc prolongation.	Paxlovid possible without modification of the associated treatment	In patients with QTc prolongation risk, an EKG monitoring is recommended.
Maraviroc	Increase in maraviroc exposure	Paxlovid not recommended with the comedication	
Tenofovir	An increase in tenofovir exposure is expected	Paxlovid possible without modification of the associated treatment	
Nucleoside reverse transcriptase inhibitors (Abacavir, Emtricitabine, Lamivudine)	No interaction expected	Paxlovid possible without modification of the associated treatment	
Hepatitis C direct acting antiviral			

Table 1 (*Continued*)

Substrate	Nature and magnitude of the effect	Therapeutic strategy	Comments
Sofosbuvir/ Velpatasvir	No interaction expected	Paxlovid possible without modification of the associated treatment	
Glecaprevir/Pibrentasvir	Large increase in glecaprévir/pibrentasvir exposure expected. Increase in liver enzymes due to glecaprevir accumulation.	Paxlovid not recommended with the comedication	
Voxaliprevir	Increase in voxaliprevir exposure, possible liver enzymes increase.	Paxlovid not recommended with the comedication	
Herpes - Cytomegalovirus treatment			
Aciclovir/valaciclovir	No interaction expected	Paxlovid possible without modification of the associated treatment	
Ganciclovir/valganciclovir	No interaction expected	Paxlovid possible without modification of the associated treatment	
Other drugs			
Thyroid hormone therapy	Decrease in thyroid hormone exposure particularly if antiviral treatment duration is more than 5 days	Paxlovid possible without modification of the associated treatment	Thyroïd clinical and biological monitoring,
Hormonal contraception whatever the route of administration	Decrease in hormonal contraception exposure	Paxlovid possible without modification of the associated treatment	Use an additional contraceptive method (mechanical) during the combination and one complete cycle after the antiviral dscontinuation
Ergot alkaloids	Ergotism risk	Paxlovid contra-indicated with the comedication	
Domperidone	Large increase in domperidone exposure. Heart rythm disorders.	Paxlovid contra-indicated with the comedication	
Naloxegol	Large increase in Naloxegol exposure	Paxlovid contra-indicated with the comedication	

Recommendations for drugs/therapeutic classes aiming to secure prescription of nirmatrelvir/ritonavir in patients treated for Covid-19 [5,7—28].

PAXLOVID™ was also used to provide recommendations [7]. The specialists in clinical pharmacology based their recommendations on inhibitory and inducing properties of ritonavir depending on the metabolic and safety profile of the target drugs. Five situations were identified, for which the specialists in clinical pharmacology's recommendations were formulated as follows:

- contra-indications, which was strictly reported in the document whenever mentioned in the PAXLOVID™ SmPC or in the national handbook for DDI, even if some of them may have been challenged by recent reassuring data;
- ''PAXLOVID™ not recommended with the comedication'';
- ''PAXLOVID™ possible whether the comedication is discontinued'';
- ''PAXLOVID™ possible only after an expert advice'';
- and ''PAXLOVID™ possible without modification of the associated treatment''.

After finalizing a first draft, these recommendations were submitted to a panel of 12 other clinical pharmacologists, namely the proofreaders, who verified them and proposed modifications. The final draft was then validated by all 18 participants.

Results

As already stated, the specialists in clinical pharmacology identified several situations for DDI with nirmatrelvir/ritonavir. The most frequent situations were: co-administration of drugs which are not substrates of CYP, or those for which the metabolic pathway was minimally affected by ritonavir, and those with large therapeutic index. For these drugs no major adverse drug reaction is expected during the 5-day nirmatrelvir/ritonavir treatment course, therefore the recommendation was: ''PAXLOVID™ possible without modification of the associated treatment''. In the case of drugs contra-indicated in the SmPC of PAXLOVID™ or in the French national handbook for DDI, the recommendation was: ''PAXLOVID™ contra-indicated with the comedication''. area contra-indication is mentioned mainly for:

- drugs for which a large variation in exposure is expected when associated with nirmatrelvir/ritonavir (usually over a 5-fold increase of the area under the curve of the drug);
- drugs for which an increase in exposure may lead to serious adverse drug reactions, including life-threatening reactions even during as short a period as 5 days (the typical example being colchicine);
- drugs for which a pharmacodynamic potentiation of adverse drug reaction with serious consequences is expected and;
- drugs known as potent CYP3A4 inducers potentially leading to a decrease in nirmatrelvir, with a risk of antiviral treatment failure (the typical case is rifampicin but carbamazepine is concerned as well). For drugs not strictly contra-indicated in the regulatory documents (SmPC or the French national handbook for DDI), but having a high risk of accumulation, the recommendation was: ''PAXLOVID™ not recommended with the comedication''.

Associated with PAXLOVID™, these drugs may show large variations in exposure, potentially leading to concentration-related severe adverse event. Therefore, the specialists in clinical pharmacology considered that the combination may put the patient at risk for toxicity and general practitioners had to be warned about this. Alternatives COVID-19 treatments should be proposed in these situations. Some drugs can be safely discontinued during the antiviral treatment without causing harm to patients. For these drugs, the clinical pharmacologists' recommendation was: ''PAXLOVID™ possible whether the comedication is discontinued''. The typical case is HMG-CoA reductase inhibitors, i.e statins. The discontinuation of this pharmacological class can be safely proposed during the treatment with nirmatrelvir/ritonavir to avoid myopathy and potential rhabdomyolysis. Finally, the specialists in clinical pharmacology evidenced a fifth case. The recommendation in that situation was: ''PAXLOVID™ possible only after an expert advice'' for drugs which have to be pursued during the nirmatrelvir/ritonavir treatment and the exposure of which would be largely changed by the inhibiting or inducing action of ritonavir. Discontinuing these drugs would be harmful for patients and cannot be considered. For these drugs, a dosage adjustment is, then, required and a clinical pharmacologist expert advice must be sought. The typical examples are immunosuppressive drugs, substrates of both CYP3A4 and P-glycoprotein. Their titration should be reduced (up to 40-time factor for tacrolimus) and therapeutic drug monitoring appears paramount to manage inter-patient variability during this DDI.

The final document comprises recommendations for 171 drugs/therapeutic classes aiming to secure prescription (Table 1) [5,7—28]. In complex situations, clinicians are advised to contact their pharmacology department to obtain specific recommendations on the management of DDI with nirmatrelvir/ritonavir.

Discussion

Nirmatrelvir combined with ritonavir is a first line option for the oral treatment of patients developing a COVID-19 infection with a subsequent risk of severe disease. Despite its seducing efficacy, the drug has some limitations due to safety. Among them, data in severe renal or hepatic failure and on the high risk of DDI related to ritonavir are lacking. Given this concern on DDI and in cases where the combination of the PAXLOVID™ with commonly prescribed drugs is impossible, other pharmacological options are available taking into account the viral ecology. Sotrovimab is a monoclonal antibody neutralizing SARS-CoV-2 and has shown a 85% decrease in hospitalization and death in infected patients [29]. This drug can also be proposed in patients at-risk of severe disease infected by susceptible virus strains. Another alternative is remdesivir, a nucleotide inhibitor of the viral RNA-dependent RNA polymerase, which has been reported to decrease the death and hospitalization rates of 87% [30]. However, while they do not carry the DDI risk, none of these drugs can be administered in both inpatients and outpatients. For patients in who nirmatrelvir/ritonavir is considered the best option, the recommendations of the French Society of Pharmacology and Therapeutics aim at guiding the clinicians' prescription to alleviate the risk of adverse drug reaction due to DDI. This risk is mainly subsequent to the use of ritonavir as a pharmacokinetic booster, already used in the field of HIV and HVC treatments. Ritonavir is well known as a potent CYP3A4 inhibitor but it is also expected to inhibit CYP2C9, CYP2D6, breast cancer resistance protein (BCRP) and P-glycoprotein (P-gp) [31]. DDI studies showed that the magnitude of these latter interactions may be lower than expected. For example, ritonavir only leads to a 60% increase of desipramine, a reference substrate of CYP2D6 [32]. Limited interaction is therefore expected with most neuropsychiatric drugs. When associated with dabigatran, a reference substrate for intestinal P-gp, at the dose of 100 mg, ritonavir has few effects on the anticoagulant exposure [33]. However, P-gp renal inhibition might be a bit more pronounced, as digoxin exposure may increase from 30 to 80% according to different studies. Ritonavir is also expected to induce CYP1A2, CYP2B6, CYP2C19 and UDP-glucuronyl transferases (UGTs) [31]. CYP2C19 induction may lead to significant decrease in drug exposure as highlighted by the data on voriconazole [34].

The induction of UGT may be different according to isoenzymes. Indeed, if a lower exposure in lamotrigine, which is metabolized by UGT1A4, is expected, a much lower impact

has been described on mycophenolic acid, a drug metabolized by UGT1A9 and 2B7 [20,35].

Interestingly, contra-indications in the SmPC of ritonavir have been extensively maintained in SmPC of PAXLOVID™. Ritonavir was approved in 1996 and many DDI studies have been conducted since then, shedding a light on its pharmacokinetics [25]. Hence, some contra-indications seem quite conservative, and may result from the speed with which the dossier was urgently compiled for the rolling review. For example, the association of PAXLOVID™ with clozapine which is mainly metabolized by the CYP1A2 is contra-indicated even though minimal interaction is expected. Another example is amiodarone, metabolized into an equipotent metabolite, for which no major clinical impact is therefore expected when associated with ritonavir [36]. Nevertheless, as contra-indications in SmPCs are enforceable, we chose to strictly report these contra-indications in our recommendations.

Conclusion

As specialists of both pharmacokinetics and adverse drug reactions evaluation, clinical pharmacologists are at the very heart of professional expertise to help clinicians with the prescription of drugs in a context of DDI. These recommendations intend to be a help for clinicians willing to prescribe nirmatrelvir/ritonavir and to prevent DDI leading to adverse drug reactions or loss of efficacy. They constitute a guideline for primary care situations. Of course, some complex situations may require expert advices and here, again, clinical pharmacologists are at the forefront in providing therapeutic advice.

Disclosure of interest

The authors declare that they have no competing interest.

References

[1] Hilgenfeld R. From SARS to MERS: crystallographic studies on coronaviral proteases enable antiviral drug design. FEBS J 2014;281:4085—96.

[2] Li P, Wang Y, Lavrijsen M, Lamers MM, de Vries AC, Rottier RJ, et al. SARS-CoV-2 Omicron variant is highly sensitive to molnupiravir, nirmatrelvir, and the combination. Cell Res 2022;32:322—4.

[3] Owen DR, Allerton CMN, Anderson AS, Aschenbrenner L, Avery M, Berritt S, et al. An oral SARS-CoV-2 Mpro inhibitor clinical candidate for the treatment of COVID-19. Science 2021;374:1586—93.

[4] Hammond J, Leister-Tebbe H, Gardner A, Abreu P, Bao W, Wisemandle W, et al. Oral nirmatrelvir for high-risk, nonhospitalized adults with COVID-19. N Engl J Med 2022 [10.1056/NEJMoa2118542. Sous presse].

[5] Lemaitre F, Solas C, Grégoire M, Lagarce L, Elens L, Polard E, et al. Potential drug-drug interactions associated with drugs currently proposed for COVID-19 treatment in patients receiving other treatments. Fundam Clin Pharmacol 2020;34:530—47.

[6] Agence Nationale de Sécurité du Médicament. Thesaurus des interactions médicamenteuses. 2020. https://ansm.sante.fr/documents/reference/thesaurus-des-interactions-medicamenteuses-1.[Accessed 18 March 2022].

[7] EMA. Paxlovid, Summary of products characteristics. 2022. https://www.ema.europa.eu/en/documents/product-information/paxlovid-epar-product-information_en.pdf.[Accessed 18 March 2022 (44 pp.)]].

[8] Ancrenaz V, Daali Y, Fontana P, Besson M, Samer C, Dayer P, et al. Impact of genetic polymorphisms and drug-drug interactions on clopidogrel and prasugrel response variability. Curr Drug Metab 2010;11:667—77.

[9] Itkonen MK, Tornio A, Lapatto-Reiniluoto O, Neuvonen M, Neuvonen PJ, Niemi M, et al. Clopidogrel increases dasabuvir exposure with or without ritonavir, and ritonavir inhibits the bioactivation of clopidogrel. Clin Pharmacol Ther 2019;105:219—28.

[10] Badri P, Dutta S, Coakley E, Cohen D, Ding B, Podsadecki T, et al. Pharmacokinetics and dose recommendations for cyclosporine and tacrolimus when coadministered with ABT-450, ombitasvir, and dasabuvir. Am J Transplant 2015;15:1313—22.

[11] Badri PS, Parikh A, Coakley EP, Ding B, Awni WM, Dutta S, et al. Pharmacokinetics of tacrolimus and cyclosporine in liver transplant recipients receiving 3 direct-acting antivirals as treatment for hepatitis C infection. Ther Drug Monit 2016;38:640—5.

[12] Niu W, Li S, Jin S, Lin X, Zhang M, Cai W, et al. Investigating the interaction between nifedipine- and ritonavir-containing antiviral regimens: A physiologically based pharmacokinetic/pharmacodynamic analysis. Br J Clin Pharmacol 2021;87:2790—806.

[13] Grimm SW, Richtand NM, Winter HR, Stams KR, Reele SB. Effects of cytochrome P450 3A modulators ketoconazole and carbamazepine on quetiapine pharmacokinetics. Br J Clin Pharmacol 2006;61:58—69.

[14] Greenblatt DJ, von Moltke LL, Harmatz JS, Durol AL, Daily JP, Graf JA, et al. Differential impairment of triazolam and zolpidem clearance by ritonavir. J Acquir Immune Defic Syndr 2000;24:129—36.

[15] Greenblatt DJ, von Moltke LL, Harmatz JS, Durol AL, Daily JP, Graf JA, et al. Alprazolam-ritonavir interaction: implications for product labeling. Clin Pharmacol Ther 2000;67:335—41.

[16] Schmitt C, Hofmann C, Riek M, Patel A, Zwanziger E. Effect of saquinavir-ritonavir on cytochrome P450 3A4 activity in healthy volunteers using midazolam as a probe. Pharmacotherapy 2009;29:1175—81.

[17] Johnson FM, Agrawal S, Burris H, Rosen L, Dhillon N, Hong D, et al. Phase 1 pharmacokinetic and drug-interaction study of dasatinib in patients with advanced solid tumors. Cancer 2010;116:1582—91.

[18] Freise KJ, Hu B, Salem AH. Impact of ritonavir dose and schedule on CYP3A inhibition and venetoclax clinical pharmacokinetics. Eur J Clin Pharmacol 2018;74:413—21.

[19] Elens L, Langman L, Hesselink D, Bergan S, Moes D, Molinaro M, et al. Pharmacologic treatment of transplant recipients infected with SARS-CoV-2: considerations regarding therapeutic drug monitoring and drug-drug interactions. Ther Drug Monit 2020;42:360—8.

[20] Lemaitre F, Ben Ali Z, Tron C, Jezequel C, Boglione-Kerrien C, Verdier M, et al. Managing drug-drug interaction between ombitasvir, paritaprevir/ritonavir, dasabuvir, and mycophenolate mofetil. Ther Drug Monit 2017;39:305—7.

[21] de Jong J, Skee D, Murphy J, Sukbuntherng J, Hellemans P, Smit J, et al. Effect of CYP3A perpetrators on ibrutinib exposure in healthy participants. Pharmacol Res Perspect 2015;3(4):e00156.

[22] Wind S, Giessmann T, Jungnik A, Brand T, Marzin K, Bertulis J, et al. Pharmacokinetic drug interactions of afatinib with rifampicin and ritonavir. Clin Drug Investig 2014;34:173—82.

[23] Dingemanse J, van Giersbergen PLM, Patat A, Nilsson PN. Mutual pharmacokinetic interactions between bosentan and lopinavir/ritonavir in healthy participants. Antivir Ther 2010;15:157—63.
[24] Sekar V, Lefebvre E, De Marez T, De Pauw M, De Paepe E, Vangeneugden T, et al. Effect of repeated doses of darunavir plus low-dose ritonavir on the pharmacokinetics of sildenafil in healthy male subjects: phase I randomized, open-label, two-way crossover study. Clin Drug Investig 2008;28: 479—85.
[25] EMA. Ritonavir summary of product characteristics. 2022. https://www.ema.europa.eu/en/documents/product-information/norvir-epar-product-information_en.pdf.[Accessed 18 March 2022 (109 pp.)]].
[26] King JR, Menon RM. Ombitasvir/paritaprevir/ritonavir and dasabuvir: drug interactions with antiretroviral agents and drugs forsubstance abuse. Clin Pharmacol Drug Dev 2017;6:201—5.
[27] Olkkola KT, Palkama VJ, Neuvonen PJ. Ritonavir's role in reducing fentanyl clearance and prolonging its half-life. Anesthesiology 1999;91:681—5.
[28] Ouellet D, Hsu A, Qian J, Locke CS, Eason CJ, Cavanaugh JH, et al. Effect of ritonavir on the pharmacokinetics of ethinyl oestradiol in healthy female volunteers. Br J Clin Pharmacol 1998;46:111—6.
[29] Gupta A, Gonzalez-Rojas Y, Juarez E, Crespo Casal M, Moya J, Falci DR, et al. Early treatment for COVID-19 with SARS-CoV-2 neutralizing antibody sotrovimab. N Engl J Med 2021;385:1941—50.
[30] Gottlieb RL, Vaca CE, Paredes R, Mera J, Webb BJ, Perez G, et al. Early remdesivir to prevent progression to severe Covid-19 in outpatients. N Engl J Med 2022;386:305—15.
[31] Cattaneo D, Cossu MV, Rizzardini G. Pharmacokinetic drug evaluation of ritonavir (versus cobicistat) as adjunctive therapy in the treatment of HIV. Expert Opin Drug Metab Toxicol 2019;15:927—35.
[32] von Moltke LL, Greenblatt DJ, Duan SX, Daily JP, Harmatz JS, Shader RI. Inhibition of desipramine hydroxylation (Cytochrome P450-2D6) in vitro by quinidine and by viral protease inhibitors: relation to drug interactions in vivo. J Pharm Sci 1998;87:1184—9.
[33] Kumar P, Gordon LA, Brooks KM, George JM, Kellogg A, McManus M, et al. Differential influence of the antiretroviral pharmacokinetic enhancers ritonavir and cobicistat on intestinal P-glycoprotein transport and the pharmacokinetic/pharmacodynamic disposition of dabigatran. Antimicrob Agents Chemother 2017;61:e01201—17.
[34] Liu P, Foster G, Gandelman K, LaBadie RR, Allison MJ, Gutierrez MJ, et al. Steady-state pharmacokinetic and safety profiles of voriconazole and ritonavir in healthy male subjects. Antimicrob Agents Chemother 2007;51:3617—26.
[35] van der Lee MJ, Dawood L, ter Hofstede HJM, de Graaff-Teulen MJA, van Ewijk-Beneken Kolmer EWJ, Caliskan-Yassen N, et al. Lopinavir/ritonavir reduces lamotrigine plasma concentrations in healthy subjects. Clin Pharmacol Ther 2006;80:159—68.
[36] Ghovanloo M-R, Abdelsayed M, Ruben PC. Effects of amiodarone and N-desethylamiodarone on cardiac voltage-gated sodium channels. Front Pharmacol 2016;7:39.