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Review

Paxlovid (Nirmatrelvir/Ritonavir): A new approach to Covid-19 therapy?

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ABSTRACT

Despite the need for novel, effective therapeutics for the COVID-19 pandemic, no curative regimen is yet available, therefore patients are forced to rely on supportive and nonspecific therapies. Some SARS-CoV-2 proteins, like the 3 C-like protease (3CLpro) or the major protease (Mpro), have been identified as promising targets for antiviral drugs. The Mpro has major a role in protein processing as well as pathogenesis of the virus, and could be a useful therapeutic target. The antiviral drug nirmatrelvir can keep SARS-CoV-2 from replicating through inhibiting Mpro. Nirmatrelvir was combined with another HIV protease inhibitor, ritonavir, to create Paxlovid (Nirmatrelvir/Ritonavir). The metabolizing enzyme cytochrome P450 3 A is inhibited by ritonavir to lengthen the half-life of nirmatrelvir, so rintonavir acts as a pharmacological enhancer. Nirmatrelvir exhibits potent antiviral activity against current coronavirus variants, despite significant alterations in the SARS-CoV-2 viral genome. Nevertheless, there are still several unanswered questions. This review summarizes the current literature on nirmatrelvir and ritonavir efficacy in treating SARS-CoV-2 infection, and also their safety and possible side effects.

1. Introduction

The culprit agent for coronavirus disease 2019 (COVID-19) pandemic is severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2, formerly 2019-nCoV), which is an enveloped positive-sense single-stranded RNA virus (+ssRNA). Taxonomically speaking, SARS-CoV-2 belongs to the *Sarbecovirus* subgenus, *Betacoronavirus* genus, and *Coronaviridae* family, which includes a variety of species that can cause mild to severe human infections, as well as many animal infections. There were six previously identified human coronaviruses 229E, NL63, OC43, HKU1, middle East respiratory syndrome (MERS)-CoV, and SARS-CoV-1; so SARS-CoV-2 became the seventh coronavirus able to infect humans [1–4].

Several treatments for COVID-19 have been proposed, including immunomodulatory drugs, monoclonal antibodies, and various antiviral drugs. However, these treatments have had one or more of these three problems: low efficacy, high price, and toxic side effects, which hampered their use on a large scale [5–7]. It has been reported that Pfizer's novel antiviral drug called "Paxlovid" exhibited good effectiveness against COVID-19. Paxlovid™ is the brand name for the drug, which is made up of two generic medications—nirmatrelvir and ritonavir. The recommended dosage is 300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir. (one 100 mg tablet) all taken together orally every 12 h for 5 days. Nirmatrelvir/ritonavir is composed of two antiviral protease inhibitors, i.e. PF-07321332 (also known as nirmatrelvir) and ritonavir. Nirmatrelvir is a new agent that inhibits the

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3CLpro enzyme in SARS-CoV-2, while ritonavir is an HIV protease inhibitor. Ritonavir inhibits cytochrome P450 3A4, the enzyme responsible for Nirmatrelvir metabolism, which lengthens Nirmatrelvir presence in the body and boosts its activity [8,9]. Adults with COVID-19 who were symptomatic but not-hospitalized, had risk factors (at least one) for severe disease, and were seronegative for SARS-CoV-2, were recruited in the EPIC-HR (Evaluation of Protease Inhibition for COVID-19 in High-Risk Patients) trial. On the day 28 of the trial, the nirmatrelvir/ritonavir group showed a reduction of 88% and 75% in the death and hospital admission rate, respectively, in comparison to control [8].

2. Nirmatrelvir and SARS-CoV-2 variants

The papain-like protease (PLpro) as well as the 3CLpro (aka Mpro) are two promising molecules to target for designing medical agents against SARS-CoV-2. Both of these cysteine proteases play important roles for the SARS-CoV-2 to keep living. Antiviral protease inhibitors may be relatively safe drugs in humans because mammalian protease enzymes have different substrate specificity. In particular, the enzyme 3CLpro (cysteine protease; EC 3.4.22.69) is needed for the cleavage and maturation of proteins to make them functional for the viral replication processes [10,11]. Various medicinal chemistry strategies have focused on the enzyme that catalyzes the process of protein cleavage, which is characterized by a catalytic dyad of Cys145 and His41 [12]. Nirmatrelvir was discovered in 2021 in an attempt to produce agents that inhibit SARS-CoV-2 3CLpro, and functions as a protease inhibitor and can be taken orally; it binds from its nitrile site to the cited dyad of Mpro [13]. Ritonavir is a tripeptide structure which inhibits HIV protease by binding to its functional site. According to the literature, the half-life of nirmatrelvir was 5.1 h in rats and 0.8 h in monkeys. When taken by os, monkeys show relatively poor bioavailability for Nirmatrelvir (8.5%), primarily because this species carries out oxidative metabolism throughout the gastrointestinal tract, while the bioavailability is moderate in rats (34–50%). Overall, nirmatrelvir showed moderate plasma protein binding, with 0.310–0.478 being the average proportion of its free plasma level in rats, monkeys, and humans [14]. In hepatocytes of these species, nirmatrelvir was similarly metabolized with the cytochrome P450 (CYP450) being the main enzyme that oxidized different functional groups of this drug. CYP3A4 was the main mediator of Nirmatrelvir oxidation in humans (fraction metabolized = 0.99). Sandwich-cultured human and animal hepatocytes (between two collagen sheets) showed there was likely to be minor elimination of unchanged nirmatrelvir by renal and biliary excretion. In vitro studies demonstrated that nirmatrelvir reversibly inhibited Mpro in a time-dependent manner and could also promote CYP3A function. The first study in humans showed increasing concentrations of nirmatrelvir when coadministered with ritonavir which inhibited CYP3A4 as the main metabolizer of nirmatrelvir [14].

Moreover, nirmatrelvir can potently inhibit the Mpro proteolytic activity in all seven types of human coronavirus, which include alphacoronaviruses (HCoV-NL63 and HCoV-229E) as well as betacoronaviruses (MERS-CoV, SARS-CoV-1, SARS-CoV-2, HCoV-OC43, and HCoV-HKU1) [13,15]. At the highest tested dose of nirmatrelvir (100 μM), no inhibitory activity was observed against several mammalian proteases, including aspartyl, serine, and cysteine proteases, as well as the HIV protease, which is a retroviral aspartyl protease (retropepsin). In a study by Owen et al. [13], A549 and dNHBE cell lines (two cell lines with human respiratory epithelium origin) were infected by human coronaviruses and nirmatrelvir was administered to assess this drug activity against these species. Nirmatrelvir showed significant antiviral activity against SARS-CoV-2, MERS-CoV, HCoV-229E, and SARS-CoV-1; Moreover, cytotoxic effects were not observed at doses lower than 3 μM. They also infected a murine model with SARS-CoV-2 to assess nirmatrelvir efficacy in vivo. Nirmatrelvir significantly lowered weight loss as well as death rate in comparison to control. Furthermore, viral titer levels measured in the lungs of euthanized mice were significantly lower in the nirmatrelvir group [13].

High risk COVID-19 patients at emergent conditions were prescribed nirmatrelvir after it was approved by FDA on December 2021. Nirmatrelvir may be started after the disease has lasted for 5 days, and should be continued for 5 consecutive days [9]. The EPIC-HR trial assessed nirmatrelvir efficacy in adults with precited criteria [8]. This research was performed at the time of delta variant pandemic; therefore, it lacks data about nirmatrelvir effects on the Omicron variant and also adults with previous exposure to SARS-CoV-2. Arbel et al. recently evaluated nirmatrelvir effects in adults with previous exposure to SARS-CoV-2 and at the time of Omicron pandemic [16]. They included 3902 individuals who met the inclusion criteria and then administered nirmatrelvir. They observed that for patients $\geq$ 65 years, nirmatrelvir induced a significant reduction in admission as well as death rate, compared to the control. However, for younger cases, nirmatrelvir did not notably alter the course of the disease [16]. Furthermore, in a study by Li et al. nirmatrelvir effects on Omicron-infected Calu-3 cells was evaluated [17]. The researchers found that even low concentrations of nirmatrelvir were able to suppress Omicron variant replication. To model the effect of nirmatrelvir in COVID-19–vaccinated patients, Calu-3 cells were treated with the serum of vaccinated individuals and then exposed to either wild-type (WT) or Omicron form. Wild-type SARS-CoV-2 was unable to replicate in the serum-incubated cells while Omicron variant did replicate, albeit at low levels. However, nirmatrelvir treatment was able to successfully suppress the residual replication [17]. Nirmatrelvir antiviral activity was evaluated in another investigation against several different SARS-CoV-2 variants of concern (VOCs) (alpha, beta, gamma, delta, and Omicron) by Vangeel et al. [18]. They showed that nirmatrelvir was effective against all currently known VOCs, including Omicron. They used ORF1ab software to show that there were two known amino acid alterations in the 3CLpro sequence (K90R at position 3353 in Beta, and P132H at position 3395 in Omicron), which did not involve the active site of the 3CLpro, making them unlikely to affect the sensitivity to nirmatrelvir. Similarly, they predicted that nirmatrelvir would remain effective against the alpha, beta, gamma, and delta forms [18]; furthermore, an in silico study of P132H mutation by Dawood showed similar results [19].

It has been shown that some missense point mutations in SARS-CoV-1 3CLpro (with 96% similarity to SARS-CoV-2 3CLpro in the order of amino acids) may affect the protease activity [20]. Catalytic activity may be somewhat higher (S284, T285, I286) or significantly decreased (F140, R298, N28, G11, N214, S139, E166) as a result of these known mutations [21–24]. Lineage comparison [25] of the SARS-CoV-2 genomic material showed three missense mutations with $>$ 20% frequency at the Mpro portion of the ORF1a/b gene [26]. In addition, it has been reported that some of these mutations and SARS-CoV-2 variants may be associated with each other. For example, Lambda (or C.37 in PANGO nomenclature) has a G15S mutation that is $>$ 85% common. Beta (B.1.351) carries a K90R mutation that is $>$ 95% common, and Omicron (B.1.1.529) carries a P132H mutation that is $>$ 95% common [20,25,27,28]. However, the Delta (B.1.617.2) had no association with any specific mutations [25]. This suggests the similarity of Mpro of Delta and WT virus. Recently, Ullrich et al. examined whether nirmatrelvir efficacy alters with Mpro mutations [20]; and therefore, recruited six SARS-CoV-2 variants: Lambda, Omicron, Beta, P.2 Zeta, B.1.1.318, and B.1.2, each of them carrying a specific mutation. The results suggested that nirmatrelvir would be just as effective against the variations as it is against the WT virus, and that the current COVID-19 variations would not impact the effectiveness of nirmatrelvir [20].

The results obtained after various regimens of nirmatrelvir therapy were documented by Peluso et al. in four consecutive cases from a post-COVID cohort analysis [29]. Despite timely antiviral treatment, the first patient suffered a clinical rebound and ultimately acquired long COVID-19. In the two subsequent patients, who took nirmatrelvir 25 and 60 days after their COVID-19 symptoms first appeared, both participants

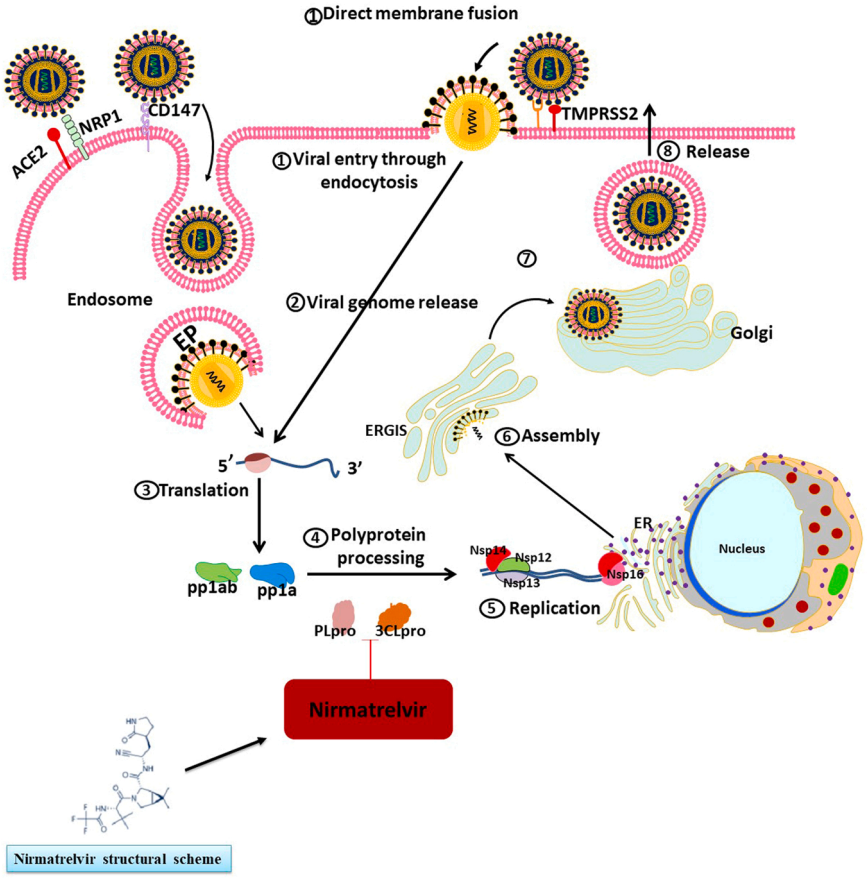

Fig. 1. Nirmatrelvir can inhibit 3CLpro, an enzyme involved in maturation of proteins, in different variants of SARS-CoV-2, and therefore, suppress their replication.

showed an improvement in their condition. The last patient, who had suspected long COVID for two years with a new superimposed COVID, experienced significant relief from chronic symptoms after taking nirmatrelvir. In conclusion, further research is required to elucidate the effects of timely nirmatrelvir therapy on progression of acute COVID to long COVID and also its effects on long COVID itself. [29].

As a surface protein, the S (spike) protein of SARS-CoV-2 functions as a major antigen for the host immune system [30]. This intense selection pressure against the S protein leads to the appearance of variant mutations, thus decreasing the effectiveness of vaccines based on this protein [31–34]. Thus, other proteins with fewer variations may be better targets for facing this virus; Mpro as well as RNA-dependent RNA polymerase (RdRp) are two of these proteins mainly focused on, in the studies [35], which are also exposed to possible mutations. Iketani and

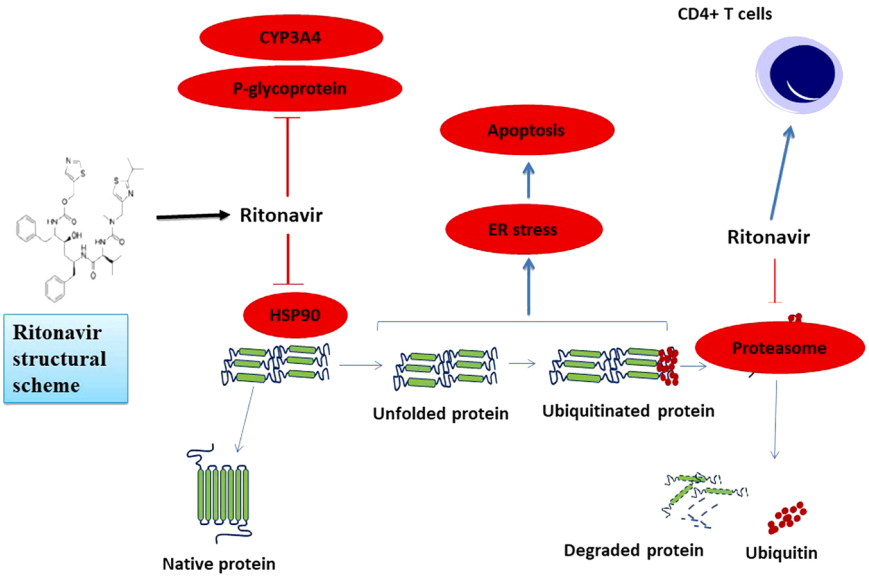

Fig. 2. Cellular processes affected by Ritonavir. Ritonavir may inhibit proteasomes, HSP90 (heat shock protein 90), CYP3A4, as well as P-glycoprotein; it may also modulate the function of immune cells [54].

colleagues recently examined possible mechanisms of resistance to nirmatrelvir [36]. They used different SARS-CoV-2 variants for cellular infection and nirmatrelvir in different doses to evaluate resistance development. They reported that several resistant viruses appeared, and analysis of their genomes showed that they included several 3CL protease mutations. Their large-scale experiment found mutations in 23 different amino acid residues in 53 distinct viral lineages. T21I, P252L, or T304I were found in most viral lineages as precursor mutations which only conferred mild resistance, but the accumulation of further mutations could lead to increased resistance. The most significant resistance was found with the E166V mutation, which reduced the replicative competence of the virus, but this was restored by compensating mutations T21I and L50F. In conclusion, unlike the study of Ullrich et al. [20], their results showed that 3CLpro mutations may cause resistance to nirmatrelvir in SARS-CoV-2 variants, a finding that needs further evaluation [36]. (Fig. 1).

3. Ritonavir implications in COVID-19 treatment

After saquinavir, ritonavir was the second agent with protease inhibition property which was confirmed by FDA to be used in AIDS treatment. Studies have shown that, in addition to inhibiting the HIV protease, ritonavir can also inhibit CYP450–3A4 (Fig. 2). It is now used primarily to enhance the bioavailability of co-administered antiretroviral drugs (ARVs); its combination with standard anti-HIV triple therapy, resulted in increased CD4 + counts and lower HIV RNA levels in treatment-naive individuals [37]. Ritonavir has been found to increase the effectiveness of various ARVs. For example, the combination of lopinavir plus ritonavir significantly reduced viral load and improved immunological parameters in HIV-infected patients who were both previously treated and treatment-naïve [38,39]. Because of its mechanisms of action, ritonavir is being studied in combination with antineoplastic drugs for treating cancer. In addition, its combination with ombitasvir, paritaprevir, as well as dasabuvir has received FDA approval for HCV genotype 1 treatment. Moreover, the FDA approved lopinavir/ritonavir for HIV treatment in the early 2000 s [38].

Pharmacologic enhancement is used to increase the tolerability and effectiveness of protease inhibitors. Ritonavir inhibits two essential metabolic processes, making it the ideal pharmacologic enhancer. Ritonavir inhibits first-pass metabolism, which takes place during absorption. Both P-glycoprotein, a drug efflux transporter that pumps drugs out of the gut wall and back into the intestinal lumen, as well as CYP3A4, an important cytochrome P450 isoenzyme involved in drug metabolism, are found in the enterocytes that line the intestine [40]. Firstly, since ritonavir inhibits P-glycoprotein it may increase the Cmax of the ARV drug. Secondly, ritonavir lengthens the plasma half-life of the drug by inhibiting CYP3A4. The P-glycoprotein in CD4 + cells may also be inhibited by ritonavir to prolong the intracellular half-life of the ARV drug [40]. Although ritonavir-mediated inhibition of CYP3A4 is clinically significant, its precise mechanism of action is not yet established. Still, ritonavir stands out as a powerful mechanism-based enhancer because of its ability to irreversibly inhibit CYP3A4. This irreversible inhibition is thought to occur by four distinct mechanisms: (a) ritonavir metabolites bind to the heme group; (b) unmodified ritonavir strongly binding to the heme iron; (c) damage to the heme molecule; (d) covalent attachment of a reactive ritonavir intermediate to the CYP3A4 apoprotein [41]. Ritonavir can inhibit CYP3A4 and CYP3A5 with almost equivalent potency, and since it has been used in patients from different racial origins, these results are significant. None of the suggested hypothesized mechanism are likely to be completely erroneous, but it is hard to establish what the principal mechanism of action in vivo actually is. In addition, its function through different mechanisms may enhance its inhibitory effectiveness [41].

Patients with HIV who have failed all available treatments have complex mutations that make them resistant to or unable to tolerate nucleoside reverse transcriptase inhibitors, and are therefore eligible for double-boost protease inhibitor combinations such as lopinavir/ritonavir [42,43]; a strategy that may also be used against SARS-CoV-2. It is necessary to mention that although it has been suggested that ritonavir is of the ability to inhibit SARS-CoV-2 protease, ritonavir alone has not shown in vitro activity against this virus [44]. Talking about combination of ritonavir and lopinavir in COVID-19 treatment, lopinavir can also inhibit Mpro of coronavirus, and ritonavir delays its clearance from the body [45,46]. The use of lopinavir-ritonavir in the treatment of a marmoset model infected with MERS-CoV resulted in positive clinical, radiological, as well as pathological results, and also reduced viral load [47]. Lopinavir-ritonavir decreased clinical symptoms in ferrets infected with SARS-CoV-2, but had no impact on viral load [48]. In a human study of COVID-19, the combination of lopinavir-ritonavir and ribavirin resulted in more favorable prognosis as well as decreased virus titer [49]. Lopinavir-ritonavir shortened the duration of viral shedding [50], and was successful in controlling fever [51] in some COVID-19 cases. In another clinical study of COVID-19, lopinavir-ritonavir made no alterations in the course of disease or the outcomes [52]; there was similar lack of efficacy in the study of Horby et al. [53].

4. Nirmatrelvir/ritonavir and COVID-19 therapy

At the time of Omicron pandemic and to assess nirmatrelvir/ritonavir efficacy against SARS-CoV-2, Najjar-Debbiny et al. recruited adults (≥18 years) who were experiencing COVID-19 for the first time and had risk factors for progression into severe disease and followed them for 28 days [55]. They observed that COVID-19 patients receiving nirmatrelvir/ritonavir had significant reduction in the death rate as well as the risk of progression into severe disease in comparison to control; furthermore, the cited effects were more pronounced in the conditions of immunosuppression and also neurological or cardiovascular comorbidities. In conclusion, their findings is in favor nirmatrelvir/ritonavir ability to alter the course of the disease and also death rate [55].

After FDA approved nirmatrelvir/ritonavir in December 2021 to be used for non-severe COVID-19 cases but in risk of progressing into severe disease, Malden et al. decided to evaluate its efficacy in lowering the risk of the concerned progression [56]. Therefore, they gathered the data of 5287 patients who received nirmatrelvir/ritonavir between December 2021 and May 2022, and explored whether they needed presence to health care system between 5 and 15 days after nirmatrelvir/ritonavir course had finished. They observed that of these cases only 45 presented to the health care system of whom six were hospitalized; furthermore, approximately half of these 45 cases had either the risk factor of age (≥65) or the presence of medical comorbidity. Taken together, the low rate of further requirement to medical care observed in their study is again in favor of nirmatrelvir/ritonavir ability to alter the course of the diseases [56].

In a similar retrospective work, Shah et al. analyzed the data of a population of 699,848 Americans who were diagnosed with COVID-19 in the spring and summer of 2022, and evaluated the proportion of them who received nirmatrelvir/ritonavir, and also how nirmatrelvir/ritonavir altered the course of disease [57]. They observed that nirmatrelvir/ritonavir, in general as well as with various demographic adjustments, was of the ability to significantly reduce the rate of admission to hospital, which could be interpreted into its ability to inhibit the progression toward severe COVID-19; regarding their findings, they insisted on a more pervasive use of this medication in outpatient settings [57].

Regarding examining nirmatrelvir/ritonavir use in pregnant women, Loza et al. performed a short term follow up on seven pregnant women of different gestational ages who received nirmatrelvir/ritonavir with a diagnosis of non-severe COVID-19 [58]. Of these seven patients, four with smaller gestational ages did not come to delivery in the time of follow up, and neither showed any specific maternal or fetal adverse events. Of the three remaining patients who came to delivery in the time of follow up, one did not complete the five day course of treatment, and

Table 1
Summary of clinical trials and preclinical studies using nirmatrelvir/ritonavir and nirmatrelvir.

Drug	Model	Cell line, species, number of patients	Administrative way	Does	Time	Findings	Follow up	Phase	Ref
Nirmatrelvir/ ritonavir	Human	Overall: 2246	Oral	nirmatrelvir (300 mg) + ritonavir (100 mg)	Every 12 h for 5 days	Reduced development of severe cases	28 days	2–3	[8]
Nirmatrelvir/ ritonavir	Human	Overall: 180,351 Paxlovid group: 4737	-	-	-	Reduced death rate as well as number of severe cases	28 days	-	[55]
Nirmatrelvir/ ritonavir	Human	-	Oral	Single-ascending dose (SAD): nirmatrelvir (150–1500 mg) and next nirmatrelvir (250–750 mg) +ritonavir (100 mg) and final dose: nirmatrelvir (250 mg) + ritonavir (100 mg). Multiple-ascending dose (MAD): nirmatrelvir dose (75, 250, and 500 mg)+ ritonavir (100 mg).	SAD: − 12, 0, and 12 h relative to nirmatrelvir MAD: twice daily for 10 days	Reduced development of severe cases	28 days	1	[59]
Nirmatrelvir/ ritonavir	Human	14	Oral	-	6.5-days	-	14 days	-	[60]
Nirmatrelvir/ ritonavir	Human	30322	Oral	-	-	Reduced hospitalization, better effects in unvaccinated and obese patients	28 days	-	[61]
Nirmatrelvir/ ritonavir	Human	25 (solid organ transplant recipients)	Oral	-	5 days	It is better to use a lower dose in transplant recipients	30 days	-	[62]
Nirmatrelvir	In vitro	HeLa, S3–ENT1, S3-ENT2	-	-	-	Human ENT1 as well as ENT2 are not affected by Nirmatrelvir	-	-	[63]
Nirmatrelvir/ ritonavir	Human	mild (n = 8), moderate (n = 8), and severe renal impairment (n = 8)	Oral	100–mg nirmatrelvir with 100 mg ritonavir	5 day (ritonavir received 12 h before, together with and 12 and 24 h after the nirmatrelvi)	Renal insufficiency may implicate dose adjustment for nirmatrelvir/ritonavir (150/ 100 mg nirmatrelvir/ritonavir)	28–35 days	1	[64]
Nirmatrelvir/ ritonavir	Human	5287	Oral	nirmatrelvir (300 mg) + ritonavir (100 mg)	Every 12 h for 5 days	Reduced hospitalization and Emergency Department visits	5–15 days	-	[56]
Nirmatrelvir/ ritonavir	Human	482	Oral	nirmatrelvir (300 mg) + ritonavir (100 mg)	Every 12 h for 5 days	Lowered number of the shed viruses and therefore, hampered ability of the virus to infect new cases	7–21 days	-	[65]
Nirmatrelvir/ ritonavir	Human	7	Oral	-	-	Improvement in symptoms as well as elevated rate of negative rapid tests	17 days	-	[66]
Nirmatrelvir, Nirmatrelvir/ ritonavir	In vitro	BL21 (DE3)	-	-	-	Ritonavir significantly lengthens the half-life of nirmatrelvir	-	-	[67]
Nirmatrelvir, Nirmatrelvir/ ritonavir	In vivo	Rats and monkeys	-	-	-	No significant adverse effects were observed for the drug	2-week, 1-month	Cardiovascular, pharmacokinetics, recovery phase	[68]
Nirmatrelvir/ ritonavir	Human	2260	Oral	nirmatrelvir (300 mg) + ritonavir (100 mg)	Every 12 h for 5 days	Reduced death rate as well as number of severe cases	30 days	-	[69]
Nirmatrelvir/ ritonavir	Human	1279 (469 patients (36.7%) received Paxlovid)	Oral	nirmatrelvir (300 mg) + ritonavir (100 mg)	Every 12 h for 5 days	Reduced viral load and mortality	-	-	[70]
Nirmatrelvir	In vitro	VeroE6	-	-	-	The L50F, E166A, and L167F mutation are resistance to nirmatrelvir.	-	-	[71]

the remaining two did not show any specific complications attributable to nirmatrelvir/ritonavir. In conclusion, their study had various pitfalls, the most important one being lack of long term follow up, and therefore, not much could be concluded from it regarding the safety of nirmatrelvir/ritonavir use in pregnancy [58].(Table 1).

5. Safety and tolerability of nirmatrelvir/ritonavir

Although nirmatrelvir/ritonavir seems potent in combating COVID-19, its interactions with transplant drugs should be taken into account [72]. Transplant patients often suffer from immunosuppression and vaccination failure, which along with other concurrent conditions make them vulnerable to development of severe COVID-19 and death [73,74]. Because ritonavir inhibits CYP3A, it has been reported that the concentrations of CYP3A-metabolized drugs can rise by 1.8 up to 20 fold [75]. The rapid increase in plasma levels of tacrolimus, cyclosporine, calcineurin inhibitors (CNIs), or mTOR inhibitors: everolimus and sirolimus in patients exposed to ritonavir is due to the dependence of these drugs on CYP3A metabolism [76]. The intestinal cytochrome CYP3A enzymes break down the tacrolimus molecule, and a sudden rise in its concentration in the bloodstream could cause posterior reversible encephalopathy syndrome, seizures, kidney damage, and even death [76,77]. Recently, Prikis and Cameron reported that nirmatrelvir/ritonavir therapy in a kidney transplant patient receiving tacrolimus was associated with acute renal damage, and a suddenly higher tacrolimus level, which required treatment discontinuation [78]. Their results suggested that elevated concentration of tacrolimus and its metabolites could produce harmful effects, including acute renal damage, resulting from the inhibition of its metabolism by nirmatrelvir/ritonavir; therefore, alternative immunosuppressive drugs or a decrease in daily tacrolimus dosage should be considered throughout the COVID-19 treatment [78].

In addition to the cited immunosuppressive drugs, other drugs like statins, calcium channel blockers, and warfarin must also be taken into account, when administering nirmatrelvir/ritonavir. The FDA European Union Authorization document has a more comprehensive list of possible drug interactions [72].

Considering the novelty of nirmatrelvir/ritonavir, not much is known about its long-term efficacy or any possible adverse effects. However, some studies have reported that nirmatrelvir/ritonavir could induce common side effects like headache, emesis, loose stool, as well as a disturbed sense of taste. Infrequently, muscular aches and elevated blood pressure were also reported [79].

Specifically talking about calcium channel blockers, a case of verapamil toxicity induced by nirmatrelvir/ritonavir was reported, which resulted in decreased level of consciousness as well as bradycardia [80]. The bradycardia prompted the use of an internal pacemaker, besides discontinuation of both verapamil and nirmatrelvir/ritonavir. Fortunately, no serious complications occurred, and the pacemaker was removed after four days [80]. Furthermore, the potential of nirmatrelvir/ritonavir to interfere with normal sinoatrial node function has also been reported [81].

Sathish et al. used rats and monkeys to evaluate the safety profile of nirmatrelvir [68]. The duration of oral nirmatrelvir administration was one month for both species, and the max dose was 1000 mg/kg.day for rats and 600 mg/kg.day for the monkeys. In rats, locomotion, respiratory rate, and bleeding time were observed to be increased. In monkeys, the max dose of nirmatrelvir caused the blood pressure to transiently elevate, the pulse rate to drop, and the transaminase levels to increase, but there were no arrhythmic changes. Taken together, they concluded that nirmatrelvir seems reasonably safe for use in human cases [68].

To assess the efficacy as well as the side effects of nirmatrelvir/ritonavir, Zheng et al. performed a meta-analysis on 13 studies [82]. Their final statistical results denied the nirmatrelvir/ritonavir efficacy in reducing the number rebound cases of COVID-19, but showed that the side effects attributed to nirmatrelvir/ritonavir were not significant [82].

6. Conclusion

Nirmatrelvir, alone or in combination with ritonavir (Paxlovid), seems to be a potent antiviral drug to treat COVID-19, but there are some unanswered questions. First, the full findings of extensive clinical studies are yet to be released. Second, keeping a careful eye on the efficacy of nirmatrelvir against new COVID-19 strains in the years to come is essential. Selection pressure on the virus can cause additional mutations to arise in the protease protein, resulting in a decline in nirmatrelvir/ritonavir effectiveness. Third, regarding the inhibitory effect of ritonavir on CYP3A4, the interactions with other drugs should be kept in mind. Despite these facts, the existing evidence from randomized trials has shown that nirmatrelvir/ritonavir is effective in treating COVID-19 with a reasonable safety profile, and with the most prominent effects of this drug being reduced chance of progression to severe disease and also death rate. Finally, further evaluation is needed to confirm nirmatrelvir/ritonavir efficacy in treatment of COVID-19 and it low manufacturing cost and easy administration make it a valuable tool in fighting COVID-19, especially for countries with a low vaccination rate.

CRediT authorship contribution statement

Hamed Mirzaei involved in conception, design, and drafting of the manuscript. Seyed Mohammad Reza Hashemian, Amirhossein Sheida, Mohammad Taghizadieh, Mohammad Yousef Memar, Michael R Hamblin, Hossein Bannazadeh Baghi, Javid Sadri Nahand and Zatollah Asemi contributed in data collection and manuscript drafting. All authors approved the final version for submission.

Conflict of interest statement

The authors have no relevant financial or non-financial interests to disclose.

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