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PERSPECTIVE

New Perspectives on Antimicrobial Agents: Molnupiravir and Nirmatrelvir/Ritonavir for Treatment of COVID-19

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ABSTRACT Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has emerged to cause pandemic respiratory disease in the past 2 years, leading to significant worldwide morbidity and mortality. At the beginning of the pandemic, only nonspecific treatments were available, but recently two oral antivirals have received emergency use authorization from the U.S. Food and Drug Administration for the treatment of mild to moderate coronavirus disease (COVID-19). Molnupiravir targets the viral polymerase and causes lethal mutations within the virus during replication. Nirmatrelvir targets SARS-CoV-2's main protease, and it is combined with ritonavir to delay its metabolism and allow nirmatrelvir to inhibit proteolytic cleavage of viral polyproteins during replication, preventing efficient virus production. Both drugs inhibit *in vitro* viral replication of all variants tested to date. Each is taken orally twice daily for 5 days. When started in the first 5 days of illness in persons at risk for complications due to COVID-19, molnupiravir and nirmatrelvir/ritonavir significantly decreased severe outcomes (hospitalizations and death) with adjusted relative risk reductions of 30% and 88%, respectively, for the two treatments. Molnupiravir should not be used in children or pregnant persons due to concerns about potential toxicity, and reliable contraception should be used in persons of childbearing potential. Nirmatrelvir/ritonavir may cause significant drug-to-drug interactions that limit its use in persons taking certain medications metabolized by certain cytochrome P450 enzymes. Both treatment regimens are important additions to the management of early COVID-19 in at-risk patients in the outpatient setting.

KEYWORDS COVID-19, SARS-CoV-2, antiviral, molnupiravir, nirmatrelvir/ritonavir

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was recognized in early 2020 as the cause of an outbreak of pneumonia in Wuhan, China (1). Since that time SARS-CoV-2 spread around the world to cause a pandemic that as of February 7, 2022, has led to a reported 394 million infected persons and 5.7 million deaths (2). Its impact on health led to the pursuit of strategies to lessen the risk of infection, disease, and severe outcomes, including the development and evaluation of antivirals. As a *Betacoronavirus* belonging to the *Coronaviridae* family, it has a positive-sense RNA genome. Two viral proteins, the RNA-dependent RNA polymerase (RdRp) and the viral protease, have been successfully targeted in the development of antivirals for other RNA viruses (e.g., influenza, hepatitis C virus), and these also were therapeutic targets for SARS-CoV-2. Remdesivir, an inhibitor of RdRp, was the first effective antiviral identified and licensed (3, 4), but it must be administered parenterally and is used primarily to treat hospitalized patients. Outpatient treatments are needed to decrease the risk of serious complications, including hospitalization and death. Although monoclonal antibodies have been effective for both prevention of disease when administered prophylactically (5) and for decreasing the risk of complications when administered early in disease (6, 7), they also must be administered parenterally and may become ineffective when virus mutations change the epitope targeted by the monoclonal

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antibody. Orally administered therapy is desirable so that it can be used early in infection to prevent serious complications. Two drugs, molnupiravir (Lagevrio, Merck) and a combination of nirmatrelvir and ritonavir (Paxlovid, Pfizer), received emergency use authorization from the U.S. Food and Drug Administration for treatment of mild to moderate SARS-CoV-2 disease in persons at high risk for progression to severe COVID-19, including hospitalizations or death (8, 9).

The pathway for nirmatrelvir/ritonavir to EUA built on previous work (10). The 3-dimensional structure of the SARS-CoV-2 main protease (M^{pro}) was solved quickly after the full viral sequence was reported (11), and it was highly homologous to the SARS-CoV-1 M^{pro}. Prospective inhibitors of the protease were quickly identified based upon prior work with other viruses, including picornaviruses and hepatitis C virus (12, 13). One of these candidates, PF-07321332 (or nirmatrelvir), was identified as significantly inhibiting the SARS-CoV-2 M^{pro} and was further investigated as a treatment for COVID-19 (13).

The active component of molnupiravir, beta-D-N^4-hydroxycytidine (NHC), has been evaluated as an antiviral candidate since the early 2000s, when its activity against hepatitis C virus and bovine viral diarrhea virus and then against SARS coronavirus were reported (14, 15). It subsequently was identified as having activity against other flaviviruses in screens conducted at the Emory Institute for Drug Development (EIDD), and it was designated EIDD-1931. Later high-throughput screening activities showed that NHC had antiviral activity against influenza and respiratory syncytial viruses (RSV) (16), identifying it as a drug with broad antiviral activity. However, the drug in this form was rapidly metabolized when administered orally in nonhuman primate (NHP) studies; modification to the 5′-isopropyl ester of NHC yielded EIDD-2801 (or molnupiravir) and increased its oral bioavailability and *in vivo* anti-influenza activity in the NHP model (17). The emergence of the SARS-CoV-2 pandemic and the need for antiviral treatments led to the evaluation of molnupiravir as a potential therapeutic agent for COVID-19 (18).

CHEMISTRY AND PHARMACOLOGY

Nirmatrelvir/ritonavir. Nirmatrelvir is a peptidomimetic inhibitor of the SARS-CoV-2 M^{pro}, which is also referred to as 3C-like protease (3CLpro) or nsp5 protease (19). Targeting M^{pro} is an attractive therapeutic target, as human host proteases have different substrate specificities and are unlikely to have off-target effects (20). By binding directly and inhibiting the SARS-CoV-2 M^{pro} active site, nirmatrelvir prevents the processing of polyprotein precursors, such as pp1a and pp1ab, that are critical for viral replication. Without proteolytic processing, replication-essential enzymes like RdRp cannot fully function (20). Nirmatrelvir inhibited the activity of recombinant SARS-CoV-2 M^{pro} in a biochemical assay with a K_i value of 3.1 nM and an IC50 of 19.2 nM. Nirmatrelvir is coformulated with ritonavir, an HIV-1 protease inhibitor that lacks activity against SARS-CoV-2 M^{pro}; similar to its role in many treatments of HIV, ritonavir inhibits the CYP3A4-mediated metabolism of nirmatrelvir, resulting in increased plasma concentrations of nirmatrelvir.

Molnupiravir. Molnupiravir is an orally bioavailable isopropylester prodrug (EIDD-2801, MK-4482) of NHC. After absorption, molnupiravir is hydrolyzed by host kinases in plasma to the cytidine nucleoside analogue NHC. Once NHC enters host cells, it is triphosphorylated intracellularly to its pharmacologically active form NHC-TP, which acts as a competitive alternate substrate for the viral RdRp (ns12) (21, 22). NHC-TP is subsequently incorporated as NHC-monophosphate (NHC-MP) into the growing viral RNA strand. Molnupiravir's mechanism of action, known as viral error catastrophe or viral lethal mutagenesis, results from incorporation of NHC-MP into viral RNA, resulting in an accumulation of errors within the viral genome and leading to inhibition of replication (22).

A variety of antivirals that target RdRp are FDA approved for a variety of viral infections. Considering the conserved structure of RdRp between coronaviruses (CoVs), the repurposing of RdRp inhibitors is an attractive approach to combat SARS-CoV-2 infection. Ribavirin has been ineffective at targeting CoVs alone due to the proofreading abilities of the viral 3′–5′ exoribonuclease (ExoN) (23). The ExoN encoded by CoVs functions by removing misincorporated nucleotides from the growing RNA 3′end, creating a potential barrier to effective use of nucleoside analogues against SARS-CoV-2

(24). However, ExoN may not have an important role in preventing NHC inhibition based on the observation that NHC decreased the titers of both wild type (WT) and proofreading-deficient ExoN (ExoN[-]) murine hepatitis virus (MHV) in a dose dependent manner (24). Of note, ExoN(-) MHV demonstrated a statistically significant, but minimal, increase in sensitivity to NHC inhibition compared to WT (EC90 ExoN[-] MHV: 0.72 μM versus WT MHV: 1.59 μM). NHC may evade removal due to ExoN's inability to excise certain nucleoside analogues (25). Alternatively, RdRp may have a natural propensity for nucleoside mismatches despite presence of NHC resulting in an ExoN that cannot prevent dipping below the error threshold and ultimately results in lethal mutagenesis of both WT and ExoN(-) CoV (24, 26).

RdRp produces nascent RNA strands by adding ribonucleosides to the 3′-hydroxyl end, therefore synthesizing RNA strands in a 5′–3′ direction (27). As a pyrimidine nucleoside analog, NHC-MP is incorporated into the RNA strand as a substitute for cytosine (C) or uracil (U) in either the positive- or negative-sense nascent chain during genome replication (28). Cell culture models have demonstrated a propensity for increased G-to-A and C-to-U transitions in viral RNA after NHC treatment in a dose-dependent manner (16, 17, 24, 28–30). These studies support that molnupiravir exerts its antiviral activity through viral error catastrophe or lethal mutagenesis. The mechanism for molnupiravir-induced mutagenesis has also been fully elucidated as a two-step process in biochemical models. NHC-TP preferentially competes with CTP for incorporation into the nascent RNA, whereas UTP also competes but is less likely to be a functional analog. Both studies found that incorporation of NHC-MP into nascent RNA did not interrupt RNA elongation, indicating that NHC-MP is not a chain terminator. When NHC is incorporated into viral RNA that serves as a template for synthesis of new RNA, it can form base pairs and incorporate either guanosine (G) or adenosine (A) bases that are then incorporated into the newly made RNA, causing coding errors (31, 32).

ANTIVIRAL SPECTRUM AND RESISTANCE

Nirmatrelvir/ritonavir. Nirmatrelvir has broad *in vitro* activity against both alpha and beta coronaviruses that infect humans. EC_{50}'s against 229E, MERS and SARS-CoV-1 were 190 nM, 166 nM, and 151 nM, respectively, while for SARS-CoV-2 the EC_{50}s ranged from 32.6 to 77.9 nM depending on the cell culture system and test conditions used (13). The potency of nirmatrelvir to inhibit M^{pro} activity also is similar for *in vitro*-expressed M^{pro}'s (including beta, lambda [C.37], and zeta [P.2]) and inhibiting *in vitro* replication of several variants of concern (including alpha, beta, gamma, delta and omicron [B.1.1.529]) (33, 34). No data are yet available about the occurrence or risk of emergence of resistance to nirmatrelvir. However, biochemical studies with recombinant M^{pro} enzyme have identified several naturally occurring mutations associated with decreased enzyme activity (19). Some of these have been evaluated in cell culture and no change in susceptibility to the drug was observed. Mutations in the M^{pro} alanine 260 to threonine (A260T) or valine (A260V) have been observed in samples from nirmatrelvir/ritonavir-treated study participants; the A260V M^{pro} substitution was not associated with a reduction in nirmatrelvir Mpro activity (19).

Molnupiravir. Molnupiravir's active metabolite, NHC, has broad antiviral activity against a large number of RNA virus families, but it does not inhibit DNA polymerases (or DNA viruses) (35). Human viruses that are inhibited *in vitro* include flaviviruses (hepatitis C) (14), togaviruses (Mayaro virus) (36), alphaviruses (Venezuelan equine encephalitis virus [VEEV], chikungunya virus) (29, 37), filoviruses (Ebola virus) (38), caliciviruses (norovirus) (39), orthomyxoviruses (influenza A and B viruses), pneumoviruses (RSV) (16), and coronaviruses (seasonal, Middle East Respiratory Syndrome virus [MERS], and SARS-CoV-1 and -2) (15, 28, 40). Among SARS-CoV-2 strains, the effective concentration 50% (EC_{50}) ranged from 1 to 2 μM for the Wa-1 strain and variants of concern, including alpha (B.1.1.7), beta (B.1.351), gamma (P.1), delta (B.1.617.2), lambda (C.37), mu (B.1.621), and omicron (B.1.1.529/BA.1 and BA1.1) strains (22, 35). There also was no loss of molnupiravir's *in vitro* activity noted among strains with mutations that reduced the strain's susceptibility to remdesivir (41).

Attempts to generate resistance to NHC have led to low-level resistance for VEEV and MERS but not for RSV or influenza viruses (16, 24, 29). The low-level resistance observed was associated with multiple transition mutations occurring throughout the viral genome, and these findings suggest a high barrier to resistance. To date, no resistance to molnupiravir resistance has been observed in clinical studies (35).

ANIMAL STUDIES

Nirmatrelvir/ritonavir. There are few data reported publicly on the evaluation of nirmatrelvir in animal models. A mouse-adapted SARS-CoV-2 strain (MA10) induces weight loss in infected 10-week-old BALB/c mice. Treatment with nirmatrelvir prevented the weight loss that followed challenge. It also decreased the geometric mean titer of infectious virus in the lung at day 4 by as much as 1.9 $\log_{10}$ 50% cell culture infectious dose, and it decreased the amount of inflammatory lung infiltrate found on histopathology (13). Similar dosages of nirmatrelvir starting 4 h postinfection led to even larger decreases in virus shedding ($\sim$4 $\log_{10}$) and decreased lung pathology in the mouse strain 129 (42). Nirmatelvir also significantly decreased viral lung titers in Syrian hamsters infected with beta and delta variants compared to untreated controls. Transmission of the delta variant to other hamsters cohoused with treated animals was not observed as measured by detection of infectious virus in lung tissues at study day 4 (43).

Molnupiravir. Molnupiravir was studied in animal models of other respiratory virus infections before being evaluated for SARS-CoV-2. A ferret model of influenza A virus infection first demonstrated the efficacy of molnupiravir to decrease virus shedding, symptoms (fever), and histopathologic changes following virus challenge (17). Oral administration of molnupiravir prophylactically (starting 2 h prior to virus challenge) or therapeutically (starting 12 h after virus challenge) prevented weight loss, improved lung function, and decreased viral titers in a SARS-CoV-1 mouse model; similar findings were observed when MERS was the challenge virus (28).

Several different SARS-CoV-2 infection and illness animal models have been used to evaluate the antiviral and therapeutic effects of molnupiravir. The lung-only mouse model is a mouse-human chimera when human lung tissue is implanted subcutaneously into an immunodeficient mouse. The model can be used to assess viral replication in human lung tissue. When molnupiravir prophylactic administration was begun 12 h prior to inoculation of the human lung tissue with SARS-CoV-2, virus titers in the human lung implants were more than 6 $\log_{10}$ plaque-forming units/gram of tissue (PFU/g) lower 48 h after challenge compared to untreated controls. Significant decreases in viral loads in the lung tissue were also noted when molnupiravir was started 24 or 48 h after inoculation of the lung tissue (4.4 $\log_{10}$ and 1.5 $\log_{10}$ PFU/g, respectively) (21).

Syrian hamsters can be infected with SARS-CoV-2 but have little clinical symptomatology; thus, they serve as another *in vivo* model of viral replication. Molnupiravir significantly decreased study day 4 viral levels in the lung when begun 12 h (prophylactic) before of 12 h after (therapeutic) after challenge with the Wa-1 strain (30). Similar antiviral effects were observed when molnupiravir was started 1 h prior to inoculation with alpha and beta variant strains; the extent of bronchopneumonia, edema, and perivascular inflammation also were reduced on histopathological examination in animals that received molnupiravir (44).

Ferrets also have minimal clinical symptoms with SARS-CoV-2 infection other than transient weight loss, so this animal model is also largely an infection model. Molnupiravir administered starting 12 h after inoculation with the Wa-1 strain completing suppressed shedding of infectious virus from the nose within 24 h of treatment. It also prevented transmission of virus to other ferrets that were co-housed with the challenged and treated ferret beginning 30 h after the original virus challenge. In contrast, contacts of untreated ferrets were all infected (45). Thus, molnupiravir treatment decreased viral shedding and decreased the risk of subsequent transmission. From these animal studies, it was clear that molnupiravir has *in vivo* antiviral activity against SARS-CoV-2.

TABLE 1 Pharmacokinetic properties of molnupiravir and nirmatrelvir/ritonavir in healthy subjects (19, 47)

Pharmacokinetic parameter	Molnupiravir		Nirmatrelvir/ritonavir[a]
	Single dose 800 mg (n = 6)	Multiple dose–day 6 800 mg q12h (n = 5)	Single dose 300 mg/100 mg (n = 12)
Cmax[b]–geometric mean μg/mL (% CV)	3.64 (13.4)	2.97 (16.8)	2.21 (33)
AUC_{inf}–geometric mean μg*h/mL (% CV)	8.74 (10.4)	Not reported	23.01 (23)
AUC_{0-12hr}–geometric mean μg*h/mL (% CV)	Not reported	8.33 (17.9)	Not reported
T_{max}–median h (min-max)	1.00 (0.50–1.00)	1.50 (1.00–2.02)	3.00 (1.02–6.00)
$T_{1/2}$–geometric mean h (% CV)	1.29 (7.10)	7.08 (154)	6.05 (1.79)[c]

[a]Administered as two 150-mg tablets. Values are for nirmatrelvir pharmacokinetics.
[b]Cmax, maximum observed concentration; AUC_{inf}, area under the plasma concentration-time curve from zero extrapolated to infinity; AUC_{0-12hr}, area under the plasma concentration-time curve during a dosing interval; T_{max}, time of the maximum observed concentration; $T_{1/2}$, half-life.
[c]Represents arithmetic mean (standard deviation).

PHARMACOKINETICS

Nirmatrelvir/ritonavir. Several pharmacokinetic phase 1 trials of nirmatrelvir/ritonavir have been performed or are under way (NCT05129475, NCT04909853, NCT05005312, NCT05178654) (42). Nirmatrelvir displays less than dose-proportional pharmacokinetics up to 750 mg as a single dose and up to 500 mg delivered twice daily orally as multiple doses (19). Ritonavir acts as a pharmacokinetic enhancer to improve systemic exposure and prolong the half-life of nirmatrelvir. After absorption, nirmatrelvir/ritonavir has a T_{max} of 3.00 h and a $t_{1/2}$ of approximately 6 h. By administering nirmatrelvir with a PK booster, it can be administered twice daily. Table 1 summarizes published data on the pharmacokinetics of nirmatrelvir/ritonavir (19).

Nirmatrelvir combined with ritonavir displays moderate protein binding (69%), whereas ritonavir alone is highly protein bound (~99%) (19). Delivered in combination with ritonavir, nirmatrelvir exhibits minimal metabolic clearance despite being a CYP3A substrate. This is in contrast to ritonavir, which demonstrates significant hepatic metabolism via CYP3A and, mildly, CYP2D6. Approximately 50% of nirmatrelvir is recovered as unchanged drug in the feces and ~35% as unchanged drug in the urine. A high-fat meal only modestly increased exposure to nirmatrelvir/ritonavir, with an increase in mean Cmax by approximately 15% and mean AUC_{last} by 1.6%. As such, nirmatrelvir/ritonavir can be taken with or without food and without regard to meals.

Molnupiravir. Molnupiravir as a prodrug is either not detectable or is only detectable at low concentrations 0.5 h and 1 h after administration (46). Following first-dose oral administration in humans, NHC has a rapid uptake (time [T_{max}] to maximal concentration [Cmax]: 1.0 – 1.75 h) but short plasma half-life ($t_{1/2}$: ~1h; mean 0.918 – 1.18 h), as it quickly transforms intracellularly to its active antiviral form, NHC-TP. After repeated administration of NHC at therapeutic doses, biphasic elimination is observed, and the mean $t_{1/2}$ increases to 7.08 h (47). There also was no observed accumulation of serum concentrations after single or multiple doses, similar to findings in animal studies (16, 17, 47). NHC-TP has an intracellular $t_{1/2}$ of 3 h in cultured Huh-7 cells and 6.6h in murine lung tissue, providing support for a twice-daily administration regimen. Following single and multiple doses, the mean Cmax and area under the curve (AUC) versus time curve increased. In addition, food affects the rate, but not the extent, of absorption of molnupiravir (47). Following administration of 200 mg of molnupiravir in a fed state, the T_{max} occurred later (median 3 h fed versus 1 h fasted postdose), resulting in a lower Cmax of approximately 36%. However, the exposure (AUC_{inf}) was similar for both fed (1,890 ng x h/mL) and fasted states (1,980 ng x h/mL). As such, molnupiravir can be administered with or without regard to timing of food or meals. Table 1 summarizes the molnupiravir pharmacokinetics (22, 47).

Molnupiravir exhibits no appreciable protein binding (22). However, it has a modest volume of distribution of 142 L. *In vivo* PK studies in mice revealed a dose-dependent exposure in respiratory tissue similar to plasma (16). Additionally, NHC-TP has sustained concentrations in lung tissue for over 8 h after administration. Ferrets orally administered molnupiravir also had sustained amounts of active NHC-TP in respiratory tissues (>3.2 nmol/g lung tissue), the primary site of influenza and SARS-CoV-2

infection (17), and comparable levels were observed in hamsters (30). To date, there are no additional data on distribution of molnupiravir outside the respiratory tract. After conversion to NHC-TP, molnupiravir does not exhibit appreciable metabolism. Molnupiravir (NHC) is minimally excreted as an unchanged drug in the urine (22). Only 0.85% and 3.61% of the dose is recovered in urine after single and multiple-dose administrations, respectively. Therefore, renal clearance is unlikely to be a major contributor to the elimination of molnupiravir. This is unique among other currently available nucleoside analogues, which are actively secreted by the kidney.

DOSAGE AND DRUG ADMINISTRATION

Nirmatrelvir/ritonavir. Paxlovid consists of nirmatrelvir tablets combined with ritonavir tablets. Nirmatrelvir is supplied as 150-mg tablets, and ritonavir is supplied as 100-mg tablets. The current recommended dosage of Paxlovid for persons 12 years of age and older and at least 40 kg in weight is 300 mg nirmatrelvir (two 150-mg tablets) with 100 mg ritonavir (one 100-mg tablet), with all three tablets taken together orally twice daily for 5 days (19). Ritonavir must be coadministered with nirmatrelvir to ensure nirmatrelvir's therapeutic effect. It is currently only available in a carton holding five blister cards that designate morning and evening doses with the aforementioned dosing instructions. Nirmatrelvir/ritonavir requires dose adjustment to 150 mg/100 mg orally twice daily for patients with moderate renal impairment (eGFR $\geq$30 – 60 mL/min; see "Special Populations: Renal dysfunction" below). In the latter group, the additional doses (one 150-mg nirmatrelvir tablet from the morning dose and one 150-mg tablet from the evening dose) can be removed from the blister cards and the patients educated about the rationale for the adjustment (19, 48).

Molnupiravir. Molnupiravir is supplied as a 200-mg capsule. The current recommended dosing for adults 18 years of age and older is 800 mg (four 200-mg capsules) taken by mouth every 12 h for 5 days (22). Molnupiravir is currently not recommended for use in pediatrics, as safety and efficacy have not been established at the time of this writing.

Therapy with nirmatrelvir/ritonavir and molnupiravir should be initiated within 5 days of symptom onset in patients with a diagnosis of COVID-19. Both drugs can be taken with or without food.

Molnupiravir and nirmatrelvir/ritonavir are two of the first authorized COVID-19 therapeutics to be patient administered. Compliance with previous therapies have been ensured, as they were administered in a controlled hospital setting or as a one-time infusion in various outpatient settings. Patient compliance with the prescribed regimens is imperative to ensure maximum efficacy and minimal toxicities or downstream effects.

DRUG INTERACTIONS

Nirmatrelvir/ritonavir. While evidence from decades of use in the treatment of HIV can help to navigate potential drug interactions with ritonavir, little is known to date about nirmatrelvir's interaction potential or the significance of certain interactions with combination nirmatrelvir/ritonavir after a short, 5-day course of therapy. *In vitro* data have identified nirmatrelvir as a substrate for human MDR-1 (P-gp) and 3A4, but it is not a substrate for human BCRP, MATE1, MATE2K, NTCP, OAT1, OAT2, OAT3, OCT1, OCT2, PEPT1, OATPs 1B1, 1B3, 2B1, or 4C1. Nirmatrelvir can reversibly inhibit CYP3A4 in a time-dependent fashion and inhibit P-gp, but at clinically relevant concentrations it does not reversibly inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6. Additionally, it does not induce any CYPs. There are several ongoing clinical trials investigating the drug-drug interaction effects of nirmatrelvir in combination with ritonavir (NCT05064800, NCT04962022, NCT05032950, NCT04962230). Preliminary data on the coadministration of nirmatrelvir/ritonavir after five doses with itraconazole and carbamazepine are available (19). Importantly, this preliminary data only assessed the effect of concomitant medications on nirmatrelvir and did not provide further details on the effect of ritonavir on these medications, which are also CYP3A substrates. Carbamazepine, a potent CYP3A inducer, titrated to 300 mg orally twice daily, resulted in approximately 50% reduction in Cmax (Cmax ratio: 56.8) and AUC (AUC_{inf} ratio: 44.5). Therefore, potent CYP induction resulted in significant reduction in nirmatrelvir

exposure and could result in suboptimal concentrations. Conversely, concomitant itraconazole, a potent CYP3A inhibitor, resulted in a 20% and 30% increase in Cmax (Cmax ratio: 118.6) and AUC (AUC_{tau} ratio: 138.8), respectively. It is unclear at this time how increased exposure may affect tolerability and toxicities of nirmatrelvir.

Ritonavir is a CYP3A4 and CYP2D6 substrate. Ritonavir has dose-dependent and time-dependent inhibition of CYP3A, P-gp, and, to a lesser extent, CYP2D6. Additionally, it induces metabolism of CYP3A, CYP1A2, CYP2C9, and CYP2B6. Of course, the use of ritonavir in combination with nirmatrevlir is an intentional drug-drug interaction that allows for optimized pharmacokinetics of nirmatrelvir, a CYP3A4 substrate. However, these same interactions that make ritonavir an advantageous pharmacokinetic booster also precipitate numerous clinically significant drug interactions that can cause accumulation of drugs and potential toxicity. It has been estimated that the CYP3A subfamily of enzymes plays a role in the metabolism of approximately 50% of available medications, resulting in a significant number of impacted medications when prescribed alongside ritonavir (49). Ritonavir displays irreversible, mechanism-based inhibition that is a result of the inactivation of the CYP3A enzyme via the formation of metabolic intermediates that bind tightly to the enzyme (50). Consequently, ritonavir exhibits dose- and time-dependent inhibition. While initially FDA approved at doses of 600 mg orally twice daily for treatment of HIV-1, current prescribed doses of 100 to 200 mg daily are adequate to produce maximal or near maximal inhibition (51, 52). CYP3A inhibition by ritonavir is rapid, and maximal inhibition occurs after 48 h of therapy with over 90% reduction in metabolic clearance compared to baseline (53). One study in patients receiving ritonavir with midazolam illustrated that midazolam AUC increased significantly after 2 to 4 h postadministration compared to baseline (49.63 versus 9.81 [hr x nmol/l]/mg) and achieved maximal inhibition after 48 h of therapy with over 90% reduction (8.4% CLmet versus baseline) in metabolic clearance compared to baseline (53). Due to the irreversible, mechanism-based inhibition, CYP3A metabolic activity is only marginally restored (27% CLmet versus baseline) 3 days after discontinuation of therapy. Continued inhibition postdiscontinuation has been demonstrated in other studies with triazolam (51, 54). Despite nirmatrelvir/ritonavir's short 5-day duration for the treatment of COVID-19, it is likely that CYP3A inhibition by ritonavir will be quick and profound, particularly in drugs that rely on CYP3A isoform primarily for metabolism (51). While it is not known when complete metabolism is restored after discontinuation of potent CYP inhibitors, it may be reasonable to assume concomitant therapies will need to be held or reduced for longer than 3 days after discontinuation.

Conversely, ritonavir can induce the metabolism of various CYP enzymes. Maximal induction effect by CYP enzyme inducers is seen after 7 to 14 days with $t_{1/2}$ of 3.5 days (50, 55). Ritonavir is suspected to be an autoinducer as trough concentrations of ritonavir decline and clearance of concomitant interacting agents increases slowly over time (53, 55). In the short term, it appears that CYP induction plays a minor role compared to active inhibition. With extended or chronic use of ritonavir, induction becomes increasingly important. With a short 5-day course of nirmatrelvir/ritonavir, it is less clear how important this aspect of ritonavir metabolism is on drug interactions.

Given prolonged inhibition after discontinuation of the drug, concomitant drugs may need to be held or dose reduced for a period of time after completion of therapy with nirmatrelvir/ritonavir. While we await clinical-trial and real-world drug-drug interaction data on the use of nirmatrelvir/ritonavir, prescribers and pharmacists must be diligent in their approach to mitigating drug-drug interactions. Many drugs are listed as absolute contraindications with nirmatrelvir/ritonavir (see EUA). If these medications cannot be safely held or dose-reduced based on available data, patients will be unable to receive this preferred therapy. Other drugs may only be listed as relative contraindications, making the decision of whether to start nirmatrelvir/ritonavir challenging to the prescriber. This becomes increasingly challenging when patients on are multiple interacting medications. Utilizing new and existing resources to assess the potential and significance for drug-drug interactions and therapeutic approaches (e.g., holding

or reducing doses of interactions drug) is highly recommended before prescribing or dispensing this drug. An in-depth review of interacting medications is beyond the scope of this review, but the Liverpool COVID-19 Drug Interactions website can be used to identify important drug-drug interactions (56).

Molnupiravir. Significant drug interactions in humans have not been studied or reported for molnupiravir. Since molnupiravir is a prodrug and is metabolized by human esterases to its active form, the potential for drug interactions is limited. *In vitro* studies indicate that molnupiravir and active NHC are not substrates of CYP enzymes, human P-gp, or BCRP transporters (22). Additionally, *in vitro* studies demonstrate that molnupiravir and NHC are not inhibitors of CYP1A2, 2B6, 2C8, 2C9, 2D6, and 3A4 or inhibitors of OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3, MATE1, MATE2K, MRP2, MDR1, and BCRP. They are also not inducers CYP1A2, 2B6, and 3A4.

CLINICAL DATA

Nirmatrelvir/ritonavir. The efficacy of nirmatrelvir/ritonavir was evaluated in nonhospitalized adults in a phase 2/3 randomized, double-blind, placebo-controlled study, EPIC-HR (19, 57). Eligible patients had confirmed COVID-19, symptom onset within 5 days, and at least one risk factor for progression to severe disease; persons with a history of prior COVID-19 or COVID-19 vaccination, active liver disease, moderate to severe renal impairment, HIV with a viral load >400/mL, hypoxemia, and receiving medications that depend on CYP3A4 were excluded. The primary endpoint was COVID-19-related hospitalization or death due to any cause through 28 days from study start, and persons who received or were expected to receive monoclonal antibody therapy at the time of randomization were excluded from the modified intent-to-treat (mITT; symptom onset 3 or fewer days from treatment initiation) and mITT1 (symptom onset 5 or fewer days from treatment initiation) analyses. The final study population included in the mITT1 analysis was 2,085 patients, and recipients of nirmatrelvir/ritonavir had a relative risk reduction of 88% (95% CI 75% to 95%) and an absolute reduction in the primary endpoint of 5.6% compared to placebo using a Kaplan-Meier method (0.8% versus 6.3%, respectively). There were 12 (1.1%) deaths among placebo recipients compared to none in the nirmatrelvir/ritonavir group. The reduction in COVID-19-related hospitalization or death due to any cause was similar in those with symptom onset of 3 or fewer days and those with onset of more than 3 days (up to 5 days) (19, 57).

After nirmatrelvir/ritonavir received emergency use authorization and it has been used in clinical practice, the occurrence of rebound illness and increases in viral load following completion of a 5-day treatment course have been reported (58–60). The frequency in which this occurs is unclear, although increases in viral load were noted in 1 to 2% of participants in the phase 3 clinical trial (61).

Molnupiravir. The MOVe-OUT study is a phase 2/3 randomized, placebo-controlled, double-blind clinical trial that assessed the safety and efficacy of molnupiravir in a nonhospitalized adult population. In the phase 2 component of the study participants with mild to moderate COVID-19 with onset of up to 7 days earlier were randomized in a 1:1:1:1 distribution to receive 200 mg, 400 mg, or 800 mg of molnupiravir or placebo twice a day for 5 days. The primary efficacy endpoint was hospitalization or death by study day 29, although the study was not powered to find significant differences between the treatment groups. Overall, 7 (3.1%) of the 225 persons randomized to one of the molnupiravir groups was hospitalized compared to 4 (5.4%) of the 74 placebo recipients. Hospitalization frequencies were similar between the molnupiravir dosage groups (62).

The phase 3 portion of the MOVe-OUT study examined only the 800-mg dosage of molnupiravir compared to placebo. Participants had mild-moderate laboratory-confirmed COVID-19 with onset no more than 5 days earlier and had at least one underlying condition that placed them at increased risk of severe illness. Exclusion criteria included dialysis, chronic kidney disease stage 4 or higher, pregnancy, unwillingness to practice contraception for at least 4 days after treatment completion, neutropenia

(absolute neutrophil count <500 per microliter), thrombocytopenia (<100,000 per microliter), and prior SARS-CoV-2 vaccination. The primary efficacy outcome remained the incidence of hospitalization for 24 h or longer or death through study day 29. An interim analysis was planned after data from the first 775 enrolled participants became available, and molnupiravir achieved prespecified superiority over placebo in preventing hospitalization or death in the mITT population (7.3% versus 14.1%, respectively). However, the absolute reduction in hospitalization frequency decreased from 6.8% in the interim-analysis population to 3.0% for the 1,408 persons in the final mITT population (6.8% and 9.7% in molnupiravir and placebo groups, respectively; adjusted relative risk reduction 30%). A single death occurred in the molnupiravir group compared to 9 among placebo recipients during the 29-day follow-up period. Reductions from baseline nasopharyngeal SARS-CoV-2 RNA levels as measured by RT-qPCR were also significantly lower on study days 3 and 5. The delta variant was the most common variant identified among study participants (63).

A phase 2 randomized, placebo-controlled, double-blind study, MOVe-IN, of molnupiravir also was conducted among hospitalized patients who were not critically ill and whose symptoms began within the prior 10 days. The primary efficacy endpoint was sustained recovery through day 29 and was defined as discharge from the hospital without rehospitalization or medically ready for discharge without requirement for ongoing medical care. The study evaluated the same drug dosage groups as in the phase 2 MOVe-OUT study (200 mg, 400 mg, or 800 mg administered twice daily for 5 days). No clinical benefit of molnupiravir was observed, with median time to recovery being 9 days in all treatment groups and the percentage of recovered participants at study day 29 ranging from 81.5% (200-mg group) to 85.2% (800-mg group) in the molnupiravir groups and 84.7% in the placebo group. Almost three-quarters of enrolled participants had been ill for more than 5 days, and the study team concluded that the lack of a clear therapeutic effect was due to initiating therapy later in the course of the disease (64).

SPECIAL POPULATIONS

Pregnancy and lactation. There are no available data on the use of molnupiravir or nirmatrelvir/ritonavir in pregnant or lactating women (19, 22). Embryo-fetal developmental studies of nirmatrelvir were performed in rats and rabbits (65). In rats, no significant abnormalities were observed, while in the rabbit studies lower fetal body weights were observed at the highest dose (~10 times the expected nirmatrelvir treatment exposure). Because of the risks associated with SARS-CoV-2 infection in pregnancy, the benefit of treatment with nirmatrelvir/ritonavir may exceed the associated risks. However, based upon animal data, molnupiravir may pose a risk of fetal harm when it is administered during pregnancy. Doses eight times the expected NHC treatment exposure (at 800 mg twice daily) caused developmental toxicity, including lethality, teratogenicity, and other developmental abnormalities in a pregnant rat model. Fetal growth was also reduced, a finding that was also observed in a pregnant rabbit model at 18 times the expected NHC treatment exposure. Although NHC could be detected in the plasma of the pups of lactating rats, no effects on pup development, growth, or behavior was noted (35). Because of the potential for embryo-fetal toxicity, molnupiravir is not recommended for use in pregnancy (22). In women of childbearing potential, reliable contraception should be used during treatment and for 4 days after completion of therapy. In sexually active men with reproductive potential with partners of childbearing potential, reliable contraceptive methods are recommended while taking molnupiravir and for at least 3 months after the final dose of treatment (22).

Pediatrics. Nirmatrelvir/ritonavir is not recommended for use in children under 12 years of age or in persons weighing less than 40 kg. Although the safety and efficacy of nirmatrelvir/ritonavir have not been demonstrated in pediatric patients, the adult dosing is expected to yield similar drug exposures in persons 12 years of age and older who weigh at least 40 kg (19).

Molnupiravir is not recommended for use in persons under 18 years of age. Animal studies demonstrated impaired transformation of growth cartilage into new bone in

rats in a 3-month study at ≥500 mg/kg/day (five-times the human NHC exposures at the RHD) (22). This effect was not seen in a shorter 1-month study in mice and rats at higher exposures (2,000 mg/kg/day [19 times human NHC exposure] and 500 mg/kg/day [4 to 8 times human NHC exposure], respectively) or in dogs after 14 days in dosages similar to human exposures (50 mg/kg/day). As growth cartilage is not present in mature skeletons, these findings do not apply to adult humans but may pose a risk for pediatric patients.

Renal dysfunction. The dosage of nirmatrelvir should be halved to 150 mg (1 tablet) with the 100 mg of ritonavir in persons with moderate renal dysfunction (estimated glomerular filtration rate [eGFR] ≥30 to <60 mL/min/1.73 m^2). Nirmatrelvir/ritonavir should not be used in persons with severe renal impairment (eGFR <30 mL/min/1.73 m^2) at this time due to lack of data to inform appropriate dosage adjustments (19). In contrast, molnupiravir does not require dosage adjustment in persons with renal dysfunction. Population pharmacokinetic analyses did not find a meaningful effect of mild to moderate dysfunction on molnupiravir's pharmacokinetics, and although the pharmacokinetics have not been studied in persons with more advanced kidney dysfunction, including in those on dialysis, the kidneys do not contribute meaningfully to the drugs' clearance (22).

Hepatic impairment. No dosage adjustments are recommended for nirmatrelvir/ritonavir in persons with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) liver disease, but it is not recommended for persons with severe (Child-Pugh Class C) liver disease (19). No dosage adjustment of molnupiravir is required for persons with hepatic impairment (22).

ADVERSE EVENTS

Nirmatrelvir/ritonavir. There are limited data on the adverse event profile of nirmatrelvir/ritonavir in combination. To date, the safety of nirmatrelvir/ritonavir is based on data from the EPIC-HR trial (57). A total of 2,224 symptomatic patients received treatment or placebo and were followed for adverse events while on study medication and through day 34 after initiating therapy (19). The most common adverse events in the nirmatrelvir/ritonavir group (≥1% compared to placebo and ≥5 subject difference) were dysgeusia (6% in nirmatrelvir/ritonavir groups versus <1% placebo group), diarrhea (3% versus 2%), hypertension (1% versus <1%), and myalgia (1% versus <1%). The proportion of adverse events resulting in discontinuation of therapy was 2% in the nirmatrelvir/ritonavir group versus 4% in the placebo group. While ritonavir has been used for decades in combination with other antiretroviral therapies in HIV, its safety and tolerability with prolonged use is likely not applicable to a short 5-day course of therapy in COVID-19, except in patients taking medications with significant drug interactions where even short exposures to ritonavir could cause dangerous changes leading to toxicity (e.g., tacrolimus in transplant recipients) or lack of efficacy of nirmatrelvir/ritonavir (e.g., rifampin).

Molnupiravir. Data related to the adverse-effect profile of molnupiravir are limited to clinical trials. At the time the EUA was issued, only 900 subjects had been exposed to therapeutic doses, with the majority of doses given in the phase 3 MOVe-OUT study (22). In the MOVe-OUT trial, molnupiravir had a favorable adverse-event profile overall (63). Approximately 30% of patients in the molnupiravir group experienced at least one adverse event compared to 33% in the placebo group. However, only 8.0% versus 8.4% of the total adverse events for molnupiravir and placebo, respectively, were considered related to the trial regimen. The proportion of serious adverse events reported was 6.9% in the molnupiravir arm compared to 9.6% in placebo, the majority of which were related to COVID-19. No patients experienced a serious adverse event or discontinued the assigned regimen due to a serious adverse event related to the therapeutic regimen. The most common adverse events reported in the trial (≥2% of participants in either group) were COVID-19 pneumonia (6.3% versus 9.6% in the molnupiravir group versus the placebo group), diarrhea (2.3% versus 3.0), and bacterial pneumonia (2.0 versus 1.6%). Additionally, the most common adverse events deemed to be

directly related to the trial regimen (≥1% of participants) were diarrhea (1.7% versus 2.1%), nausea (1.4% versus 0.7%), and dizziness (1.0 versus 0.7%). Selected grade 3 and 4 laboratory abnormalities in chemistry (alanine aminotransferase, aspartate aminotransferase, creatinine, lipase) and hematology (hemoglobin, platelets, leukocytes) occurred in ≤2% and at similar rates between arms. Frequencies of reported adverse events among participants in the MOVe-IN trial were similar among molnupiravir (55.5%) and placebo (61.3%) recipients, and investigators could not clearly identify adverse events that were attributable to molnupiravir use (64).

FUTURE DIRECTIONS

The oral drugs molnupiravir and nirmatrelvir/ritonavir are now available for the treatment of mild to moderate COVID-19 in adults at high risk for progression to more severe illness. Future studies will need to assess the utility, if any, of these drugs in pediatric and highly immunocompromised populations (e.g., transplant recipients) and those who have some immunity to SARS-CoV-2 through prior vaccination or infection. Additional studies are needed in populations for which insufficient pharmacokinetic and safety data are available, such as for nirmatrelvir/ritonavir in persons with advanced renal or liver disease. Information about the development of drug resistance, especially in highly immunocompromised patients, will be an important determinant of the ultimate utility of these drugs in these populations. Studies also will assess the effectiveness of the drugs to treat disease in persons not at risk for progression and as prophylactic agents such as after high-risk exposures to SARS-CoV-2-infected persons. The occurrence of rebound illness also raises the question of the optimal duration of therapy; repeat courses of treatment are not recommended at this time (59). Future studies are needed to evaluate the value of extending initial courses of therapy beyond 5 days. Finally, there is also a need to develop additional oral medications that do not have the limitations of these drugs for more widespread use.

EXPERT OPINION

The availability of molnupiravir and nirmatrelvir/ritonavir increases the options for treating mild to moderate COVID-19 early within the first 5 days from illness onset among adults at high risk for disease progression. Other available treatments require parenteral delivery, which increases the complexity of care delivery in outpatient settings, and availability of the different treatments has been variable in different locations and at different times. Nirmatrelvir/ritonavir is preferred because of its high efficacy and ease of administration for eligible patients who do not have a contraindication for the drug (Fig. 1) (66, 67). Remdesivir administered intravenously once daily for 3 days is effective at preventing complications, but the need for access to an infusion center poses a problem for many clinical sites (68). Monoclonal antibodies have similarly high efficacy, but they also must be delivered parenterally, and their activity can vary with different variants (66). In addition, patients must be monitored for reactions during and after administration of the monoclonal antibody, a requirement that can pose logistical challenges for some health care systems. Molnupiravir is the least effective of the options available, and the restrictions around its use in pregnancy (or potential for pregnancy) limits its attractiveness as a therapeutic. Nevertheless, it effectively decreases the risk of complications in high-risk patients and can be considered for persons who are at risk, have no contraindications for its use, and have no other options available. It is unlikely that the magnitude of treatment benefits with nirmatrelvir/ritonavir or molnupiravir in persons who are fully vaccinated or those who are not at risk for severe disease will be similar to those of unvaccinated persons or those without risk factors for disease progression; future studies are needed to assess the level of benefit from these treatments in such patients.

The pattern of the pandemic thus far has been the emergence of new variants and subvariants as the population develops partial immunity. To date, these two antivirals have maintained activity against the emerging strains. While it is possible that resistance

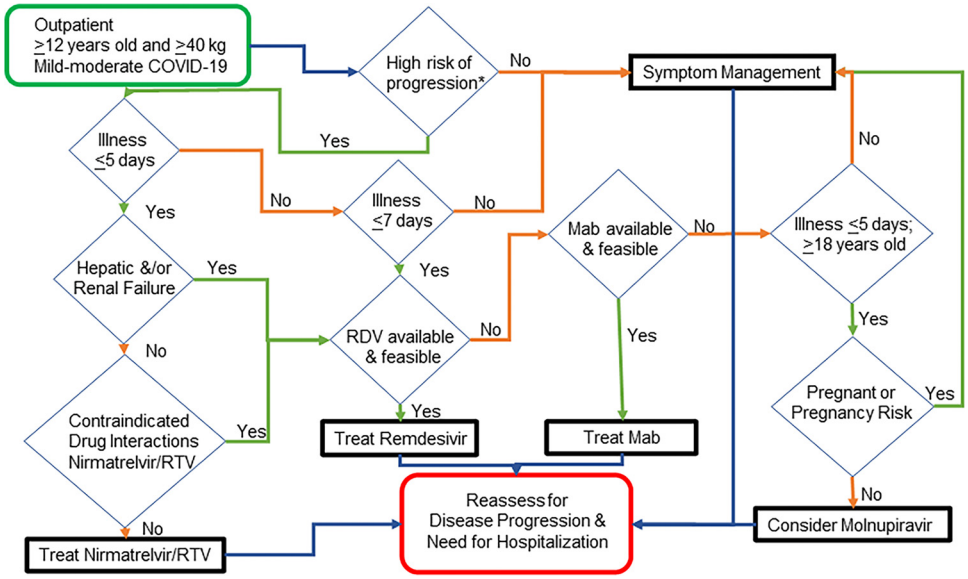

FIG 1 Algorithm for treatment selection in outpatients with mild to moderate COVID-19 at risk of progression* to severe disease (as of June 1, 2022). Several therapies are available, including nirmatrelvir/ritonavir, a 3-day course of remdesivir, monoclonal antibody infusions, and molnupiravir. Prevalent circulating variants in a population will affect the choice(s) of monoclonal antibody treatment options. *Risk of progression to severe disease is as defined by the CDC (https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html).

to nirmatrelvir/ritonavir could emerge, it is unlikely that this will become a major problem for the general population without widespread drug use. Molnupiravir's high barrier to resistance also makes the emergence of drug resistance unlikely. Thus, it is expected that circulating and emerging SARS-CoV-2 strains will continue to be susceptible to these two antivirals.

CONCLUSIONS

Molnupiravir and nirmatrelvir/ritonavir are oral therapies that have received emergency use authorization to treat mild to moderate COVID-19 in the first 5 days of illness in persons at increased risk of complications from their infection. The potential utility of molnupiravir is limited by its lower reported effectiveness at preventing hospitalization compared to other outpatient therapies and by its potential toxicity in children and pregnant women. Nirmatrelvir/ritonavir has a higher reported effectiveness for preventing hospitalizations, but its potential for drug-drug interactions and drug clearance pathways may prevent its use in some at-risk patients. Nevertheless, the availability of these new drugs should facilitate the management of high-risk patients with early COVID-19.

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