The new oral antiviral agents for COVID-19

Seneviratne SL[1'2], Dalugama C[3], Madanayake P[4], Samaraweera B[5], Kariyawasam J[6], Abeysuriya V[7]

[1]Professor in Immunology, Institute of Immunity and Transplantation, Royal Free Hospital and University College London, UK
[2]Consultant Physician Nawaloka Hospital Research and Education Foundation, Nawaloka Hospitals PLC, Sri Lanka
[3]Consultant Physician (Acting) and lecturer in medicine, Department of Medicine, Faculty of Medicine, University of Peradeniya, Sri Lanka
[4]Specialist Registrar in Acute Medicine, Department of Acute Medicine, John Radcliffe Hospital Oxford, UK
[5]Research Fellow, Liberty Publishers Private Limited, Sri Lanka
[6]Scientist, Biomedical Laboratory 2, Sir John Kotalawala Defence University, Ratmalana, Sri Lanka
[7]Medical Officer, Institute of Immunity and Transplantation, Royal Free Hospital and University College London, UK

Abstract

Coronavirus Disease-2019 (COVID-19), has so far affected more than 275 million individuals globally and caused over 5.3 million deaths. With an effective vaccine, disease and infection could be prevented, whereas with antivirals and monoclonal antibodies, disease progression could be mitigated. In recent months, there has been much interest in evaluating the use of oral antivirals, in those having mild disease and associated risk factors for disease progression (such as multiple comorbidities),in view of preventing severe COVID-19. Our review discusses the known properties and identified effectiveness of three oral antiviral drugs (Molnupiravir, Paxlovid and AT-527) for COVID-19 (as at end of December 2021) and explores their potential role in mitigating the ill effects of the on-going COVID-19 pandemic.

Key words: COVID-19, SARS-CoV-2, antivirals, Molnupiravir, protease inhibitor

Correspondence to:

Suranjith L Seneviratne
Professor in Immunology
Institute of Immunity and Transplantation,
Royal Free Hospital and University College London, UK

Tel No: 0094770274865

E-mail: suran200@yahoo.co.uk

Introduction

Coronavirus Disease-2019 (COVID-19), has so far affected more than 275 million individuals globally and caused over 5.3 million deaths. Although pulmonary manifestations have been identified as the major symptoms, several other organ abnormalities have also been identified (1, 2). Following a SARS-CoV-2 infection, most persons recover uneventfully, but in a variable proportion of individuals the disease may become severe (3). From a public health perspective, we need different strategies to deal with this pandemic. With an effective vaccine, disease and infection could be prevented (4), whereas with antivirals and monoclonal antibodies, disease progression could be mitigated. Effective, direct acting antivirals would be an excellent complement to the COVID-19 vaccines. In the context of the rapid global spread of the Omicron variant, oral antiviral agents would potentially take on a more important role, owing to observed reduction in vaccine neutralisation and monoclonal antibody responses against this variant.

Antiviral medications act by either blocking the entry of viruses into healthy cells or reducing the amount of viral replication within the cell (5). Currently, antivirals are essential treatment

modalities for viral infections such as hepatitis C and HIV (6, 7). Tamiflu is one of the best-known antiviral medications, and if given early, could shorten the duration of influenza and reduce the risk of hospitalisation (8, 9). In recent months, there has been much interest in evaluating the use of oral antivirals, in those with mild disease who have associated risk factors for disease progression (such as multiple comorbidities), in view of preventing severe COVID-19. Their potential ability to reduce illness duration and limit viral transmission to household members has also been of interest. This article discusses the known properties and identified effectiveness of three oral antiviral drugs (Molnupiravir, Paxlovid and AT-527) for COVID-19 and explores their potential role in mitigating the ill effects of the on-going COVID-19 pandemic.

Molnupiravir

What is it and how does it work?

Molnupiravir is a prodrug that is metabolised to a ribonucleoside analogue. It was invented at the Drug Innovations at Emory (DRIVE) Centre, USA and has since been evaluated as a possible COVID-19 medication by Ridgeback Biotherapeutics and Merck & Co (10). The drug interferes with the SARS-CoV-2 virus's ability to replicate (that makes it less able to multiply), as it introduces copying errors during viral replication. Because of this, the viral load in the respiratory tract is reduced and this in turn prevents severe disease (11).

When the SARS-CoV-2 virus enters a cell, it needs to duplicate its RNA genome to form new viruses. Molnupiravir, gets incorporated into the growing RNA strands and these strands then become faulty blueprints for the next set of viral genomes (12). Molnupiravir is able to shift its configuration, mimicking the nucleoside cytidine on some occasions and uridine at other times. Wherever the compound gets inserted in the RNA chain, a point mutation occurs. When sufficient mutations accumulate, the viral population collapses (this process is called lethal mutagenesis or viral error catastrophe) (12, 13). As the mutations accumulate randomly, it is difficult for the viruses to evolve resistance to Molnupiravir. It has been shown to be active in several preclinical models of SARS-CoV-2. The pre-clinical studies also found it to be active against the most common SARS-CoV-2 variants (14).

Pharmacodynamic and pharmacokinetic effects

During metabolism, it gets converted to an active ribonucleoside analogue N-hydroxycytidine (NHC). This gets phosphorylated to the triphosphate form (NHC-TP) and gets incorporated into viral RNA by viral RNA polymerase. NHC was active in cell culture (EC50 value of 0.67 to 2.66 μM in A-549 cells and 0.32 to 2.03 μM in Vero E6 cells) and showed a similar activity against the different SARS-CoV-2 variants; Alpha, Beta, Gamma and Delta with EC50 values of 1.59, 1.77 and 1.32 and 1.68 μM, respectively (15). The pharmacokinetics of NHC has been found to be similar in healthy individuals and those with COVID-19. At steady-state, following administration of 800 mg Molnupiravir every 12 hours, the area under the concentration-time curve 0 - 12h (AUC0-12hr) was 8260, Maximum concentration (CMax) was 2790 and the concentration after 12 hrs (C12hr) was 31.1. Following oral administration of 800mg of Molnupiravir, the median time to peak plasma NHC concentrations (T_{max}) was found to be 1.5 hours. The half-life of Molnupiravir is 3.3 hrs. In healthy individuals, the fraction of the dose excreted as NHC in urine is ≤3%. Age, gender, race and ethnicity do not significantly influence the pharmacokinetics of NHC (15).

What are the current clinical trial findings?

An early trial of 202 participants found Molnupiravir to rapidly reduce SARS-CoV-2 viral loads (16). Virus isolation was significantly lower in participants receiving 800mg Molnupiravir versus placebo at day 3. The MOVe-OUT trial (NCT04575597) was an international trial, conducted in more than 170 sites in many countries (in Latin America, Europe, and Africa). It was a Phase 3, randomised, double-blind, placebo-controlled, multi-site study of non-hospitalised adult patients with laboratory-confirmed mild to moderate COVID-19 (17). In addition, the

participants needed to have at least one risk factor that was associated with poor disease outcome. The most common risk factors for poor disease outcome included: obesity, older age (>60 years), diabetes mellitus, and heart disease. Symptom onset had to be less than five days before randomization. The primary objective was to evaluate the efficacy of Molnupiravir vs placebo, by comparing the percentage of participants who are hospitalised and/or die, from the time of randomization till day 29 (17, 18).

At a planned interim analysis, Molnupiravir significantly reduced the risk of hospitalisation or death by approximately 50% (19). Through Day 29 following randomization, 7.3% of patients who received Molnupiravir were either hospitalised or died, compared to 14.1% of placebo-treated patients. During the same period, no deaths were reported in patients who received Molnupiravir, compared to 8 deaths in patients who received placebo. Viral sequencing data were available in approximately 40% of the participants and in these individuals Molnupiravir showed consistent efficacy across the Gamma, Delta, and Mu SARS-CoV-2 variants. Because of the strongly positive and protective results found at this interim analysis, the independent Data Monitoring Committee in consultation with the U.S. Food and Drug Administration (FDA) recommended that the study be stopped early (19). A final analysis of data from 1433 infected volunteers showed a more modest effect (20). The percentage of participants who were hospitalised or died through day 29 was 6.8% in the Molnupiravir recipients and 9.7% in those who received placebo. There were one and nine deaths in the Molnupiravir and placebo groups respectively (20).

What are the side effects of Molnupiravir?

The incidence of any adverse event was 35% and 40% in the Molnupiravir and placebo groups respectively. The most common side effects observed in the clinical trial were: diarrhoea (3%), nausea (2%), dizziness (1%) and headache (1%). All were mild or moderate. Fewer patients discontinued therapy due to an adverse event in the Molnupiravir (1.3%) compared to the placebo (3.4%) group. One needs to remember that some other nucleoside analogue drugs have caused birth defects in animal studies (19).

Who should receive this drug and at which dose?

The drug is indicated for those with mild to moderate COVID-19 and having at least one risk factor for developing severe illness such as being older than 60, obesity, diabetes mellitus or heart disease. It should be used as soon as possible after a positive RT-PCR test for SARS-CoV-2 and within five days of the appearance of symptoms . Eight hundred milligrams (that is four 200 mg capsules), are taken orally every 12 hours for 5 days. No dose adjustments are needed for renal or liver disease. The advantages include that it is an oral medication and hence can be taken at home. It could be very useful in those that do not make good immune responses to the COVID-19 vaccine such as immunodeficient patients or those with cancers. A possible disadvantage is its cost, but this is still less than the price of Remdesivir or monoclonal antibodies.

What is the current status of its approval?

Molnupiravir (Lagevrio), became the first oral anti-SARS-CoV-2 drug to be approved by a leading drug regulatory body. On 4th November 2021, it was approved for use in adults by the UK medicines regulator (MHRA). They concluded the drug was safe and effective at reducing the risk of hospital admission and death in people with mild to moderate COVID-19 who are at extra risk from the virus (21). Merck and Co. applied for FDA emergency use authorization of the drug on 11th October 2021 and obtained this on 23rd December 2021. The initial studies were conducted in adults and the paediatric studies should follow shortly. In June 2021, the US agreed to purchase 1.7 million treatment courses of Molnupiravir, at a cost of $1.2 billion. Furthermore, a deal has been reached with five Indian generic drug manufacturers and this would allow them to set their own price for around 100, low and lower-middle-income countries. Merck and Co, predicts they could produce more than 10 million courses of the drug by the end of this year. One needs to remember that even if poorer countries could afford the cost of the drug, steps would need to be put in place for

early diagnosis of SARS-CoV-2 infections. This is because in order to give Molnupiravir in the first five days after symptom onset, the diagnosis needs to be done rapidly and this may be a challenge in some countries.

Future studies using Molnupiravir

In the MOVe-AHEAD trial, Molnupiravir is being evaluated for post-exposure prophylaxis. This is an international, multicenter, randomised, double-blind, placebo-controlled, Phase 3 study, evaluating the efficacy and safety of Molnupiravir in preventing the spread of COVID-19 within households. The dose of Molnupiravir is 800mg every 12 hours, for five days. To be included in the study, the participant should live in a household with a person having documented COVID-19 (PCR test positive for less than 5 days) and at least one symptom (fever, difficulty with breathing etc) that could be put down to COVID-19. The primary outcome measure is the percentage of participants with COVID-19, through Day 14. If this drug is found to be effective, it could be given to those in a household or school, following exposure to a person carrying the SARS-CoV-2 virus (17). The Panoramic study is led by the University of Oxford and aims to recruit 10,600 people across the UK to test if Molnupiravir reduces the need for the over-50s and those with underlying health problems to be admitted to hospital. All the initial clinical trials were done in unvaccinated people and with the variants that were circulating at that time. The study wishes to ascertain how the drug works in a population that is largely vaccinated and against the currently circulating Omicron variant.

Paxlovid

It contains the protease inhibitor nirmatrelvir and a low dose of ritonavir. Nirmatrelvir is a specially designed peptidomimetic inhibitor of the SARS-CoV-2 main protease (Mpro). X-ray crystallography found nirmatrelvir to bind directly to the SARS-CoV-2 Mpro active site. It inhibits the cysteine residue of the enzyme (22), which is responsible for its catalytic activity (23). Inhibition of SARS-CoV-2 Mpro makes it incapable of processing the polyprotein precursors and viral replication is thus prevented (24). Ritonavir is an HIV-1 protease inhibitor. It is not active against the SARS-CoV-2 Mpro, but is able to inhibit the CYP3A (Cytochrome P3A)-mediated metabolism of nirmatrelvir. This leads to increased plasma concentrations of nirmatrelvir. As a result, nirmatrelvir would remain active in the body for a longer period of time and at higher concentrations. Ritonavir acts as a pharmacokinetic enhancer and supports a twice daily administration schedule.

Pharmacokinetics

The pharmacokinetics of nirmatrelvir/ritonavir has been studied in healthy subjects. The median Tmax (the amount of time the drug is present at the maximum concentration in the serum) is 3 hours, mean half-life ($T_1/_2$) is six hours and the major route of elimination is renal. At clinically relevant concentrations, nirmatrelvir does not induce any CYPs, whilst ritonivir is a substrate for CYP3A. Overall, Paxlovid inhibits CYP3A and to a lesser extent CYP2D6. Itraconazole, a CYP3A inhibitor and carbamazepine, a CYP3A inducer may affect the metabolism of Paxlovid. Nirmalrelvir has potent cell-culture based antiviral activity against the Alpha, Beta, Gamma, and Delta SARS-CoV-2 variants of concern (VOC) and the Lambda variant. Of them the Beta variant was the least susceptible. In a biochemical assay, the Mpro P132H substitution found in the Omicron variant did not reduce nirmalrelvir activity. Based on their mechanisms of action, cross resistance is not expected between nirmalrelvir and the anti-SARS-Cov-2 monoclonal antibodies or remdesivir.

What are the current clinical trial findings?

The Evaluation of Protease Inhibition for COVID-19 in High-Risk Patients (EPIC-HR) study was a randomised, phase 2/3, double-blind study of non-hospitalised adult patients with COVID-19 who were at high risk of progressing to severe disease. Interim data from 1219 participants, who were enrolled as at 29 September 2021, were reported on 5th November 2021. Three (0.8%) of 389 patients and 27(7%) of 385 patients who received Paxlovid and placebo respectively, within 3 days of symptom onset were hospitalised through day

28 (25). None in the Paxlovid and seven (1.8%) in the placebo groups died. Reductions in hospitalisations and deaths were also observed among those treated within 5 days of symptom onset. Here, six (1%) of 607 patients who received Paxlovid were hospitalised through day 28 compared to 41 (6.7%) of 612 patients in the placebo arm and no deaths were reported in the Paxlovid arm compared to 10 (1.6%) in those who received the placebo. The final results on 2246 high risk patients were similar to the interim findings. There was an 89% and 88% reduction in risk of hospitalisation and death when taken within 3 or 5 days of symptoms. There were no deaths in those taking Paxlovid and 12 in the placebo group. Another trial was completed in unvaccinated adults at standard risk and vaccinated high risk adults. The primary goal of 4-day symptom alleviation was missed, but the medication reduced hospitalisation risk by 70% and had a ten-fold decrease in viral load at five days. This medication has the potential to save patient lives, reduces the severity of COVID-19, eliminates up to nine out of 10 hospitalisations and could be prescribed for use at-home.

What are the side effects of Paxlovid?

For assessing Paxlovid's safety profile, 1881 participants were analysed. The proportion of patients experiencing an adverse effect was similar in the Paxlovid (19%) and placebo (21%) groups. The possible side effects of Paxlovid included: an impaired sense of taste, diarrhoea, high blood pressure and muscle aches. Most of the side effects were mild in nature. Those receiving Paxlovid were less likely to have a serious adverse effect or to have discontinued the study due to an adverse effect. There were no signs of mutagenic DNA interactions. Because Paxlovid works, in part, by inhibiting a group of enzymes that break down certain drugs, it is contraindicated with certain drugs that are highly dependent on those enzymes for metabolism. It should also not be used with drugs that strongly induce such enzymes, as it would lead to the faster breakdown of nirmatrelvir or ritonavir. This could result in a reduced virologic response and a higher risk of developing viral resistance. Thus, potentially significant drug interactions may occur if Paxlovid is used at the same time as some other drugs. This could be prevented by checking the list of medications that should not be taken in combination with Paxlovid. One needs to remember that the effects may remain for a short time after discontinuation of these medications and it may not be possible to start Paxlovid immediately after discontinuing such medications. Using Paxlovid in people with uncontrolled or undiagnosed HIV-1 infection may lead to HIV-1 drug resistance. Ritonavir may cause liver injury and thus caution should be exercised when giving Paxlovid to patients with liver enzyme abnormalities, liver inflammation or pre-existing liver disease. Paxlovid is not recommended in patients with severe kidney impairment. In those with moderate renal impairment, a reduced dose of Paxlovid should be used.

Who should receive Paxlovid and at which dose?

Currently, it is indicated for the treatment of mild-to-moderate COVID, in those aged twelve years or older and weighing at least 40 kilograms (88 lb). In addition, they should have a positive result on direct SARS-CoV-2 testing, and be at high risk for progression to severe COVID, hospitalisation or death. Paxlovid is administered as three tablets (two tablets of nirmatrelvir and one tablet of ritonavir) taken together orally, twice daily for five days (that is a total of 30 tablets). Paxlovid is not authorised for use longer than five consecutive days. As it is administered orally, COVID patients can take this drug at home at early stages of infection. The hope is that the new antiviral agents would allow people with mild or moderate COVID to be treated sooner to prevent disease progression and thus help avoid hospitals from being overwhelmed.

What is the current status of authorisation of Paxlovid?

On 22nd December 2021, Paxlovid received emergency use authorisation by the US FDA for the treatment of COVID. Currently, this medication is not authorized for the pre-exposure or post-exposure prevention of COVID. It is also not approved as initiation treatment in those who are hospitalised due to severe or critical COVID. On

16th December 2021, The European Medicines Agency (EMA) issued guidance about the use of Paxlovid for COVID in the EU. The process of getting regulatory authorisation has been commenced in other countries such as Australia, the UK, New Zealand and South Korea. It has been stated that the US is to purchase ten million courses of this medication. In October 2021, the United Kingdom placed an order for 250,000 courses of Paxlovid and Australia has pre-ordered 500,000 courses. It has also been announced that this medication is to be offered through a tiered pricing model. This would see high- and upper-middle income countries pay more than lower-income countries for this treatment. In November 2021, Pfizer signed an agreement with the United Nations-backed Medicines Patent Pool to allow generic companies to manufacture and sell nirmatrelvir in 95 low- and middle-income countries, thus providing greater access to the world population. Currently, the deal excludes some countries such as Argentina, Brazil, China, Russia and Thailand. With richer countries jostling to acquire supplies of the most promising COVID medications, there is concern that poorer countries would be left behind, like that which occurred with the COVID vaccines.

AT-527

This is a prodrug of a guanosine nucleoside analogue and is made by Roche and Atea Pharmaceuticals. It has shown both *in vitro* and *in vivo* antiviral activity against several enveloped single-stranded RNA viruses (such as coronaviruses and flaviviruses). The drug is designed to uniquely inhibit viral RNA polymerase, an enzyme that is essential for the replication of RNA viruses (26). The safety of AT-527 has previously been demonstrated in the phase 2 clinical studies of hepatitis C patients. Its high solubility promotes rapid absorption of the drug. The phase 2, MOONSONG trial missed its primary efficacy endpoint. This trial enrolled patients with mild to moderate COVID-19, where around two thirds of the participants were low risk and with mild symptoms (26). In the overall study population, AT-527 was no better than placebo at reducing the SARS-CoV-2 viral load. However, a subgroup analysis of high-risk patients with underlying health conditions saw a reduction in viral loads. The MORNINGSKY study is a phase 3 study evaluating the efficacy, safety, antiviral activity and pharmacokinetics of AT-527 (27, 28). It was planned to enrol up to 1400 adult and adolescent patients with mild to moderate COVID-19 in an outpatient setting. However, the failure of the phase 2 study, has prompted a reassessment of the phase 3 trial design and thus a potential one year delay in the availability of phase 3 study outcomes is predicted (29).

How do the oral antiviral agents compare with Remdesivir?

The parenteral antiviral agent Remdesivir, received approval from the US Food and Drug Administration a short time ago (30). It is a prodrug of an adenosine nucleoside analogue and a RNA chain terminator, where the drug stops the enzyme that builds the RNA chains (31). In a phase 3 trial, it shortened recovery time by a median of 5 days. It is given intravenously to patients who are ill enough to be hospitalised, and is not intended for early, widespread use. When used in a hospital setting, its beneficial effects are modest (32).

Conclusions

Currently, it is envisaged that oral anti-SARS-CoV-2 drugs would join monoclonal antibody therapies for treating and preventing serious illness and hospitalisations in COVID-19. Some properties of antiviral agents, monoclonal antibodies and other drugs for COVID-19, are given in Table 1. Synthetic monoclonal antibodies, which mimic the body's natural response to infection, have been easier to develop but need to be given as an intravenous infusion. On the other hand, the availability of effective oral antiviral agents should allow the earlier and more widespread use of these agents. The global health impact of a directly acting oral antiviral is to rapidly inhibit viral replication in the early phase of infection (33). This would have the effect of reducing disease progression and curtailing the spread of SARS-CoV-2 infection.

Table 1: properties of antiviral agents, monoclonal antibodies and other some drugs for COVID-19

Name of the drug	Indications for use	For use at which stage of the illness	Route	Dosing	Clinical outcomes
Molnupiravir	Mild to moderate COVID-19 and at least one risk factor for developing severe illness such as older than 60, obesity, diabetes mellitus or heart disease	As soon as possible after a positive RT-PCR test for SARS-CoV-2 and within five days of symptoms appearing	Oral	800mg to be taken twice a day for 5 days	Significantly reduced (by approximately 30%) the risk of hospitalization or death
Paxlovid	Mild to moderate COVID-19 and at least one risk factor for developing severe illness and high risk of infection after exposure	Within 3 to 5 days of symptom onset	Oral	300mg twice a day for 5 days	Reduces the severity of COVID-19. Shows an 89% decrease in the risk of hospitalization or death
AT-527	Mild to moderate COVID-19 and at least one risk factor for developing severe illness	As soon as possible after a positive RT-PCR test for SARS-CoV-2 (less than 72hours)	Oral	550mg twice a day for 5 days	Ongoing phase III clinical trial
Remdesivir	The treatment of coronavirus disease 2019 (COVID-19) requiring hospitalization	Less than 9 days of onset of symptoms	Intravenous	200 mg on Day 1 followed by once-daily maintenance doses of 100 mg for 10 days	Reduces all-cause mortality rate in ±20%
Dexamethasone	Patients with COVID-19 pneumonia	Oxygen saturation reducing to less than 94%	Oral / intravenous	6mg daily for 10 days	Incidence of death was lower than the usual care group among patients receiving invasive mechanical ventilation (29.3% vs 41.4%) and among those receiving oxygen without invasive

					mechanical ventilation (23.3% vs 26.2%), but not among those who were receiving no respiratory support at randomization (17.8% vs 14%).
Tocilizumab	Patients with COVID-19 pneumonia	Require supplemental oxygen, noninvasive or invasive mechanical ventilation, or ECMO	Intravenous infusion	8 mg/kg dose (May administer 1 additional IV infusion 8 hr after first infusion if clinical signs or symptoms worsen or unimproved)	Significant reduction of all-cause mortality rate and reduced the chance of progressing to invasive mechanical ventilation
Regeneron Mab	Mild to moderate COVID-19 and post-exposure prophylaxis in those with high risk of progression to severe disease	As soon as possible after a positive RT-PCR test for SARS-CoV-2 (and within 10 days)	Intravenous	A single dose of 600 mg of casirivimab and 600 mg of imdevimab administered together as a single intravenous infusion	Single dose of its antibody treatment reduced the risk of contracting COVID-19 by 81.6% for up to eight months
AstraZeneca Mab	Mild to moderate COVID-19 and post-exposure prophylaxis in those with high risk of progression to severe disease	As soon as possible after a positive RT-PCR test for SARS-CoV-2	Intra muscular(IM)	A single dose (× 2 IM injections) of 300 mg	Reduce the risk of developing symptomatic COVID-19 by 77%

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