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News & Views

COVID-19 can be called a treatable disease only after we have antivirals

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More than two years have passed since the first cases of coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), were reported. Ever since then, people have been striving to turn COVID-19 into a preventable and treatable disease. The triumph of vaccines has led to a significant decrease in symptomatic illness, severe and critical disease, and death. Nonetheless, the efficacy of vaccines has been affected by virus evolution and the emergence of new variants, and global access is sub-optimal [1]. Meanwhile, antibody responses to vaccination are poor in immunosuppressed patients [2], exactly the population most at risk of severe or critical COVID-19. Therefore, vaccines alone are not enough and potent treatments are needed. Whilst suppressing hyperinflammation stimulated by SARS-CoV-2 has been a breakthrough in hospitalized patients [3], progress is also needed in antiviral therapy for COVID-19.

Antiviral drugs offer opportunities at various stages of SARS-CoV-2 infection, including pre- or post-exposure prophylaxis, early treatment, and late treatment. Recently published studies illustrated the efficacy and safety of early use of small-molecule antivirals in reducing hospitalization or death among the high-risk population with mild to moderate COVID-19 [4–6]. Before that, neutralizing monoclonal antibodies have been approved successively, including BRII-196/BRII-198, casivirimab with imdevimab, and bamlanivimab. However, monoclonal antibodies have several intrinsic drawbacks, such as drug resistance of variants [7], route of administration (i.e., intravenous), and high price. In contrast, small-molecule antivirals can be manufactured at a large scale, conveniently transported and stored, and even orally administrated, thus are potentially more accessible and affordable.

Though efforts to identify antiviral therapies began at the very onset of the pandemic, small-molecule antivirals with clear benefits in COVID-19 have not emerged until recently. Three key parameters are important when considering antivirals: (i) the potency and concentration of the drug in the target tissues, (ii) the optimal patient population, and (iii) resistance. At the beginning of the pandemic, due to the urgent need for therapeutics, many theoretically effective antivirals were repurposed for COVID-19 in clinical trials, and lopinavir-ritonavir, a drug for human immunodeficiency virus type 1 (HIV-1), was one of them. There was prior *in vitro* and *in vivo* evidence that lopinavir-ritonavir had activity against severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV). However, randomized controlled trials (RCTs) did not show significant benefits of lopinavir-ritonavir among patients hospitalized with COVID-19 [8,9]. Later, data emerged showing that clinically achieved serum concentrations of 9.4 μmol/L (interquartile range, 7.2 to 12.1 μmol/L) were much lower than the 50% effective concentration (EC_{50}, 26.1 μmol/L) against SARS-CoV-2 in Vero E6 cells, highlighting the importance of understanding antiviral inhibitory concentrations and drug pharmacokinetics [10].

For antiviral drugs to have optimal impact, the appropriate patient population is fundamental. Remdesivir, with its failures and successes, gives a good example. Remdesivir, which was deployed to confront the Ebola outbreak in 2014, is an intravenous nucleoside analog prodrug targeting RNA-dependent RNA polymerase (RdRp) to inhibit viral replication. Subsequent studies demonstrated its broad activity against other RNA viruses, including coronaviruses [11]. The first remdesivir RCT for COVID-19 was launched as early as February 2020 [12] amongst hospitalized patients, the main patient population of subsequent remdesivir RCTs. Up to February 3rd, 2022, none of the six already-published RCTs have demonstrated that remdesivir can impact the mortality of hospitalized patients with COVID-19 (https://covid19evidence.net.au/). Conversely, no trial in non-hospitalized patients got published until December 2021. The phase 3 PINETREE trial recruited 562 non-hospitalized patients at risk of disease progression within 7 d after symptom onset. Patients in remdesivir group benefited significantly in terms of the rate of hospitalization or death through day 28 (0.7% (2/279) vs. 5.3% (15/283); an 87% decrease; $P = 0.008$) [4]. The differential effectiveness of remdesivir in hospitalized and non-hospitalized patients emphasizes the importance of the patient population. Since viral replication peaks early in COVID-19, the chances of a therapeutic effect with an antiviral probably diminish with time. However, viral replication is detect-

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Table 1
Information of small-molecule antivirals in COVID-19 treatment clinical trials.

Drug	Leading country	Target	Progress
Remdesivir (GS-5734)	Multiple	Polymerase, redirected	It was approved by the US FDA in hospitalized patients. Benefits in non-hospitalized high-risk patients were observed in the phase 3 trial and EUA was issued by the US FDA.
Paxlovid (nirmatrelvir (PF-07321332) and ritonavir)	USA	Protease, new	Benefits in non-hospitalized high-risk patients were observed in the phase 2/3 trial and EUA was issued by the US FDA. Phase 3 trials are in progress for non-hospitalized standard-risk patients and closely contacted subjects.
Molnupiravir (MK-4482)	USA	Polymerase, redirected	Benefits in non-hospitalized high-risk patients were observed in the phase 3 trial and EUA was issued by the US FDA. Phase 3 trials is in progress for closely contacted subjects.
VV116 (JT001)	China	Polymerase, new	Phase 2/3 trial is in progress for patients with mild/moderate COVID-19 at high risk for progression to severe COVID-19, including death.
S-217622	Japan	Protease, new	Phase 2/3 trial is in progress for patients with mild/moderate COVID-19 and asymptomatic patients.
FB2001	China	Protease, new	Phase 1/2 trial is in progress.
PBI-0451	USA	Protease, new	Phase 1 trial is in progress.
Enisamium (FAV00A)	Ukraine	Polymerase, repurposed	Interim analysis of the phase 3 trial showed faster recovery in hospitalized patients requiring oxygen. Phase 3 trial is in progress for hospitalized patients.
Azvudine	China	Polymerase, repurposed	Phase 3 trials are in progress for patients with different disease severity.
Favipiravir (Avigan, T-705)	Multiple	Polymerase, repurposed	Phase 2 and 3 trials in hospitalized patients showed ambiguous results. Phase 2 and 3 trials are in progress for hospitalized, non-hospitalized, and closely contacted subjects.
RO7496998 (AT-527)	USA and Switzerland	Polymerase, redirected	Phase 3 trial in non-hospitalized patients was suspended for protocol amendment because of the results from the phase 2 trial.
Triazavirin	Russia	Polymerase, repurposed	Phase 3 trials are in progress for hospitalized patients.
Upamostat (RHB-107)	USA	Protease, redirected	Phase 2/3 trial is in progress for non-hospitalized patients.
Lopinavir/Ritonavir (Kaletra)	Multiple	Protease, repurposed	Phase 3 trials showed no benefits in hospitalized patients, non-hospitalized patients, or close contacts.

able even in late disease, which is associated with poorer outcomes, and a therapeutic benefit from monoclonal antibody therapy has been shown in hospitalized patients [13].

Nevertheless, the administration route of remdesivir limits its value as an antiviral. Encouragingly, RCT data on two oral small-molecule antivirals, molnupiravir and paxlovid, have recently been released. Molnupiravir developed by Merck Sharp and Dohme is a ribonucleoside analog targeting RdRp of SARS-CoV-2, while paxlovid developed by Pfizer functions through blocking the main protease (M^{pro}), also known as 3C-like protease ($3CL^{pro}$) or nsp5 protease. Paxlovid consists of nirmatrelvir, which binds to M^{pro} directly to impair polyprotein precursors processing and suppress viral replication, and ritonavir, which inhibits CYP3A-mediated metabolism of nirmatrelvir to increase its plasma concentration. The phase 3 RCT (MOVe-OUT trial) of molnupiravir [5] and the phase 2/3 RCT (EPIC-HR trial) of paxlovid [6] both recruited non-hospitalized, unvaccinated, adult patients with COVID-19 at high risk of progressing to severe illness within 5 d after symptom onset. In the MOVe-OUT trial, the molnupiravir group experienced a significant decline in the rate of hospitalization or death by day 29 (6.8% (48/709, including one death) vs. 9.7% (68/699, including 9 deaths); difference, −3.0%; 95% confidence interval, −5.9% to −0.1%). Similarly, paxlovid significantly decreased the incidence of hospitalization or death through day 28 compared with placebo (0.8% (8/1039, including no deaths) vs. 6.3% (66/1046, including 12 deaths); difference, −5.6%; 95% confidence interval, −7.2% to −4.0%; $P < 0.001$) in the EPIC-HR trial. Accordingly, the US Food and Drug Administration (FDA) issued Emergency Use Authorization (EUA) for both molnupiravir (https://www.fda.gov/media/155054/download) and paxlovid (https://www.fda.gov/media/155050/download) in adult patients with mild-to-moderate COVID-19 at high risk for progressing to severe disease in December 2021. On February 12th, 2022, the National Medical Products Administration also approved emergency use of paxlovid in China (https://www.nmpa.gov.cn/yaopin/ypjgdt/20220212085753142.html).

Although we expect that small-molecule antivirals would be cheaper than other drugs such as monoclonal antibodies, to date, antivirals currently commercialized are still expensive, in particular for countries with limited resources. The good news is that both Merck Sharp and Dohme (https://www.merck.com/news/merck-and-ridgeback-announce-supply-agreement-with-unicef-for-molnupiravir-an-investigational-oral-antiviral-covid-19-medicine/) and Pfizer (https://www.pfizer.com/news/press-release/press-release-detail/pfizer-provide-us-government-additional-10-million) offer a tiered pricing approach based on the income level of each country to promote equity of access to molnupiravir and paxlovid across the globe. Another concern for molnupiravir is the mutagenic potential in human cells. Up to now, the *in vivo* studies employing animal models demonstrated either equivocal or negative results regarding its mutagenicity (https://www.fda.gov/media/155054/download). Studies on germ cell mutagenicity should be conducted and the long-term effects need to be carefully monitored in people having received molnupiravir.

Informed by the experience of antivirals in influenza, the effects of oral small-molecule antivirals as pre- and post-exposure prophylaxis need to be carefully investigated for COVID-19. Influenza trials have shown that prophylactic administration of oseltamivir or zanamivir could reduce the risk of developing symptomatic influenza [14]. Several trials on prophylactic usage in household contacts with COVID-19 patients are recruiting subjects now, including one for molnupiravir (ClinicalTrials.gov number, NCT04939428) and one for paxlovid (ClinicalTrials.gov number, NCT05047601).

According to RCT information extracted from COVID-NMA mapping database (https://www.covid-nma.com/dataviz/#void), even though the hunt for effective antivirals has been intensive since SARS-CoV-2 emerged, as small-molecule drugs development is

usually time-consuming, the number and classes of antivirals entering clinical trials are both restricted up to now (Table 1). Among them, China has led the development of three (i.e., VV116, FB2001, and azvudine). Most antivirals entering clinical trials for COVID-19 are either repurposed (i.e., drugs already approved for other viruses) or redirected ones (i.e., drugs developed for other viruses originally before COVID-19 and are not approved for any disease yet), and only five are newly developed for SARS-CoV-2 (i.e., paxlovid, VV116, S-217622, FB2001, and PBI-0451). Though the number is currently limited, we believe that these are only the tip of the iceberg, beneath which lie a wealth of new antivirals working their way through pre-clinical stages across the world. Meanwhile, the classes of antivirals are quite restricted at present, targeting either RdRp or M^{pro}. However, as the genome, structure, and life cycle of SARS-CoV-2 are unraveled gradually, antivirals with novel targets are expected to come into the clinical arena. Additionally, the developing host-directed antivirals will further widen the choices [15].

The trials of remdesivir, molnupiravir, and paxlovid illustrate the promising efficacy of small-molecule antivirals for COVID-19 in high-risk non-hospitalized adult patients at the early stage of the disease. However, efforts to maximize the clinical application of antivirals must not stop here. In hospitalized patients, proof of the benefit of antiviral therapy has been demonstrated with monoclonal antibodies [13] and more data are needed on monotherapy with small-molecule antivirals. Moreover, the widening use of antivirals raises very real concerns about the development of drug resistance. As such, combination therapy with antivirals that target different pathways must be vigorously pursued as a therapeutic and drug-preserving (from resistance) strategy.

We believe that the flourishing development of small-molecule antivirals based on growing knowledge of COVID-19 offers the hope of turning COVID-19 into a controllable and treatable disease, even though we are not able to eliminate the threat of SARS-CoV-2 from the world. In this way, antivirals encourage us to dream of the day when catching COVID-19 is no longer a frightening prospect and we can restore our lives to the days before the pandemic. Finally, the dedications to antivirals development nowadays not only equip us better in the pandemic of COVID-19, but it will also prepare us better for many accidentally new-emerging infectious diseases in the future in our close interactions with environment and animals, just as how remdesivir and molnupiravir benefit us today.

Conflict of interest

Peter Horby has participated in a completed clinical trial for lopinavir-ritonavir donated from AbbVie, and a completed clinical trial for casivirimab with imdevimab donated from Regeneron. Bin Cao has participated in a completed clinical trial for remdesivir donated from Gilead. However, we declare no honoraria, consultancy fees, or other payments either directly or indirectly from the industry.

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