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Clinical development of antivirals against SARS-CoV-2 and its variants

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ABSTRACT

The unceasing global spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) calls for the development of novel therapeutics. Although many newly developed antivirals and repurposed antivirals have been applied to the treatment of coronavirus disease 2019 (COVID-19), antivirals showing satisfactory clinical efficacy are few in number. In addition, the loss of sensitivity to variants of concern (VOCs) and lack of oral bioavailability have also limited the clinical application of some antivirals. These facts remind us to develop more potent and broad-spectrum antivirals with better pharmacokinetic/pharmacodynamic properties to fight against infections from SARS-CoV-2, its variants, and other human coronaviruses (HCoVs). In this review, we summarize the latest advancements in the clinical development of antivirals against infections by SARS-CoV-2 and its variants.

1. Introduction

SARS-CoV-2 is the causative agent of the COVID-19 pandemic, which has resulted in more than 771 million infection cases and 6.9 million deaths worldwide (https://covid19.who.int). The continuous emergence of SARS-CoV-2 variants of concern (VOCs) with increased infectivity and transmissibility, as well as resistance to antibody neutralization from vaccine-elicited sera and convalescent plasma, has become a major obstacle against ending the COVID-19 epidemic (Wang et al., 2021b; Tao et al., 2021; Su et al., 2022). COVID-19 vaccination is expected to be an important strategy to prevent SARS-CoV-2 infection (Su et al., 2022). However, although many vaccines have been developed with clinical efficacy reaching 80–90 % (Golob et al., 2021), breakthrough infections caused by newly emerging SARS-CoV-2 VOCs still occur in vaccinated individuals (Townsend et al., 2021; Hacisuleyman et al., 2021).

As for the development of SARS-CoV-2 antivirals, although several antivirals with SARS-CoV-2 inhibitory activity once have been approved, or recommended, for clinical use to treat COVID-19, only a few have shown significant clinical efficacy (WHOST Consortium et al., 2021), thus calling for the development of more effective and broad-spectrum antivirals to treat COVID-19 caused by SARS-CoV-2 and its variants (Lu et al., 2021; Cao et al., 2021). Currently, many antivirals that are less effective or may cause serious side effects are no longer recommended for the treatment of COVID-19. Meanwhile, antivirals with greater clinical efficacy, such as Paxlovid (nirmatrelvir-ritonavir), remdesivir, and molnupiravir, are still recommended by the World Health Organization (WHO) (Lamontagne et al., 2020). In this review, we summarize the antivirals in clinical trials and clinical use according to their targets. In addition, we also discuss some promising antivirals currently in preclinical studies.

2. Targets for developing antivirals

Firstly, we discuss viral targets that play key roles in the viral replication cycle. Entry is the first step of the SARS-CoV-2 life cycle, including the following important processes: Spike (S) protein activation, receptor binding, and membrane fusion (Jackson et al., 2022). Several key viral/host factors are involved in these processes, making them important targets for the development of antivirals to inhibit viral

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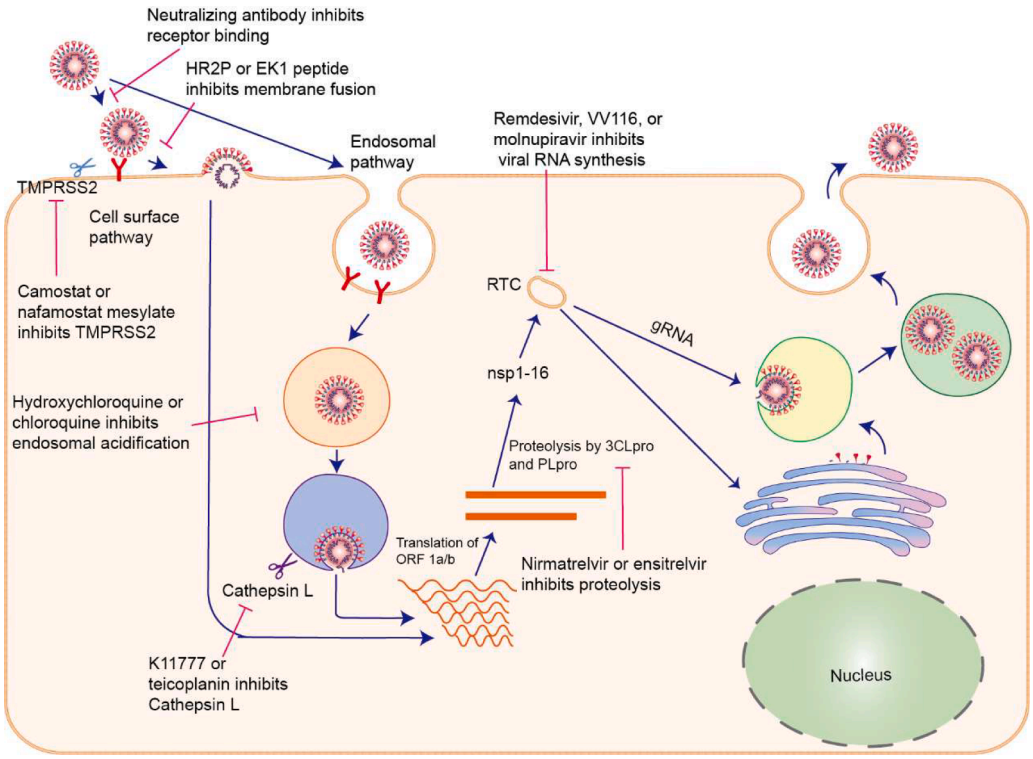

Fig. 1. The life cycle of SARS-CoV-2 and targets for some antivirals. Entry-stage: SARS-CoV-2 particles use their Spike (S) protein to interact with receptor molecules (human ACE2) for viral entry. During the viral entry process, monoclonal antibodies can inhibit the interaction of S protein and ACE2 protein to inhibit viral entry, while TMPRSS-2 inhibitors and Cathepsin B/L inhibitors can inhibit proteolytic activation of spike protein to inhibit viral entry. Peptide inhibitors targeting HR1 (EK1 and HR2P) can inhibit 6-HB formation to block viral entry. Post-entry stage: Viral protein cleavage and RNA synthesis are important processes for the SARS-CoV-2 replication cycle. Mpro and PLpro are important proteases responsible for viral protein cleavage, and these processes can be halted by protease inhibitors, for example, nirmatrelvir (PF-07321332) and ensitrelvir. RdRp is important for viral RNA synthesis, and these processes can be stopped by RdRp inhibitors, such as remdesivir, VV116, and molnupiravir.

entry. Proteolytic activation of S protein is mediated by host proteases, e.g., proprotein convertases, transmembrane serine proteases, and endosomal cysteine proteases, which can be disrupted by antivirals targeting these host proteases (Jackson et al., 2022). The receptor binding process is mediated by the interaction between the S protein and the angiotensin-converting enzyme 2 (ACE2) receptor, which can be blocked by antivirals targeting receptor-binding domain (RBD)/ACE2. The membrane fusion process is mainly mediated by important domains in the S2 subunit, which can be blocked by antivirals targeting the S2 subunit (Xia et al., 2020a; Jackson et al., 2022; Lan et al., 2022) (Fig. 1).

After viral entry, SARS-CoV-2 undergoes several processes, including proteolysis of viral protein, replication, transcription, translation, and virion packaging, to produce progeny virus particles to infect other cells (V'Kovski et al., 2021). Many viral proteins play important roles during these processes and serve as important antiviral targets, such as the main protease (3C-like protease, 3CLpro) and papain-like protease (PLpro) responsible for the proteolysis of viral protein and RNA-dependent RNA polymerase (RdRp) responsible for RNA synthesis. Several antivirals targeting these proteins are currently approved for COVID-19 treatment.

3. Antivirals targeting viral factors

3.1. Antivirals targeting S protein

S protein is expressed on the surface of SARS-CoV-2 virions and is responsible for viral entry, making it a vulnerable target for developing antivirals. S protein consists of the S1 and S2 subunits. The S1 subunit, responsible for the receptor engagement, consists of structural domains including the N-terminal domain (NTD), RBD, and subdomains SD1 and SD2. The S2 subunit, responsible for mediating the process of membrane fusion, consists of structural domains, such as fusion peptide (FP), heptad repeat 1 (HR1), stem helix (SH), heptad repeat 2 (HR2), transmembrane domain (TM), and cytoplasmic tail (CT) (Xia et al., 2020b; Jackson et al., 2022). Among these structural domains, NTD, RBD, FP, SH, HR1, and HR2 regions have all become key targets for developing antivirals, and we discuss the clinical development of antivirals targeting these domains in this section.

3.1.1. Monoclonal antibodies (MAbs)

Early on in the COVID-19 outbreak, many antibodies targeting RBD or NTD in the S1 subunit were reported to have potent SARS-CoV-2 inhibitory activity. However, further clinical development of many NTD-specific antibodies was abandoned. While many RBD-specific antibodies were further developed and assessed in the clinical stage (Xiang et al., 2021). Some RBD-specific antibodies showed promising results in clinical trials (Dougan et al., 2021; Weinreich et al., 2021; Gupta et al., 2022). These antibodies and antibody combinations acquired emergency use authorization (EUA) from the FDA to treat COVID-19, such as sotrovimab, bebtelovimab, bamlanivimab, etesevimab, ronapreve (casirivimab and imdevimab), and evusheld (tixagevimab and cilgavimab). However, the emergence of SARS-CoV-2 variants changed this landscape. Mutation of S protein in SARS-CoV-2 variants opened the door for these variants to escape antibody-mediated neutralization. Presently, many FDA-approved antibodies are no longer recommended for emergency use in COVID-19 patients (FDA, 2023).

In addition, other types of coronaviruses that can infect humans exist in nature, such as human coronavirus OC43 (HCoV-OC43). However, SARS-CoV-2 RBD-specific antibodies have little therapeutic effect in inhibiting these HCoVs because of large differences in the RBD sequences of different HCoVs. Therefore, broadly neutralizing antibodies

targeting conserved sites in the S protein, such as MAbs targeting FP (COV44-79) and MAbs targeting SH (CC40.8), were developed (Dacon et al., 2022; Zhou et al., 2022). These FP- or SH-specific MAbs showed broadly neutralizing activities and could inhibit infections of SARS-CoV-2 variants and other CoVs from the subgenus *Sarbecovirus*. Until now, the clinical activity of these broadly neutralizing antibodies has never been evaluated.

3.1.2. Recombinant protein-based antivirals

Recombinant protein-based antivirals targeting S protein are also under evaluation, and targets of these recombinant protein-based antivirals include RBD and HR2 domain. Soluble ACE2 protein (APN01) can bind with RBD of SARS-CoV-2 S protein and inhibit viral entry. Further studies also showed that APN01 could block infections by SARS-CoV-2 variants (Monteil et al., 2022). The safety and efficacy of APN01 in COVID-19 patients were under clinical evaluation, and its clinical results were pending. HH-120, an IgM-like ACE2 fusion protein targeting RBD, showed potent and broad inhibitory activity against SARS-CoV-2 and its various variants in preclinical studies (Liu et al., 2023). A small-scale clinical study demonstrated that intranasal delivery of HH-120 could shorten viral clearance time in COVID-19 patients (Median viral clearance time: 8 days vs. 10 days) (Song et al., 2023). Therefore, its safety and efficacy are worth further evaluation in large-scale clinical studies. Ensovibep, a tri-specific designed ankyrin repeat protein (DARPin, i.e., small, single domain proteins (14 kDa) selected to bind any given target protein with high affinity and specificity) targeting RBD, can bind with three RBDs in an S protein trimer, further inhibiting the receptor binding process. In vitro studies showed that ensovibep could potently and broadly inhibit infections of various SARS-CoV-2 variants (Rothenberger et al., 2022), demonstrating that it has the potential to become an effective treatment for COVID-19 caused by SARS-CoV-2 variants. However, the clinical trial of ensovibep was terminated because the antiviral was shown to have no efficacy in improving the clinical outcomes of COVID-19 patients (Barkauskas et al., 2022).

Additionally, other recombinant protein-based antivirals targeting viral RBD, including ACE2-Fc (Zhang et al., 2021), trimeric ACE2 (Guo et al., 2021), or antivirals targeting HR2 domains, such as 5-HB (Lin et al., 2022; Xing et al., 2022) and HR1 trimer (Bi et al., 2022), could interrupt the entry process and showed potent SARS-CoV-2 inhibitory activity in preclinical studies. However, many of these antivirals have not entered clinical trials or have no report on their clinical efficacy, so we do not discuss them in detail in this review.

3.1.3. Small-molecule and peptide-based antivirals

In addition to the above-mentioned MAbs and protein-based antivirals, peptide-based and small-molecule antivirals can inhibit SARS-CoV-2 entry. Arbidol, an approved anti-influenza drug in Russia and China, was reported to inhibit SARS-CoV-2 infection by inhibiting viral binding and intracellular vesicle trafficking (Wang et al., 2020a). A preclinical study discovered that arbidol binds with the S2 subunit to inhibit SARS-CoV-2 entry, and arbidol could also inhibit the entry of B.1.1.7 and B.1.351 pseudoviruses (PsVs) (Shuster et al., 2021). The clinical efficacy of arbidol in COVID-19 has been assessed in the clinical stage, and two independent clinical trials consistently suggested that arbidol treatment was superior to that of KALETRA (lopinavir-ritonavir) (Nojomi et al., 2020; Zhu et al., 2020b). One of these clinical trials demonstrated that arbidol treatment was more effective in shortening the duration of hospitalization than KALETRA treatment (7.2 days in the arbidol group versus 9.6 days in the KALETRA group) (Nojomi et al., 2020). Another clinical trial showed that arbidol could not shorten fever duration compared with KALETRA, but could accelerate SARS-CoV-2 clearance. That is, no viral load was detected in the arbidol group, but it was found in 44.1 % of patients in the KALETRA group at day 15 after admission (Zhu et al., 2020a). However, the scale of these clinical trials is relatively small, and more clinical evidence is needed to prove the clinical efficacy of arbidol.

The low mutation rate of the HR1 domain in different HCoVs makes it an attractive target for the development of pan-CoV antivirals. Peptide-based inhibitors derived from the SARS-CoV-2 HR2 domain, like SARS-CoV-2-HR2P, can broadly inhibit infections from SARS-CoV-2 and its variants (Zhu et al., 2020a; Xia et al., 2020b; de Vries et al., 2021). EK1 is a pan-CoV peptide inhibitor that is modified from the HCoV-OC43 HR2 domain. It can interact with different HCoV HR1 domains and further broadly inhibit infections from various HCoVs (Xia et al., 2021; Lan et al., 2023). Nowadays, many of these peptide inhibitors are tested in clinical trials to treat COVID-19 patients in China, and their clinical efficacy will be reported soon (Xia et al., 2021; Wu et al., 2023).

3.2. Antivirals targeting main protease (Mpro, 3CLpro)

Mpro (Nsp5) is responsible for viral protein cleavage and can specifically recognize 11 cleavage sites on pp1a and pp1ab, cleaving them into 12 functional protein fragments (NSPs) (Yang et al., 2021). Mpro plays a critical role in the SARS-CoV-2 replication cycle, and it is, therefore, considered to be an important target for developing antivirals. Antivirals targeting Mpro can disrupt the process of protein cleavage and further inhibit SARS-CoV-2 replication. Furthermore, the sequence of different HCoV Mpros is highly conserved; therefore, antivirals targeting Mpro also have better broad-spectrum HCoV inhibitory activity.

Antivirals targeting Mpro, including Paxlovid (nirmatrelvir-ritonavir) and ensitrelvir, have been approved for clinical use or emergency use. Nirmatrelvir (PF-07321332) is an oral Mpro inhibitor developed based on PF-07304814. Nirmatrelvir showed potent SARS-CoV-2 inhibitory activity in preclinical studies (Owen et al., 2021), and it maintained potent inhibitory activity against infections from various SARS-CoV-2 VOCs and other HCoVs (Vangeel et al., 2022). Paxlovid has been evaluated in several clinical trials, and clinical data showed relative risk reduction (RRR) of Paxlovid by 89.1 % in hospitalization or death of COVID-19 patients (Hammond et al., 2022). In May 2023, the FDA announced its approval of Paxlovid for COVID-19 treatment. Ensitrelvir (S-217622), a newly developed Mpro inhibitor showing potent SARS-CoV-2 inhibitory activity (Unoh et al., 2022), also accelerated SARS-CoV-2 clearance in COVID-19 patients (Median time to infectious viral clearance: 61.3 h for 125 mg ensitrelvir group or 62.7 h for 250 mg ensitrelvir group vs.111.1 h for placebo group) (Mukae et al., 2022). Ensitrelvir is now approved for emergency use in Japan.

The HIV protease inhibitor lopinavir is a repurposed antiviral targeting Mpro to inhibit SARS-CoV-2; however, its clinical applications are no longer recommended after having failed clinical efficacy (Lamontagne et al., 2020). Before the COVID-19 outbreak, lopinavir combined with ritonavir (lopinavir-ritonavir) was used in the treatment of SARS or MERS patients (Zumla et al., 2016; Arabi et al., 2020). During the COVID-19 outbreak, lopinavir-ritonavir was also used in COVID-19 patients. Clinical trials suggested that the therapeutic benefit of lopinavir-ritonavir standalone treatment was not observed in the treatment of COVID-19 (Cao et al., 2020; Group, 2020). Nonetheless, lopinavir-ritonavir combined with interferon beta-1b and ribavirin did show improved clinical efficacy (median time to negative nasopharyngeal swab: 7 days vs. 12 days) (Hung et al., 2020). The results of this clinical trial suggest its potential for use in combination with other antivirals for COVID-19 treatment, but further clinical evidence is also needed.

Similarly, an HCV protease inhibitor, danoprevir, was repurposed to treat COVID-19, and it showed promising results in a small-scale clinical study (Chen et al., 2020), but no large clinical trials have reported its clinical efficacy. Therefore, its clinical efficacy needs to be further confirmed. In addition to the abovementioned Mpro inhibitors already applied in the treatment of COVID-19, other SARS-CoV-2 Mpro inhibitors, such as pomotrelvir (PBI-0451) and EDP-235 (Enanta), are under clinical development. Clinical data showed that pomotrelvir treatment could not markedly accelerate SARS-CoV-2 clearance

compared with placebo treatment and its clinical development has been halted (NCT05543707). As for EDP-235, the phase 2 trial demonstrated that 200 mg or 400 mg EDP-235 orally once daily was safe and well-tolerated for COVID-19 patients, while key secondary endpoints evaluating antiviral effects were not reached.

In addition, several Mpro inhibitors are also under clinical development in China. Simnotrelvir-ritonavir showed satisfactory clinical efficacy and has been approved for the treatment of mild to moderate COVID-19 patients by NMPA in China (Yang et al., 2023). FB2001 and WPV01 were in clinical trials (Shang et al., 2022; Yang et al., 2023), and data on their clinical efficacy are to be reported.

3.3. Antivirals targeting RdRp

RNA-dependent RNA polymerase (RdRp), together with Nsp7 and Nsp8, forms an important part of the replication-transcription complex (RTC) responsible for the transcription and translation of the viral genome. As such, RdRp is an important target for developing antivirals. Most SARS-CoV-2 RdRp inhibitors are nucleoside analogs, including, for example, remdesivir, VV116, molnupiravir, favipiravir, and ribavirin (Hillen, 2021; Li et al., 2023). They inhibit viral replication by causing lethal mutagenesis of viral RNA (e.g., molnupiravir, favipiravir) or inducing delayed termination of RNA replication (e.g., remdesivir, VV116) (von Delft et al., 2023).

Among these RdRp inhibitors, remdesivir, VV116, and molnupiravir have been approved for clinical use/authorized for emergency use in COVID-19 patients in different countries. Remdesivir (GS-5734) showed potent SARS-CoV-2 inhibitory activity in preclinical studies (Kokic et al., 2021). Several clinical trials suggested that the clinical efficacy of remdesivir was poor in resident or severe patients (Goldman et al., 2020; Ader et al., 2022). However, more clinical trials proved its early use or its use in COVID-19 patients not requiring mechanical ventilation to be effective (Beigel et al., 2020; Gottlieb et al., 2022). Adaptive COVID-19 Treatment Trial (ACTT-1) found that remdesivir treatment shortened the time to recovery in hospitalized COVID-19 patients (median recovery time: 10 days in the remdesivir group vs.15 days in placebo group) (Beigel et al., 2020). Another phase 3 randomized, double-blind, placebo-controlled trial also demonstrated that early use of remdesivir could effectively reduce hospitalization or death in non-hospitalized patients (COVID-19-related hospitalization or death: 0.7 % in the remdesivir group vs. 5.3 % in the placebo group) (Gottlieb et al., 2022). The clinical application of remdesivir in COVID-19 is still recommended by WHO (Lamontagne et al., 2020). In addition, remdesivir also is approved by the U.S.FDA for the treatment of pediatric COVID-19 patients under 12 years old.

Although remdesivir treatment could effectively reduce viral load in COVID-19 patients, it must be administered intravenously, which limits its application. Therefore, oral drugs based on remdesivir's parental nucleoside were also developed to inhibit SARS-CoV-2 infection (Schäfer et al., 2022). VV116, an oral remdesivir derivative targeting RdRp, also showed effective and broad inhibitory activity against SARS-CoV-2 and its variants (Xie et al., 2021; Shen et al., 2022). VV116 treatment in COVID-19 patients demonstrated similar clinical efficacy and lower incidence of adverse events compared with nirmatrelvir-ritonavir treatment (median time to sustained clinical recovery: 4 days for VV116 vs. 5 days for nirmatrelvir-ritonavir and incidence of adverse events: 67.4 % vs. 77.3 %) (Cao et al., 2023). VV116 has been approved for clinical use in China.

Before the outbreak of COVID-19, β-D-N^4-Hydroxycytidine (NHC, EIDD-1931) targeting viral RdRp was reported to inhibit various viral infections (Reynard et al., 2015; Urakova et al., 2018). Mechanistic studies indicated that NHC induces viral RNA mutations to inhibit viral replication (Menendez-Arias, 2021; Kabinger et al., 2021). Molnupiravir (EIDD-2801) is an orally bioavailable ribonucleoside analog prodrug of EIDD-1931. It showed potent SARS-CoV-2 inhibitory activity and could inhibit several SARS-CoV-2 variants, including B.1.1.7 and B.1.351 (Abdelnabi et al., 2021; Vangeel et al., 2022). The MOVe-OUT study, a phase III clinical trial, proved its efficacy in reducing hospital admission in unvaccinated mild-to-moderate COVID-19 patients with a hospital admission rate of 7.3 % in the molnupiravir group vs. 14.1 % in the placebo group (Jayk Bernal et al., 2021). Although molnupravir did not reduce COVID-19-associated hospitalization or death in vaccinated individuals, it did reduce the time to recovery and viral load (Butler et al., 2023). However, it is worth noting that molnupiravir was reported to induce mutations in the SARS-CoV-2 genome (Sanderson et al., 2023), which could increase the emergence of novel SARS-CoV-2 variants.

Favipiravir, daclatasvir, sofosbuvir, and ribavirin, are clinical antivirals repurposed to treat COVID-19 (Simonis et al., 2021). However, these repurposed antivirals are no longer recommended due to their little efficacy in COVID-19 treatment. Among them, favipiravir is an antiviral approved for treating influenza; it targets viral RdRp to inhibit viral infection. Favipiravir showed effective SARS-CoV-2 inhibitory activity in preclinical studies (Kaptein et al., 2020) and was further assessed in clinical trials. Two small-scale clinical trials proved that it could accelerate viral clearance and shorten recovery time in moderate patients (Udwadia et al., 2021; Ivashchenko et al., 2021). However, more studies proved that favipiravir was not effective in reducing viral load or relieving symptoms (Bosaeed et al., 2022; Holubar et al., 2022), so its clinical use in treating COVID-19 is not recommended. Daclatasvir/sofosbuvir and ribavirin are all hepatitis C virus (HCV) inhibitors that have been used in COVID-19 patients in clinical trials (Eslami et al., 2020; Abbaspour Kasgari et al., 2020). A small-scale clinical trial suggested that sofosbuvir plus daclatasvir showed better clinical efficacy than ribavirin with mortality of 2/35 (6 %) vs. 9/27 (33 %) (Eslami et al., 2020). Still, another study reported that even a triple combination of these three HCV inhibitors in COVID-19 patients was not an effective treatment (Abbaspour Kasgari et al., 2020).

In addition, AT-527, an HCV inhibitor in the clinical stage, was found to inhibit SARS-CoV-2 RdRp and viral infection (Good et al., 2021). AT-527 was also tested in the clinical stage for COVID-19 treatment. The result from a terminated phase II clinical study suggested that oral AT-527 treatment could moderately reduce viral load in moderate COVID-19 patients from day 2 to 8 (0.61 log10 greater viral load mean change on day 2 compared with placebo), but with no significant differences in progressive respiratory insufficiency (Horga et al., 2023). Therefore, the clinical efficacy of AT-527 remains to be further confirmed in subsequent clinical trials.

4. Antivirals targeting host factors

In addition to the above antivirals directly targeting virion, some other antivirals indirectly inhibit SARS-CoV-2 infections by acting on critical host factors. Compared with antivirals targeting viral factors, antivirals targeting host factors usually have broader HCoV inhibitory activity since host factors are usually more genetically stable than viral factors (Baggen et al., 2021). However, the expression and distribution of host factors in vivo may impact the clinical efficacy of these related antivirals.

Many host factors that play key roles in the whole viral replication cycle have been identified (Baggen et al., 2021), and most developed antivirals primarily target viral entry-related host factors, thus blocking viral infection at the entry stage of SARS-CoV-2. In this section, we summarize the clinical development of these antivirals targeting host factors.

4.1. Viral receptor (ACE2)

ACE2 is the primary receptor for SARS-CoV-2 entry. Antivirals targeting the ACE2 protein may also interrupt ACE2-RBD interaction and viral entry. Moreover, ACE2 has high genetic stability, and antivirals that block ACE2 will be more broad-spectrum than those targeting RBD. However, since ACE2 is an important component of the renin-

angiotensin system, inhibitors that block the ACE2 protein may also interfere with its physiological roles. Currently, no antivirals that inhibit SARS-CoV-2 infection by blocking ACE2 are in clinical use, while some antivirals blocking ACE2 are being developed in preclinical studies.

Human ACE2 (hACE2)-specific Abs have been developed in preclinical studies. These Abs could block the RBD-binding domain in ACE2 protein to inhibit viral infection without affecting its enzymatic activity (Zhang et al., 2023). These ACE2-specific Abs showed pan-CoV inhibitory activity and could inhibit infections of all sarbecoviruses that infect target cells by interacting with hACE2. The FDA-approved drug dalbavancin was reported to bind ACE2 protein and thus interrupt receptor binding and subsequent viral entry. Although dalbavancin showed effective SARS-CoV-2 inhibitory activity in both mouse and rhesus macaque models, no study has reported its clinical application in the treatment of COVID-19 (Wang et al., 2021a).

4.2. Host proteases

Proprotein convertases, such as furin, transmembrane serine proteases, such as TMPRSS-2, and endosomal cysteine proteases, such as cathepsin B/L, are important host proteases responsible for proteolytic activation of S protein during viral entry. SARS-CoV-2 S protein contains S1/S2 and S2′ cleavage sites. Furin cleaves S proteins into S1 and S2 subunits at the S1/S2 cleavage site during the maturation of S proteins. Further, serine proteases and endosomal cysteine proteases cleave S proteins at the S2′ site during viral entry. Serine proteases, located on the surface of the host cell membrane, cleave S proteins on SARS-CoV-2 virions that enter the cell by the surface fusion pathway, while endosomal cysteine proteases cleave S proteins on SARS-CoV-2 virions that enter the cell by the endosomal pathway (Jackson et al., 2022). Host protease inhibitors can block SARS-CoV-2 S protein activation and subsequent SARS-CoV-2 infection; accordingly, these proteases have also become important targets for developing antivirals.

Camostat (FOY-305) and nafamostat are two TMPRSS2 inhibitors that showed potent SARS-CoV-2 inhibitory activity in preclinical studies (Li et al., 2021). Both camostat and nafamostat were assessed in clinical trials, and data on their clinical efficacy and safety have been reported (Zhuravel et al., 2021; Gunst et al., 2021). Although absent of obvious adverse effects, COVID-19 patients who received camostat treatment did not benefit from it compared with placebo treatment (Gunst et al., 2021). Nafamostat was reported to accelerate viral clearance, but it could not improve symptoms in patients (Zhuravel et al., 2021). In addition, aprotinin and bromhexine were reported as TMPRSS-2 inhibitors able to inhibit SARS-CoV-2 infection (Bojkova et al., 2020). Aprotinin was reported to improve clinical outcomes of COVID-19 patients (treatment time: 7.7 ± 0.4 days in the placebo group vs. 5.8 ± 0.4 days in the aprotinin group) (Redondo-Calvo et al., 2022), but the small enrollment limited this clinical trial. The clinical efficacy of bromhexine was not observed in hospitalized COVID-19 patients (Tolouian et al., 2021).

The endosomal pathway is also important for viral entry. SARS-CoV-2 entry was impacted by the activity of endosomal cysteine proteases (cathepsin B/L). K11777 (K777), a cysteine protease inhibitor, was reported to effectively inhibit SARS-CoV-2 entry by interrupting cathepsin B/L activity (Mellott et al., 2021). The natural product gallinamide A and its analogs could also potently inhibit cathepsin B/L activity and subsequent viral entry (Ashhurst et al., 2021). However, the antiviral activity of these cathepsin B/L inhibitors was always compromised when they were tested in cell lines or animal models highly expressing TMPRSS-2 because the activation of S protein is more dependent on TMPRSS-2 than cathepsin L. Considering the lack of antiviral activity of these cathepsin B/L inhibitors in animal models, these antivirals have not been reported as entering clinical trials.

4.3. Other host factors

In addition to the abovementioned common host factors, some unusual host factors also serve as targets for developing antivirals, such as TMEM16F and endosomal lipid kinase (PIKfyve). Niclosamide, an anthelminthic, was reported as a SARS-CoV-2 entry inhibitor able to block SARS-CoV-2 S protein-mediated fusion by inhibiting TMEM16F, a calcium-activated ion channel, important for S protein-induced syncytia (Braga et al., 2021). Besides its wild-type SARS-CoV-2 inhibitory activity, niclosamide could also broadly inhibit infections from several SARS-CoV-2 variants, including Alpha, Beta, and Delta (Weiss et al., 2021). Clinical data showed that niclosamide was very safe in healthy individuals (Backer et al., 2021), but it could not significantly promote viral clearance or shorten symptom duration in mild to moderate COVID-19 patients (Cairns et al., 2022).

PIKfyve plays an important role in endosomal membrane homeostasis and is thus also important for viral endosome pathway-based entry (Kang et al., 2020). Apilimod was reported to interrupt SARS-CoV-2 entry by inhibiting the activity of PIKfyve (Kang et al., 2020). Apilimod (LAM-002A) has been evaluated in clinical trials for the treatment of COVID-19 (NCT04446377), and results showed that it could significantly reduce viral load in COVID-19 patients compared with placebo. However, its clinical efficacy was not satisfactory, and the incidence of adverse events was higher than that of the placebo group (ClinicalTrials.gov, 2023). Therefore, further studies are needed to confirm its efficacy.

5. Antivirals targeting uncertain/miscellaneous factors

In addition to the above antivirals with well-defined targets, many antivirals targeting uncertain/miscellaneous factors have been found to have SARS-CoV-2 inhibitory activity and were also evaluated in clinical trials. Many of the antivirals are repurposed clinical drugs. Until now, most of these antivirals, including chloroquine/hydroxychloroquine (CQ/HCQ), azithromycin, ivermectin, nitazoxanide, cyclosporine A (CsA), and fluvoxamine, did not show promising results in clinical trials and, consequently, were no longer recommended for use in COVID-19 treatment (Lamontagne et al., 2020; Mohan et al., 2021; Axfors et al., 2021; Reis et al., 2022; Naggie et al., 2022; Bramante et al., 2022). In this section, we summarize the results from the clinical trials of these antivirals.

CQ/HCQ likely disrupts the late endosomal pathway to inhibit subsequent viral entry (Simonis et al., 2021). In addition to inhibiting viral entry, CQ/HCQ can also impact the viral post-entry stage, but the exact targets have not been elucidated. Although CQ/HCQ showed potent SARS-CoV-2 inhibitory activity in Vero-E6 cells, the inhibitory activity was compromised in lung-derived cells because of the high expression of TMPRSS-2 (Hoffmann et al., 2020). Many clinical trials were conducted to evaluate CQ/HCQ clinical efficacy in COVID-19 patients (Axfors et al., 2021). However, clinical trials conducted by different hospitals suggested that COVID-19 patients did not benefit from CQ/HCQ treatment (Axfors et al., 2021). Therefore, clinical use of CQ/HCQ in the treatment of COVID-19 is no longer recommended. Azithromycin, an antibiotic used for bacterial infections, also showed SARS-CoV-2 inhibitory activity (Du et al., 2021). Besides its direct SARS-CoV-2 inhibitory activity, azithromycin also has an immunomodulatory effect (Echeverría-Esnal et al., 2021), suggesting that it may be a promising candidate for use in COVID-19 treatment. However, clinical data suggested that neither azithromycin used alone nor used in combination with HCQ could improve clinical status or reduce the mortality of COVID-19 patients (Cavalcanti et al., 2020; Rosenberg et al., 2020).

Ivermectin is an anti-parasitic drug approved by the FDA. In vivo studies showed that ivermectin could effectively inhibit SARS-CoV-2 infection with a half-maximal inhibitory concentration (IC_{50}) at the micromolar level. The possible SARS-CoV-2 inhibitory mechanism of ivermectin involves blocking the entry of viral protein into the cell nucleus (Caly et al., 2020). In addition to its SARS-CoV-2 inhibitory

Table 1
Antivirals against SARS-CoV-2 under clinical studies/ in clinical use.

Drug name	Type	Target	Status	Reported clinical results
Antivirals targeting viral factors				
Sotrovimab	MAb	RBD	EUA withdrawn	Sotrovimab could reduce hospitalization or death in mild/ moderate COVID-19 patients (All-cause hospitalization lasting longer than 24 h or death: 1 % for sotrovimab vs. 6 % for placebo) (Gupta et al., 2022).
Bebtelovimab	MAb	RBD	EUA withdrawn	The rate of progression to severe disease in high-risk patients for bebtelovimab treatment was not significantly different from that for nirmatrelvir-ritonavir treatment (1.4 % vs. 1.2 %) (Razonable et al., 2022).
Bam + Ete	MAb	RBD	EUA withdrawn	Bam + Ete could reduce hospitalization or death in mild/moderate COVID-19 patients (COVID-19-related hospitalization or death: 1% for Bam + Ete vs. 7 % for placebo) (Dougan et al., 2021).
Ronapreve	MAb	RBD	EUA withdrawn	Ronapreve could reduce hospitalization or death in outpatients with COVID-19 (COVID-19-related hospitalization or death: 1.3 % for ronapreve vs. 4.6 % for placebo) (Weinreich et al., 2021).
Evusheld	MAb	RBD	EUA withdrawn	Evusheld could prevent SARS-CoV-2 infection (Symptomatic COVID-19 occurrence: 0.2 % for evusheld vs.1.0 % for placebo) (Levin et al., 2022).
Soluble ACE2 (APN01)	Recombinant protein	RBD	Phase II clinical trial	Not reported
Ensovibep (MP0420)	Recombinant protein	RBD	Clinical trial terminated	Ensovibep could not improve clinical outcomes of hospitalized COVID-19 patients (Barkauskas et al., 2022).
HH-120	Recombinant protein	RBD	Phase II clinical trial in China	HH-120 could shorten viral clearance time (Median viral clearance time: 8 days vs. 10 days) (Song et al., 2023)
SARS-CoV-2 HR2 based peptides	Peptide	HR1	Phase II clinical trial in China	Not reported
EK1	Peptide	HR1	Phase II clinical trial in China	Not reported
Arbidol	Small molecule	viral binding	Not recommended to treat COVID-19	Arbidol did reduce the duration of hospitalization (7.2 days for arbidol vs. 9.6 for KALETRA) (Nojomi et al., 2020). Arbidol could accelerate SARS-CoV-2 clearance (Zhu et al., 2020a).
Lopinavir-ritonavir	Small molecule	Mpro	Not recommended to treat COVID-19	No benefit from lopinavir-ritonavir treatment (Cao et al., 2020). Lopinavir-ritonavir could not reduce 28-day mortality and duration of hospital stay (Group, 2020).
Danoprevir-ritonavir	Small molecule	Mpro	Not recommended to treat COVID-19	Danoprevir-ritonavir could accelerate SARS-CoV-2 clearance (Chen et al., 2020), but more evidence is needed.
Ensitrelvir	Small molecule	Mpro	Approved by PMDA	Ensitrelvir could accelerate SARS-CoV-2 clearance in mild-to-moderate COVID-19 patients (median time to infectious viral clearance: 61.3 h for 125 mg group or 62.7 h for 250 mg group vs.111.1 h for placebo group) (H Mukae et al., 2022).
Nirmatrelvir-ritonavir	Small molecule	Mpro	Approved by FDA	Nirmatrelvir-ritonavir could reduce risk of progression to severe COVID-19 (Risk of COVID-19-related hospitalization or death by day 28: 0.77 % in nirmatrelvir-ritonavir vs.7.01 % in placebo) (Hammond et al., 2022).
Simnotrelvir-ritonavir	Small molecule	Mpro	Approved in China	Simnotrelvir-ritonavir could shorten recovery time in symptomatic adult patients (recovery time: shorten roughly 1.5 days for mild to moderate COVID-19 and 2.4 days for the subgroup of high-risk severe COVID-19 patients) (NCT05506176).
Pomotrelvir (PBI-0451)	Small molecule	Mpro	Clinical trial terminated	Pomotrelvir could not markedly accelerate SARS-CoV-2 clearance (NCT05543707).
EDP-235 (Enanta)	Small molecule	Mpro	Phase II clinical trial	EDP-235 was safe and well-tolerated for COVID-19 patients, while key secondary endpoints evaluating antiviral effect were not reached.
FB2001	Small molecule	Mpro	Phase II/III clinical trial	FB2001 has high safety and tolerability in health individuals (NCT05197179).
WPV01	Small molecule	Mpro	Phase II clinical trial	Not reported
Remdesivir	Small molecule	RdRp	Approved by FDA	Remdesivir could not improve clinical outcomes of severe COVID-19 patients (Goldman et al., 2020; Wang et al., 2020). Remdesivir could shorten recovery time (10 days for remdesivir vs. 15 days for placebo) (Beigel et al., 2020).
Molnupiravir	Small molecule	RdRp	Approved by FDA	Molnupiravir could reduce hospitalization or death in unvaccinated patients (Risk of hospitalization or death: 7.3 % for molnupiravir vs. 14.1 % for placebo) (Jayk Bernal et al., 2021). Molnupiravir could not reduce hospitalization or death in vaccinated patients, but it could reduce time to recovery and viral load (Butler et al., 2023).
VV116	Small molecule	RdRp	Approved by NMPA	VV116 could accelerate SARS-CoV-2 clearance (Median time to sustained clinical recovery: 4 days for VV116 vs. 5 days for nirmatrelvir-ritonavir) (Cao et al., 2023).
Bemnifosbuvir (AT-527)	Small molecule	RdRp	Phase II clinical trial	Bemnifosbuvir could moderately reduce viral load on day 2 to 8 (AT-527 contributed 0.61 $\log_{10}$ greater viral load mean change on day 2 compared with placebo) (Horga et al.).
Favipiravir	Small molecule	RdRp	Not recommended to treat COVID-19	Favipiravir did not accelerate SARS-CoV-2 clearance in mild COVID-19 patients (Median time to viral clearance: 10 days in the favipiravir group vs. 8 days in the placebo group) (Bosaeed et al., 2022).
Ribavirin	Small molecule	RdRp	Not recommended to treat COVID-19	Triple therapy (Ribavirin, IFN β1a, and lopinavir-ritonavir) was superior to lopinavir-ritonavir alone (Median time to negative nasopharyngeal swab: 7 days vs. 12 days) (Hung et al., 2020).
Daclatasvir	Small molecule	RdRp	Not recommended to treat COVID-19	Daclatasvir did not significantly alleviate symptoms (Eslami et al., 2020).
Sofosbuvir	Small molecule	RdRp	Not recommended to treat COVID-19	Sofosbuvir did not significantly alleviate symptoms (Eslami et al., 2020).
Antivirals targeting host factors				
Camostat	Small molecule	TMPRSS2	Not recommended to treat COVID-19	Camostat did not affect time to clinical improvement in COVID-19 patients (Gunst et al., 2021).

(*continued on next page*)

Table 1 (*continued*)

Drug name	Type	Target	Status	Reported clinical results
Nafamostat	Small molecule	TMPRSS2	Not recommended to treat COVID-19	Nafamostat did not affect time to clinical improvement in COVID-19 patients (Quinn et al., 2022).
Bromhexine	Small molecule	TMPRSS2	Not recommended to treat COVID-19	Bromhexine was not effective for hospitalized COVID-19 patients (Tolouian et al., 2021).
Aprotinin	Small molecule	TMPRSS2	Not recommended to treat COVID-19	Aprotinin improved clinical outcomes in hospitalized COVID-19 patients (treatment time: 7.7 ± 0.4 days in the placebo group vs. 5.8 ± 0.4 days in the aprotinin group) (Redondo-Calvo et al., 2022).
Apilimod	Small molecule	PIKfyve	Phase II clinical trial	Apilimod reduced viral load, but it did not improve clinical outcomes (ClinicalTrials.gov, 2023).
Niclosamide	Small molecule	TMEM16 family	Not recommended to treat COVID-19	Niclosamide could not accelerate SARS-CoV-2 clearance (Cairns et al., 2022).
Antivirals targeting uncertain/miscellaneous factors				
CQ/HCQ	Small molecule	Endosomal pH	Not recommended to treat COVID-19	No benefit is realized from CQ/HCQ treatment (Axfors et al., 2021).
Azithromycin	Small molecule	To be elucidated	Not recommended to treat COVID-19	Azithromycin did not reduce in-hospital mortality (Rosenberg et al., 2020).
Ivermectin	Small molecule	Viral protein nuclear import	Not recommended to treat COVID-19	Ivermectin did not significantly reduce viral load (Mohan et al., 2021; Reis et al., 2022; Naggie et al., 2022).
Nitazoxanide	Small molecule	TMEM16 family	Not recommended to treat COVID-19	Nitazoxanide could reduce viral load, but it could not relieve symptoms in mild COVID-19 (RT-PCR negative rate at the end-of-therapy visit: 29.9 % for nitazoxanide vs. 18.2 % for placebo) (Rocco et al., 2021). Nitazoxanide could not reduce ICU admission in hospitalized COVID-19 patients (Rocco et al., 2022).
Cyclosporine A	Small molecule	To be elucidated	Not recommended to treat COVID-19	Used as an adjuvant to steroid treatment for COVID-19, patients' outcomes could be improved (Gálvez-Romero et al., 2021).
Fluvoxamine	Small molecule	To be elucidated	Not recommended to treat COVID-19	Fluvoxamine did not reduce hospitalization and death of COVID-19 patients (Bramante et al., 2022).

Notes: NMPA, national medical products administration; PMDA, pharmaceuticals and medical devices agency; EUA, emergency use authorization.

activity, ivermectin also possesses immunomodulatory effects and can attenuate inflammation caused by SARS-CoV-2 infection (de Melo et al., 2021). Clinical trials were conducted to evaluate the clinical efficacy of ivermectin in COVID-19 patients (Mohan et al., 2021; Ahmed et al., 2021). A small-scale clinical trial suggested that a 5-day course of ivermectin might significantly reduce viral load compared with placebo treatment (Ahmed et al., 2021), but more clinical evidence suggested that ivermectin was not an effective treatment in symptomatic COVID-19 patients (Mohan et al., 2021; Reis et al., 2022; Naggie et al., 2022).

Similarly, nitazoxanide is also an antiparasitic drug repurposed to inhibit SARS-CoV-2 infection. Early use of nitazoxanide did not relieve symptoms of mild COVID-19 patients, but it could reduce viral load (negative rate of SARS-CoV-2 RT-PCR on the 5th day: 29.9 % in the nitazoxanide group vs. 18.2 % in the placebo group) (Rocco et al., 2021). CsA, an immunosuppressor used in organ transplantation, showed synergistic SARS-CoV-2 inhibitory activity in vitro when combined with remdesivir (Hsu et al., 2021). Although no study has reported on its exact inhibitory mechanisms against SARS-CoV-2, CsA showed a certain clinical efficacy when combined with steroid treatment (Mortality: 22 % in the CsA group vs. 35 % in the control group) (Gálvez-Romero et al., 2021). Therefore, more clinical data are needed to prove its clinical efficacy.

6. Conclusion

Overall, we review the clinical development of antivirals targeting various factors to inhibit SARS-CoV-2 infection, including both viral factors and host factors. Diverse viral/host factors play different roles in the viral replication cycle, thus contributing to variations in the inhibitory activity of antivirals developed against these targets. In addition, the genetic stability of these targets also impacts the broad-spectrum coronavirus inhibitory activity of antivirals. These phenomena suggested that we should target conserved and vital host/viral factors to develop antivirals (Lu et al., 2021). Such antivirals can broadly block infection caused by SARS-CoV-2 variants, thus possessing greater advantages in the treatment of COVID-19 caused by SARS-CoV-2 variants (Xia et al., 2021; Vangeel et al., 2022).

In addition, although many antivirals showed potent SARS-CoV-2 inhibitory activity in preclinical studies and have been tested in clinical trials, only a few antivirals, as shown in Table 1, showed significant clinical effects (Wang et al., 2020b; WHOST Consortium et al., 2021). Therefore, appropriate treatment regimens, such as early use or combinatorial use of antivirals, are needed for their best utilization. Generally, antivirals used in the early stage of COVID-19 progression may have a more significant effect than those used in the late stage. The combined use of antivirals also can provide a better clinical effect. Clinical trials proved that clinical outcomes from combinatorial treatments were better than standalone treatments (Hung et al., 2020; Kalil et al., 2021). Preclinical data also supported this opinion, i.e., that 1) combinations of TMPRSS-2 inhibitors and PIKfyve inhibitors showed synergistic SARS-CoV-2 inhibitory activity (Kreutzberger et al., 2021) and 2) combinations of Mpro inhibitors and RdRp inhibitors also showed synergistic activity (Boras et al., 2021). Nevertheless, these combinations are awaiting more data to prove their efficacy and safety before moving to clinical trials.

CRediT authorship contribution statement

Qiaoshuai Lan: Conceptualization, Writing – original draft. **Yan Yan:** Writing – original draft. **Guangxu Zhang:** Conceptualization. **Shuai Xia:** Writing – review & editing. **Jie Zhou:** Writing – review & editing, Supervision. **Lu Lu:** Funding acquisition, Supervision. **Shibo Jiang:** Conceptualization, Writing – review & editing, Supervision.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

Data availability

No data was used for the research described in the article.

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