

## Review Article



# COVID-19 Antiviral and Treatment Candidates: Current Status

Erica España <sup>†</sup>, Dajung Kim<sup>†</sup>, Jiyeon Kim, Song-Kyu Park , Jeong-Ki Kim <sup>\*</sup>

Department of Pharmacy, Korea University College of Pharmacy, Sejong 30019, Korea

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### \*Correspondence to

Jeong-Ki Kim

Department of Pharmacy, Korea University  
College of Pharmacy, 2511 Sejong-ro, Sejong  
30019, Korea.

E-mail: jkfrancis@korea.ac.kr

<sup>†</sup>These authors contributed equally to this work.

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### ORCID iDs

Erica España

<https://orcid.org/0000-0003-1437-9069>

Song-Kyu Park

<https://orcid.org/0000-0002-2858-2300>

Jeong-Ki Kim

<https://orcid.org/0000-0003-1520-1377>

### Conflict of Interest

The authors declare no potential conflicts of interest.

### Abbreviations

3CLpro, 3C-like protease; ACE, angiotensin-converting enzyme; ARDS, acute respiratory distress syndrome; COVID-19, coronavirus disease 2019; CP, convalescent plasma; CQ, chloroquine; CT, computed tomography;

## ABSTRACT

The coronavirus disease 2019 (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus 2 has severely impacted global health and economy. There is currently no effective approved treatment for COVID-19; although vaccines have been granted emergency use authorization in several countries, they are currently only administered to high-risk individuals, thereby leaving a gap in virus control measures. The scientific and clinical communities and drug manufacturers have collaborated to speed up the discovery of potential therapies for COVID-19 by taking advantage of currently approved drugs as well as investigatory agents in clinical trials. In this review, we stratified some of these candidates based on their potential targets in the progression of COVID-19 and discuss some of the results of ongoing clinical evaluations.

**Keywords:** COVID-19; Severe acute respiratory syndrome coronavirus 2; Antiviral agents; Immunotherapy; Drug repositioning

## INTRODUCTION

The coronavirus disease 2019 (COVID-19) was first reported in December 2019 in Wuhan, Hubei, China as cases of respiratory illness leading to pneumonia of unknown etiology. Viral isolation and genetic characterization revealed the causative agent to be closely related (79% nucleotide identity) to the severe acute respiratory syndrome coronavirus (SARS-CoV) of the genus *Betacoronavirus* of the *Coronaviridae* family (1). This family includes several veterinary and human viruses, including 4 human coronaviruses that cause the common cold (HCoV-NL63, HCoV-229E, HCoV-OC43, and HCoV-HKU1) and the Middle East respiratory syndrome coronavirus (MERS-CoV). Owing to its genetic relationship to SARS-CoV, the COVID-19 agent was named SARS-CoV-2 by the International Committee on Taxonomy of Viruses. Further phylogenetic analyses showed that SARS-CoV-2 shares 96.2% of its genome with a SARS-like CoV (RaTG13) isolated from the intermediate horseshoe bat *Rhinolophus affinis* in 2013, suggesting that SARS-CoV-2 is zoonotic in nature and emerged from a spillover event from bats (2). SARS-CoV-2 has spread at a much larger scale than either SARS-CoV or MERS-CoV, eventually leading the World Health Organization (WHO) to declare a COVID-19 pandemic on March 11, 2020. At the time of writing, the number of cases has breached 90 million, with more than 1.9 million deaths (<https://coronavirus.jhu.edu/map.html>) (3). Apart

DCV, daclatasvir; DENV, dengue virus; EBOV, Ebola virus; HA, hemagglutinin; HCQ, hydroxychloroquine; HCV, hepatitis C virus; LPVr, lopinavir-ritonavir; MERS-CoV, Middle East respiratory syndrome coronavirus; NAbs, neutralizing Abs; NIAID, National Institute of Allergy and Infectious Diseases; NS, nonstructural; pHAE, primary human airway epithelial; REACT, WHO Rapid Evidence Appraisal for COVID-19 Therapies; RECOVERY, Randomised Evaluation of COVID-19 Therapy; RdRp, RNA-dependent RNA polymerase; RDV, remdesivir; RDV-TP, triphosphate form of remdesivir; S protein, spike protein; SARS-CoV, severe acute respiratory syndrome coronavirus; SOF, sofosbuvir; WHO, World Health Organization; ZIKV, Zika virus.

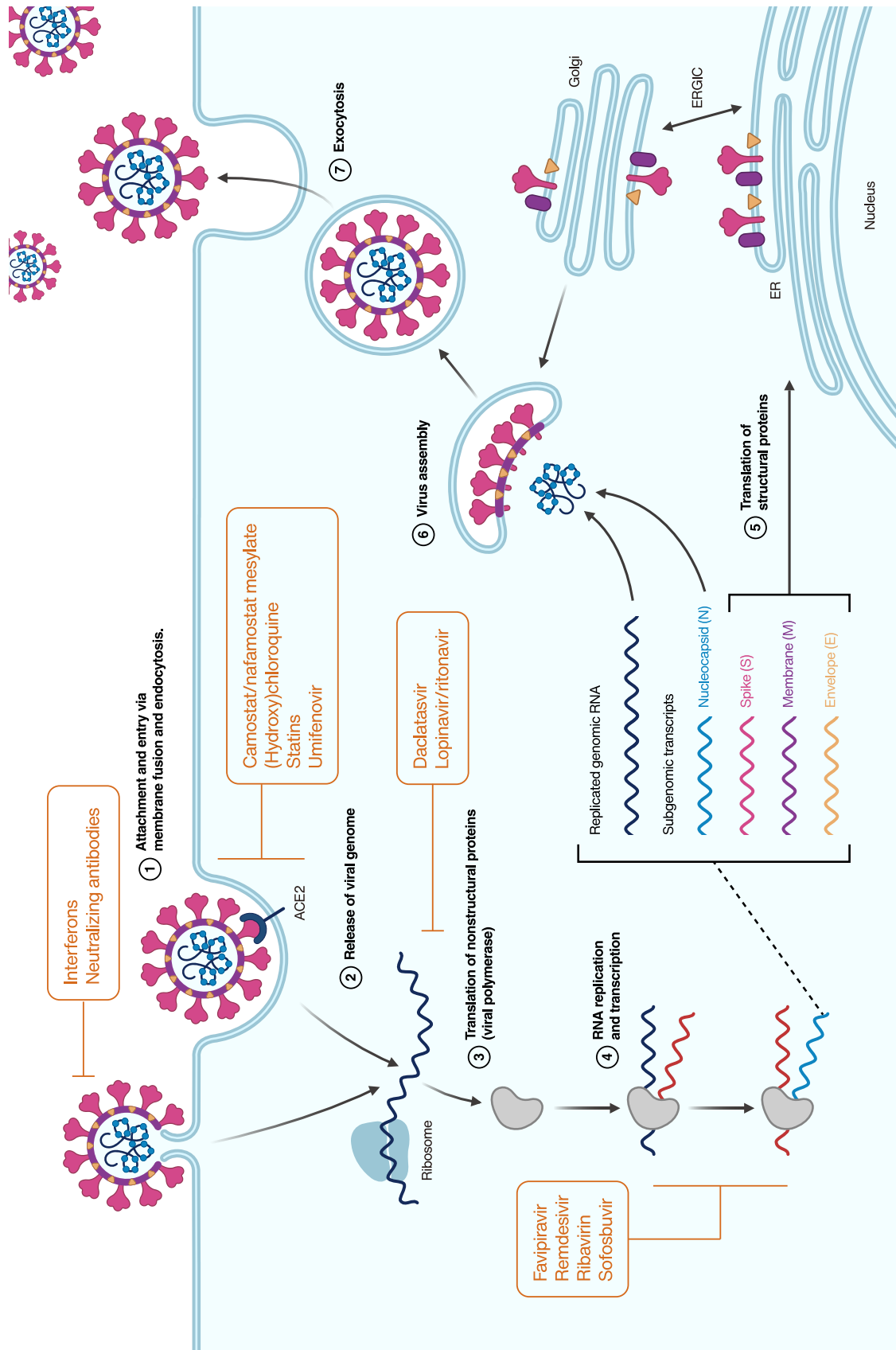
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from its apparent impact on public health, COVID-19 has severely affected global economy due to the strict measures enforced by several nations to curb the spread of SARS-CoV-2. Thus, scientists and medical practitioners are scrambling to discover agents to reduce the morbidity and mortality related to COVID-19 and to ease the socioeconomic burden of the COVID-19 pandemic.

Quantitative RT-PCR is the gold standard for the diagnosis of SARS-CoV-2 infection, and chest computed tomography (CT) scans are typically performed to monitor COVID-19 progression. People infected with SARS-CoV-2 develop symptoms at around 5 (range, 2–7) days post-exposure, and most people (97.5%) do so up to 11.5 days post-exposure (4,5). However, viral shedding starts 2–3 days before symptom onset, suggesting that people who do not display symptoms (asymptomatic or presymptomatic) can transmit the virus (6). Symptoms are mild in majority of cases ( $\leq 81\%$ ), with fever, cough, dyspnea, and anosmia as the most common presentations (7). The disease can then progress to the inflammatory or severe phase ( $\leq 15\%$  of cases) characterized by pulmonary or systemic hyperinflammation that can cause airway damage (8). High levels of pro-inflammatory cytokines (“cytokine storm” or cytokine release syndrome), including IL-6, TNF- $\alpha$ , IL2, IL-7, IL-1 $\beta$ , and GM-CSF, have been consistently observed in severe COVID-19 cases and further contribute to disease severity (9). Patients who have progressed to the inflammatory stage generally seek medical help and require respiratory support (7); they are typically 47–73 years old, with 60%–90% having comorbidities (10). If hyperinflammation persists, it can promote vascular permeability, platelet hyperactivation, and activation of coagulation factors (11). This can then lead to the thrombotic stage of COVID-19, which is characterized by venous, arterial, and microvascular thrombosis, and these factors contribute further to pulmonary damage and multiorgan injury seen in critical COVID-19 patients. Hypercoagulation, acute respiratory distress syndrome (ARDS), viral sepsis, and multiorgan failure are considered major contributors to the deterioration of critically ill COVID-19 patients, 20%–80% of whom succumb to the disease (7,11). Notably, an increasing number of studies and anecdotes suggest that patients can experience symptoms long after viral clearance and hospital discharge, indicating persisting or lingering physiological effects of SARS-CoV-2 infection (12). Children typically exhibit milder COVID-19 symptoms; however, cases of SARS-CoV-2-associated multisystem inflammatory syndrome in children have been reported (13).

There is currently no approved effective therapeutic agent for human coronaviruses. The strategy for drug discovery and development for COVID-19 treatment involves testing agents that have shown promise against other human coronaviruses (especially against SARS-CoV and MERS-CoV); agents that have shown promise or are approved against other viruses; and agents that target host mechanisms to alleviate COVID-19 symptoms and complications. With the growing knowledge on the course of SARS-CoV-2 infection, including the understanding of both viral and host factors (**Fig. 1**), several candidates have been identified. Based on the different phases of infection, antivirals can be used to target the early phases of infection to reduce viral load; anti-inflammatory agents can be used in the hyperinflammatory stage of the disease; and anticoagulants can be used to alleviate thrombosis associated with critical COVID-19. These agents may also be used in tandem to prevent further progression of the disease, and some of these agents may target both viral and host factors. In this review, we discuss some of the candidates for COVID-19 treatment, their modes of action, and the current progress of clinical evaluations.



**Figure 1.** The SARS-CoV-2 replication cycle and the known and potential targets of antivirals and other agents. The SARS-CoV-2 S protein binds ACE2 on the host cell surface, and the S protein is primed through cleavage by transmembrane protease, serine 2 to facilitate entry into the host through membrane fusion or endocytosis. The genomic RNA is uncoded in the cytosol and then translated into polypeptides that are processed to form the viral replication and transcription complex. Viral genomic RNA synthesis is facilitated by the viral RdRp. Structural proteins are translated at the endoplasmic reticulum, followed by virion assembly in the ERGIC. Virions bud out of the of the Golgi complex for shuttling to the cell surface and are released through exocytosis. ERGIC, endoplasmic reticulum-to-Golgi intermediate compartment.

## ANTIVIRALS

### Remdesivir (RDV)

RDV (GS-5374) is considered one of the leading candidates in the search for drugs against SARS-CoV-2 (Table 1). RDV is a prodrug with a triphosphate form (RDV-TP) that closely resembles ATP and has been reported to be slightly more preferentially incorporated than ATP into the nascent RNA strand by the viral RNA-dependent RNA polymerase (RdRp) (14). Unlike typical RNA chain terminators, RDV causes delayed termination at *i*+3 and *i*+5 positions (where *i* is the RDV-TP insertion position), likely due to steric strain at the RdRp active site (15).

RDV was initially reported to have the potential to inhibit filoviruses. It progressed to phase 2/3 clinical trials against the Ebola virus (EBOV) but was found to be inferior to

**Table 1.** Summary of COVID-19 treatment evaluations for developed antivirals and approved drugs with antiviral potential

Drug	Target COVID-19 stage(s)*	Known viral targets & modes of action	Status
<b>Direct-acting antivirals</b>			
RDV	Early (potential)	Adenosine analog viral RdRp inhibitor	<ul style="list-style-type: none"> <li>RECOVERY trial (phase 3) shows improved clinical outcomes in hospitalized patients</li> <li>WHO Solidarity trial (phase 3) suggests no benefits for hospitalized patients</li> <li>Approved by the US-FDA</li> <li>Ongoing phase 2/3 trials for COVID-19 outpatients, pediatric patients, and combinatorial therapy</li> <li>Ongoing phase 1 trial for inhaled RDV formulation for early-stage COVID-19</li> </ul>
	Middle (demonstrated)		
Lopinavir+ritonavir	Early (potential)	HIV protease inhibitor (approved) Potential CoV protease inhibitor	<ul style="list-style-type: none"> <li>Does not benefit hospitalized patients</li> <li>Ongoing phase 2/3 trials as prophylaxis or for early-stage COVID-19</li> </ul>
Ribavirin	Early (potential)	Guanosine analog Inhibits GTP synthesis	<ul style="list-style-type: none"> <li>Monotherapy does not benefit COVID-19 patients</li> <li>Ongoing phase 1 trial for aerosolized ribavirin in hospitalized patients</li> <li>Ongoing phase 2/3 trial for combination with IFNs and other agents</li> </ul>
SOF+DCV	Early (demonstrated)	Viral mutagenesis Immunomodulatory activity Hepatitis C virus (approved)	<ul style="list-style-type: none"> <li>Phase 2/3 randomized controlled trials suggest treatment benefits of SOF+DCV on severe COVID-19</li> <li>Ongoing phase 2/3 trials for SOF alone, with DCV or with other agents</li> </ul>
	Middle (demonstrated)	SOF may bind SARS-CoV-2 RdRp DCV may bind SARS-CoV-2 protease	
Favipiravir	Early (demonstrated)	Influenza virus emergency drug (Japan)	<ul style="list-style-type: none"> <li>Open-labeled trial shows improved therapeutic responses and accelerated viral clearance</li> <li>Ongoing trials for various degrees of COVID-19 severity</li> </ul>
Umifenovir	Early (potential)	Purine analog Viral RdRp inhibitor	<ul style="list-style-type: none"> <li>Mixed results for COVID-19 treatment</li> <li>Ongoing phase 4 trials for COVID-19 treatment</li> </ul>
		Influenza treatment and prophylaxis (China and Japan) Viral endocytosis inhibitor Inhibitor of viral genome replication	
<b>Potential antivirals with non-antiviral indications</b>			
CQ, HCQ	Early (potential)	Anti-malaria Anti-rheumatoid arthritis (HCQ) Viral endocytosis inhibitor <i>in vitro</i>	<ul style="list-style-type: none"> <li>No benefits for hospitalized COVID-19 patients</li> <li>Ongoing phase 1 trials as prophylaxis for COVID-19</li> <li>Ongoing phase 2 trials for mild to moderate COVID-19</li> </ul>
Statins	Early (potential)	Anti-cholesterol	<ul style="list-style-type: none"> <li>Continuous use or use prior to infection associated with less severe COVID-19 in retrospective studies</li> </ul>
	Middle (potential)	Evidence for antiviral activity <i>in vitro</i> Anti-inflammatory effects	
Camostat mesylate, nafamostat mesylate	Early (potential)	Acute pancreatitis	<ul style="list-style-type: none"> <li>Camostat mesylate under phase 2 trials for varying degrees of COVID-19 severity</li> <li>Nafamostat mesylate under phase 2/3 trials for varying degrees of COVID-19 severity</li> </ul>
	Late (potential)	Anticoagulatory effects Serine protease inhibitor	

CoV, coronavirus; US-FDA, United States Food and Drug Administration.

\*Target COVID-19 stages are divided into: early (first week of infection, viral phase, pre-/early symptomatic phase); middle (second week of infection, symptomatic, early stages of hyperinflammation); and late (beyond second week of infection, hyperinflammatory to thrombotic stages). Demonstrated: denotes existence of evidence based on COVID-19 clinical studies; potential: target is yet to be demonstrated in clinical trials but is based on the agent's known modes of action and other viral targets.

other treatments (16). Several *in vitro* studies have also reported the activity of RDV against other RNA viruses such as paramyxoviruses (e.g., the Nipah virus), pneumoviruses, and coronaviruses (e.g., SARS-CoV and MERS-CoV), indicating the potential of RDV as a broad-spectrum antiviral (17). The promise of RDV as an agent against coronaviruses was further extended to SARS-CoV-2 in an *in vitro* study (18). Based on its good safety profile in the EBOV trials, RDV was used against COVID-19 under the compassionate use protocol and advanced to phase 2/3 clinical trials. An early trial in China has shown that RDV treatment resulted in faster improvement in severe COVID-19 patients, but the effects were not significantly different from those of placebo (19). Compassionate use of RDV in hospitalized patients also increased recovery rate in the cohort (20). The interim results of the National Institute of Allergy and Infectious Diseases (NIAID) double-blind, randomized, placebo-controlled phase 3 trial (NCT04280705) showed that a 10-day course of RDV reduced the time to recovery of hospitalized COVID-19 patients (21). The final results of this trial show that RDV treatment improved clinical outcomes, including shorter time to improvement in an ordinal scale of patient categories, shorter time to recovery, shorter time for oxygen supplementation, and lower mortality compared to placebo (21). This trial also suggests that, while RDV is more beneficial when given early into the illness, RDV provides benefits even when administered later in the course of COVID-19. In contrast, results of the WHO Solidarity trials show that RDV does not benefit hospitalized COVID-19 patients in terms of mortality, progression to ventilation, and length of hospital stay (22). Whether RDV treatment is beneficial to mild to moderate COVID-19 patients (outpatients), to pediatric patients, and when used with other agents are still being evaluated (e.g., NCT04501952, NCT04431453, and NCT04409262).

### Lopinavir + ritonavir

Lopinavir-ritonavir (LPVr) is a combination of HIV protease inhibitors used for AIDS treatment. Most of the protease inhibitory effects are attributed to lopinavir, while ritonavir is used to elevate systemic levels of lopinavir (23). An *in silico* study suggests that LPVr bind the SARS-CoV 3C-like protease (3CL<sup>pro</sup>) (24). In line with this, a study has shown that both drugs can inhibit SARS-CoV infection *in vitro*, and treatment with LPVr has clinical benefits against SARS in a small cohort (25). Similarly, post-exposure prophylaxis with LPVr and ribavirin has been associated with protectivity against MERS in a retrospective study (26).

Given the high sequence conservation of the CoV protease, LPVr was expected to have COVID-19 treatment benefits (27). Based on the previous guidelines for MERS and SARS management, LPVr was given to patients in South Korea and in China early into the SARS-CoV-2 outbreak and appeared to have treatment benefits (28,29). However, the results of The Efficacy of Lopinavir Plus Ritonavir and Arbidol Against Novel Coronavirus Infection (30) and Randomised Evaluation of COVID-19 Therapy (RECOVERY) (31) suggest that LPVr provides little to no benefit to hospitalized COVID-19 patients (**Table 1**). The WHO's Solidarity trial revealed similar findings, leading to the WHO's decision to halt the LPVr arms of the Solidarity trial (22,32). However, whether LPVr is effective against the early stages of SARS-CoV-2 infection or as a prophylactic agent is still currently being explored in some trials (e.g., NCT04372628 and NCT04328285).

### Ribavirin

Ribavirin is a guanosine analog clinically used against the hepatitis C virus (HCV). The reported mechanisms for the antiviral activity of ribavirin include: competitive inhibition of inosine monophosphate dehydrogenase, a rate-limiting enzyme for GTP synthesis (33); and mutagenesis of the viral genome via the incorporation of ribavirin triphosphate instead of



GTP, which results in lower virus viability (34). Ribavirin has also shown immunomodulatory activity in cases of HCV infection (35).

Ribavirin has displayed antiviral effects against SARS-CoV *in vitro* and has shown synergistic effects with type I IFNs (36,37). Ribavirin alone or in combination with IFN- $\beta$ 1b improved the clinical scores and promoted viral clearance in MERS-CoV-infected rhesus macaques (38). The combination of ribavirin with LPVr and IFNs, rather than treatment with ribavirin alone, has been seen to improve clinical outcomes in some MERS cases (39,40). In line with this, a retrospective study has shown that treatment with ribavirin alone did not improve outcomes in COVID-19 patients (41). Thus, most COVID-19 trials involving ribavirin test its combination with other agents, particularly IFNs, for optimal effects. A prospective randomized study has shown that early treatment with the combination of ribavirin with IFN- $\beta$ 1b and LPVr alleviates symptoms and shortens the duration of viral shedding in patients with mild to moderate COVID-19 (42). In contrast, a randomized open-labeled prospective study suggests that ribavirin+IFN- $\alpha$ , LPVr+IFN- $\alpha$ , and ribavirin+LPVr+IFN- $\alpha$  do not have significantly different antiviral effects, and that the combination of ribavirin+LPVr may have adverse effects in patients with mild to moderate COVID-19 (43). The results of ongoing trials (e.g., NCT04551768, NCT04494399, and NCT04563208) are needed to determine whether ribavirin alone is beneficial to or enhances the benefits of other (e.g., IFNs) agents in COVID-19 treatment.

### Sofosbuvir + daclatasvir (SOF/DCV)

SOF and DCV are direct-acting antivirals used in combination to treat HCV infection. DCV inhibits the HCV nonstructural (NS) 5A protein and is hypothesized to affect HCV replication, assembly, and secretion (44). Meanwhile, SOF is a nucleotide analog that inhibits the HCV polymerase, NS5B (45). SOF has also demonstrated activity against Zika virus (ZIKV), dengue virus (DENV), yellow fever virus, and chikungunya virus (46).

The conserved nature of the RdRp in positive-sense RNA viruses prompted the interest in SOF for COVID-19 treatment. *In silico* studies have shown that the SARS-CoV-2 RdRp can bind SOF, suggesting that SOF may be used to inhibit SARS-CoV-2 replication (47,48). Indeed, a study has demonstrated that the SARS-CoV-2 RNA strand terminated by the incorporation of SOF was more resistant to the SARS-CoV-2 exonuclease proofreading activity than the RNA strand terminated by the incorporation of RDV (49). DCV was likewise shown to bind the SARS-CoV-2 3CL<sup>pro</sup> (50). An unpublished study also suggests that treatment with DCV or SOF inhibits SARS-CoV-2 production *in vitro* (51).

A series of small clinical trials to evaluate the benefits of the SOF/DCV combination against COVID-19 have been performed in Iran. One of these studies, a randomized, controlled trial, suggests that SOF/DCV shortens the time to recovery and hospital stay of severe COVID-19 patients relative to standard of care (LPVr or hydroxychloroquine [HCQ]), but without significant effects on mortality (52). SOF/DCV was superior to ribavirin in terms of safety, symptom improvement, mortality, and hospital stay in severe COVID-19 cases in another study (53). A double-blind, randomized parallel, active-controlled study on outpatients (IRCT20200403046926N1) shows that SOF/DCV with HCQ had a tendency to reduce the rate of hospital admission and a tendency towards faster resolution of appetite loss (54). Furthermore, SOF/DCV significantly improved dyspnea and fatigue within the 30-day follow-up period, suggesting that SOF/DCV may help patients who suffer from the long-term effects of COVID-19, which include both symptoms. However, these studies are small and are not placebo-controlled; larger randomized trials with placebo controls will have to be

conducted to form definite conclusions regarding the treatment benefits of SOF/DCV against COVID-19. More trials to determine the effects of SOF with DCV and with other agents (e.g., NCT04497649, NCT04530422, NCT04460443, and NCT04468087) have been registered.

### Favipiravir

Favipiravir (T-705) is a nucleoside analog that has been approved for the treatment of novel influenza virus strains in Japan. It is believed to inhibit viral RdRp either by incorporation into the nascent RNA strand as a pseudo-purine or by direct binding to the RdRp (55,56). Although the mechanisms underlying the antiviral activity of favipiravir have not yet been fully elucidated, studies across several other viruses, including, chikungunya virus (57), Rift Valley fever virus (58), HCV (59), and the West Nile virus (60) suggest that it can induce lethal mutagenesis after incorporation into the RNA chain and that it has a broad range of targets.

An *in vitro* study reports that favipiravir exerts inhibitory effects on SARS-CoV-2 as well (61). Additionally, a study using a hamster SARS-COV-2 infection model has shown that high doses of favipiravir reduced infectious viral titers in the lungs and reduced transmission to favipiravir-treated hamsters (62). In an open-labeled comparative controlled study in China, favipiravir treatment led to faster SARS-CoV-2 clearance and to improvement in chest CT scans compared to LPVr treatment (63). Another trial has reported that while favipiravir did not significantly reduce mortality and improve the overall outcome, it alleviated some of the symptoms, especially cough and pyrexia, suggesting that favipiravir may be beneficial to patients with mild COVID-19 (64). A prospective, randomized, open-label study on early (day 1 of study participation) or late (day 6 of participation) treatment with favipiravir (jRCTs041190120) on patients with asymptomatic SARS-CoV-2 infection or with mild disease showed that early treatment tended to accelerate viral clearance and defervescence, although the differences between the treatment groups were not significant (65). Remarkably, reduction in body temperature was observed as early as the day after initiation of treatment in both groups. Larger placebo-controlled clinical trials are needed to further evaluate the treatment benefits of favipiravir. Other clinical trials (e.g., NCT04359615, NCT04464408, NCT04402203, NCT04346628, JapicCTI-205238) have been registered to evaluate the effectivity of favipiravir against the various degrees of COVID-19 severity.

### Umifenovir

Umifenovir is a non-nucleoside antiviral licensed in China and Russia for the prophylaxis and treatment of influenza. It binds hemagglutinin (HA) on the envelop of the influenza virus to prevent pH-induced conformational changes to HA, thereby inhibiting viral fusion with the host (66). It has also been demonstrated to inhibit the early stages of infection by disrupting endocytosis of several viruses including the respiratory syncytial virus, hepatitis B virus, adenoviruses, and EBOV, and to inhibit the replication stage of human herpesvirus 8 (67-69). The inhibitory effects of umifenovir on SARS-CoV-2 has already been demonstrated *in vitro* (70). However, a retrospective study has shown that umifenovir did not improve patient outcomes based on time to reach a double-negative result and on time to symptom recovery (71). In contrast, a retrospective study in China has reported that the combination of umifenovir and IFN- $\alpha$ 2b significantly improved clinical symptoms and CT scans of patients with COVID-19 compared to treatment with IFN- $\alpha$ 2b alone, although viral clearance and time to recovery did not differ between combinatorial and single therapy (72). Additionally, the results of a randomized, controlled trial comparing the effects of HCQ+umifenovir with those of HCQ+LPVr show that umifenovir treatment led to significantly shorter hospital stay

and lower ICU admission rates among hospitalized COVID-19 patients (73). More trials will have to be performed to evaluate the effects of umifenovir on COVID-19 treatment.

## POTENTIAL ANTIVIRALS WITH NON-ANTIVIRAL INDICATIONS

### Chloroquine (CQ) and HCQ

CQ is a quinine used for malaria prophylaxis. HCQ is also a quinine used for rheumatoid arthritis and lupus, but it can also be used as prophylaxis against CQ-sensitive malaria. While both are effective against malaria, HCQ is better tolerated than CQ (74). Both have displayed antiviral activities against a broad range of viruses including DENV, ZIKV, filoviruses, SARS-CoV, etc. *in vitro* and in animal models, suggesting that it may also exert inhibitory effects on SARS-CoV-2 (75). In most of these viruses, CQ and HCQ are believed to increase endosomal pH, thereby interfering with viral endocytosis, which requires acidic conditions (76). A study has suggested that HCQ with azithromycin accelerates SARS-CoV-2 clearance (77). However, further studies show that CQ and HCQ do not benefit hospitalized COVID-19 patients, leading the WHO to halt the CQ and HCQ arms of the Solidarity trial (32). The final results of the RECOVERY group's HCQ trial also show that HCQ does not lower the 28-day mortality rate among hospitalized COVID-19 patients (78). Given that CQ and HCQ target early stages of infection, several trials are still ongoing to determine whether they can be used as prophylactic agents or for early stages of SARS-CoV-2 infection (Table 1).

### Statins

Statins are cholesterol-lowering agents mainly used to prevent primary or secondary cardiovascular disease. However, they have demonstrated inhibitory effects on several viruses, including ZIKV, DENV, influenza, HIV, and EBOV *in vitro* (79). Much of the statins' antiviral capacity is attributed to their ability to inhibit the synthesis of cholesterol, which is important for the formation of lipid rafts that are needed in different stages of viral infection (80). Angiotensin-converting enzyme (ACE) 2, the primary receptor used by SARS-CoV-2 (Fig. 1), is embedded in lipid rafts, suggesting that destabilizing lipid rafts through the inhibition of cholesterol production may inhibit SARS-CoV-2 infection (81). Moreover, statins have been suggested to have cholesterol-independent anti-inflammatory effects (82). Furthermore, although evidence have so far been mixed, an observational suggests that continuous or prior use of statins have benefits to patients with sepsis-related ARDS (83).

Statins seem to have multiple potential targets in the progression of COVID-19: the infection stage, the hyper-inflammatory stage, and ARDS; therefore, statins may be effective against COVID-19 (Table 1). Indeed, a large retrospective study has associated the in-hospital use of statins with lower morbidity and mortality among COVID-19 patients (84). Another retrospective study has associated the use of statins with asymptomatic SARS-CoV-2 infection and has shown that the combination of statins with ACE inhibitors and angiotensin II receptor blockers significantly reduced the risks of symptoms and serious disease (85). Another study suggests that prior statin use reduced the risk of progression to severe COVID-19 and could be linked to faster recovery of severe COVID-19 patients (86). Supporting these, an unpublished study reports that selective statins, particularly fluvastatin, inhibits SARS-CoV-2 entry (87). Several controlled trials to evaluate different statins against COVID-19 have already been registered.



### Nafamostat mesylate and camostat mesylate

Similar to SARS-CoV, SARS-CoV-2 fusion with the host cell requires priming of the spike (S) protein by a cellular protease, transmembrane protease serine 2 (**Fig. 1**); camostat mesylate, a clinically approved serine protease inhibitor, was demonstrated to partially block priming of the S protein (88). Similarly, nafamostat mesylate, another serine protease inhibitor has been shown to inhibit SARS-CoV-2 S priming and subsequently block virus-host fusion *in vitro* (89). Furthermore, nafamostat mesylate was reported to have more potent effects than camostat mesylate. Together, these reports suggest that protease inhibitors are potential candidates for COVID-19 treatment (**Table 1**). Additionally, nafamostat has anticoagulatory properties, suggesting that it may be beneficial to the management of the thrombotic stage of COVID-19 (90,91). Clinical trials evaluating the effectivity of nafamostat mesylate and camostat mesylate in COVID-19 treatment are ongoing.

## IMMUNE-BASED THERAPEUTIC AGENTS

### IFNs

IFNs are cytokines involved in the host antiviral defense system, especially in the early stages of infection. They are classified into 3 families: type I (IFN-I: 13–14 IFN- $\alpha$  subtypes, IFN- $\beta$ , IFN- $\epsilon$ , IFN- $\kappa$ , IFN- $\omega$ , IFN- $\delta$ , IFN- $\zeta$ , and IFN- $\tau$ ), type II (IFN- $\gamma$ ), and type III (IFN- $\lambda$  subtypes) and generally differ by the receptors and signaling pathways they activate.

An early study has suggested that SARS-CoV-2 does not stimulate an IFN response in patients, which may lead to disease progression (92). Supporting this, another study has shown that mild to moderate COVID-19 patients had higher systemic type I IFN levels than severe patients (93). Furthermore, mutations in type I IFN-related genes and auto-Abs against type I IFNs have been correlated with critical COVID-19 cases (94,95). An *in vitro* study also shows that although SARS-CoV-2 infection did not induce IFN production in primary human airway epithelial (pHAE) cells, pretreatment with type I and III IFNs reduced SARS-CoV-2 replication in the pHAE cells (96). In contrast, IFN-stimulated genes have been reported to be upregulated in COVID-19 patients (97). Although these studies provide contradictory evidence for the role of IFN in COVID-19 progression, a few clinical studies have already been completed and suggest that type I IFNs alone or in combination with other agents are beneficial to the treatment of mild to moderate COVID-19 (**Table 2**) (42,98). In particular, early administration of IFN- $\alpha$ 2b and IFN- $\beta$ 1 reduced the COVID-19-associated mortality but did not improve recovery time (99,100). Additionally, a prospective observational study in Cuba suggests that the use of IFN- $\alpha$ 2b in addition to standard treatment (LPVr and CQ) increased the likelihood of recovery and survival among hospitalized COVID-19 patients (101). Remarkably, adding IFN- $\beta$ 1b to standard LPVr therapy reduced the recovery time and mortality of severe COVID-19 patients (102). However, the results of the WHO Solidarity trial suggest that IFN- $\beta$ 1 treatment is not beneficial to hospitalized COVID-19 patients (22). In contrast to this, however, nebulized IFN- $\beta$ 1a increased the likelihood of improvement based on an ordinal scale and led to faster recovery of hospitalized COVID-19 patients in a phase 2 randomized, double-blind, placebo-controlled study (103). Given the contradictory results of IFN for COVID-19, several clinical trials are ongoing to further explore the benefits of IFN treatment (**Table 2**).

**Table 2.** Summary of COVID-19 treatment evaluations for immune-based therapeutics

Agent	Target COVID-19 stage(s)*	Target/mode of action	Status
IFNs	Early (potential)	Antiviral cytokines	<ul style="list-style-type: none"> <li>Type I IFNs exhibit treatment benefits in multiple small trials</li> <li>WHO Solidarity trial shows that IFN-β1 treatment does not benefit hospitalized COVID-19 patients</li> <li>Ongoing phase 2 trials for different stages of infection and varying degrees of severity</li> <li>Ongoing phase 3 trial for combination with remdesivir</li> </ul>
CP	Early (potential)	Viral neutralization	<ul style="list-style-type: none"> <li>Inconclusive results from small trials</li> <li>Randomized placebo-controlled trial shows no treatment benefits for hospitalized patients with COVID-19 pneumonia</li> <li>Ongoing phase 2/3 trials for hospitalized COVID-19 patients</li> <li>Emergency use authorization (USA)</li> </ul>
Monoclonal Abs	Early (demonstrated)	Viral neutralization	<ul style="list-style-type: none"> <li>Eli-Lilly's LY-CoV555 accelerates viral clearance and lowers hospitalization rates. It has been granted emergency use authorization by the US-FDA</li> <li>Eli-Lilly's LY-CoV555 and LY-CoV016 cocktail in phase 2/3 evaluation for mild-to-moderate COVID-19</li> <li>Regeneron's REGN-COV2 accelerates viral clearance and symptom recovery in SARS-CoV-2 seronegative patients and in patients with high viral load at baseline. It has been granted emergency use authorization by the US-FDA</li> <li>Regeneron's REGN-COV2 is undergoing phase 2/3 evaluation for COVID-19 outpatients and hospitalized patients</li> <li>Phase 1 trial for Celltrion's CT-P59 shows accelerated recovery in patients with mild COVID-19</li> <li>Celltrion's CT-P59 is undergoing phase 2/3 trials for COVID-19 outpatients</li> </ul>
<b>Cytokine inhibitors</b>			
Tocilizumab	Middle to late (demonstrated)	IL-6 receptor	<ul style="list-style-type: none"> <li>COVIDOSE (phase 2) suggests improved outcomes in hospitalized patients</li> <li>EMPACTA (phase 3) suggests lower likelihood of progression to mechanical ventilation</li> <li>Randomized, double-blind placebo-controlled study shows no reduction in mortality and progression to mechanical ventilation</li> <li>Ongoing phase 3 trial in combination with remdesivir</li> </ul>
Sarilumab	Middle to late (potential)	IL-6 receptor	<ul style="list-style-type: none"> <li>No benefits seen in phase 3 trials (halted)</li> </ul>
Siltuximab	Middle to late (potential)	IL-6	<ul style="list-style-type: none"> <li>Phase 2 of SISCO study suggests reduced mortality in COVID-19 ARDS patients</li> <li>Ongoing phase 3 trials for severe COVID-19</li> </ul>
Olokizumab	Middle to late (potential)	IL-6	<ul style="list-style-type: none"> <li>Pending results for a phase 2/3 trial for severe COVID-19</li> </ul>
Mavrilimumab	Middle to late (potential)	GM-CSF receptor α	<ul style="list-style-type: none"> <li>Phase 2 placebo-controlled trial suggests reduced mortality and shorter duration of mechanical ventilation in severe COVID-19 patients</li> <li>Ongoing phase 2/3 trials for severe COVID-19</li> </ul>
Anakinra	Middle to late (potential)	IL-1	<ul style="list-style-type: none"> <li>Retrospective study reports dampened inflammation and improved respiratory function in severe COVID-19</li> <li>Prospective study reports reduced progression to mechanical ventilation and reduced mortality in severe COVID-19</li> <li>Ongoing phase 2/3 trials for severe COVID-19</li> </ul>
<b>JAK inhibitors</b>			
Ruxolitinib	Middle to late (potential)	JAK1/2	<ul style="list-style-type: none"> <li>Case series, retrospective, and randomized controlled trials suggest improved outcomes in severe COVID-19</li> <li>Novartis phase 3 trial reports no benefits to hospitalized COVID-19 patients</li> </ul>
Baricitinib	Middle to late (potential)	JAK1/2	<ul style="list-style-type: none"> <li>Associated with improved clinical outcomes in severe COVID-19</li> <li>Combination with RDV is associated with clinical improvement and faster recovery</li> <li>Ongoing phase 2/3 trials for moderate and severe COVID-19</li> </ul>
Tofacitinib	Middle to late (potential)	JAK3	<ul style="list-style-type: none"> <li>Ongoing phase 2 trials for moderate and severe COVID-19</li> </ul>
Fedratinib	Middle to late (potential)	JAK2	<ul style="list-style-type: none"> <li>Not yet being evaluated for COVID-19</li> </ul>
<b>Anti-inflammatory agents</b>			
Corticosteroids (dexamethasone, hydrocortisone, methylprednisolone)	Middle to late (demonstrated)	Anti-inflammatory	<ul style="list-style-type: none"> <li>Reduced likelihood of progression to mechanical ventilation and reduced mortality in severe COVID-19 across several studies</li> <li>WHO strong recommendation for systemic corticosteroids in severe COVID-19</li> </ul>

US-FDA, United States Food and Drug Administration.

\*Target COVID-19 stages are divided into: early (first week of infection, viral phase, pre-/early symptomatic phase); middle (second week of infection, symptomatic, early stages of hyperinflammation); and late (beyond second week of infection, hyperinflammatory to thrombotic stages). Demonstrated: denotes existence of evidence based on COVID-19 clinical studies; potential: target is yet to be demonstrated in clinical trials but is based on the agent's known modes of action and other viral targets.

### Neutralizing Abs

Passive immunization has a long history of use in the treatment of infectious diseases. Plasma from convalescent patients carry neutralizing Abs (NABs) and a host of other factors, such as clotting factors and cytokines, that may contribute to therapy. Thus, passive immunization can be used for post-exposure prophylaxis and in disease management. The use of plasma from convalescent COVID-19 patients is one of the treatments that has been considered early into the COVID-19 pandemic (**Table 2**). Case reports and case series have suggested the benefits of convalescent plasma (CP) to severe and critical COVID-19 patients (104,105). A randomized controlled trial in China shows that the rate of negative results after 72 hours was higher in the CP group than in the control group among patients with severe disease, and the rate of negative results was higher at certain timepoints among critically ill patients treated with CP (106). However, other outcomes, such as time to clinical improvement, time to discharge, and 28-day mortality, were not significantly affected by CP treatment. The largest completed CP study to date has reported no significant differences in the outcomes of COVID-19 patients with severe pneumonia treated with CP and with placebo (107).

Potential risks that may arise from CP therapy include: Ab-dependent enhancement of infection or of disease, exacerbation of the hyper-coagulable state in COVID-19 by clotting factors in the plasma, and transfusion-related lung injury (104). Moreover, NAb titers from different individuals vary, thereby requiring titration of NABs per donor and pooling of plasma from a few donors. Thus, to minimize the adverse effects of plasma therapy, to have consistent Ab titers, and to maximize neutralization, the use of mAbs and mAb cocktails have been proposed. Several studies have already identified NABs that may be used for COVID-19 treatment (108-111). The interim analysis of Eli-Lilly's BLAZE-1 trial (NCT04427501) suggests that the administration of LY-CoV555 (bamlanivimab), an IgG1 that targets the SARS-CoV-2 S protein, at early stages of mild-to-moderate COVID-19 results in faster reduction of viral load and in the reduction of hospitalization rates (112). The combination of LY-CoV555 with LY-CoV016 (etesivimab), which also binds the S protein, is also being evaluated in the same trial. Regeneron's REGN-COV2, a cocktail of 2 anti-SARS-CoV-2 S protein Abs (REGN10933+REGN10987), has also been reported to accelerate viral clearance and symptom recovery in COVID-19 outpatients, especially among those who were seronegative for SARS-CoV-2 Abs or those who had high viral loads at baseline (113). The results of the phase 1 placebo-controlled trials for Celltrion's CT-P59 (regdanvimab), a mAb that binds the receptor-binding domain of the SARS-CoV-2 S protein, show that CT-P59 accelerated the recovery of patients with mild COVID-19 (114). A phase 2/3 trial for CT-P59 in COVID-19 outpatients has already been initiated (NCT04602000).

### Cytokine inhibitors

Because high serum IL-6 levels have been consistently observed in severe COVID-19, IL-6 has been proposed as a marker for progression to severe disease and is being widely considered as a target for treatment (**Table 2**) (115). Tocilizumab is a humanized mAb that binds the IL-6 receptor and is primarily used for the management of rheumatoid arthritis. Retrospective studies have associated subcutaneous and intravenous tocilizumab administration with improved clinical outcomes and reduced mortality in severe and critical COVID-19 patients (116-119). COVIDOSE, a phase 2, single-armed trial, has reported the alleviation of inflammation and faster defervescence following treatment with low-dose tocilizumab in non-critical hospitalized COVID-19 patients (120). Similarly, the results of EMPACTA, a global phase 3, placebo-controlled trial for tocilizumab, suggest that tocilizumab reduced the likelihood of progression to mechanical ventilation and death in COVID-19 pneumonia

patients (121). However, another randomized, double-blind placebo-controlled study shows that tocilizumab did not reduce the likelihood of death and progression to mechanical ventilation (122). Similarly, an observational study suggests that tocilizumab does not help in the management of cytokine storm in severe COVID-19 patients (123). These contradicting results emphasize the need for larger placebo-controlled studies to evaluate the treatment benefits of tocilizumab in COVID-19. On the other hand, the trials for sarilumab, which also targets the IL-6 receptor, have been halted after failing to improve clinical outcomes in severe COVID-19 patients (124).

Abs that directly bind IL-6 are also being considered for COVID-19 therapy. The unpublished results of SISCO, a phase 2 observational, control cohort study, suggest that siltuximab, a mAb that binds IL-6, reduced the death of COVID-19 ARDS patients who required mechanical support (125); a phase 3 trial (NCT04616586) has therefore been initiated. A phase 2/3 trial to evaluate the effects of olokizumab, another IL-6 inhibitor, has also been recently completed with pending results (NCT04380519). Trials comparing the effects of different IL-6 antagonists have also been registered (NCT04330638, NCT04486521).

Inhibitors of other cytokines implicated in the COVID-19 cytokine storm are also being evaluated (126). A preliminary study on mavrilimumab, a human mAb that binds the GM-CSFR $\alpha$ , has also been reported to improve clinical outcomes (127). Furthermore, early results of the phase 2 portion of Kiniksa's phase 2/3 placebo-controlled trial on mavrilimumab (NCT04399980) suggest reduced mortality and shorter duration of mechanical ventilation among patients with severe COVID-19 pneumonia and hyperinflammation (128). Anakinra, an IL-1 antagonist, has been reported to improve respiratory function, dampen inflammation, and reduce progression to mechanical ventilation in severe COVID-19 patients (129-131). Cytokine inhibitor cocktails have also been proposed to maximize the benefits of modulating the immune response (126). However, more controlled studies will have to be performed to determine the benefits and risks associated with the use of cytokine inhibitor cocktails.

### JAK inhibitors

JAK1, JAK2, JAK3, and tyrosine kinase 2 are members of the JAK family of non-receptor tyrosine kinases. They mediate cytokine signaling through the JAK/STAT pathway, making JAK inhibition a plausible option for regulating cytokine-stimulated inflammatory responses in COVID-19 (Table 2). Ruxolitinib, which binds the kinase domain of JAK1 and JAK2, was the first approved JAK inhibitor and is currently used for the management of myelofibrosis, hemophagocytic lymphohistiocytosis, and graft-versus-host disease. It has been shown to reduce C-reactive protein, TNF- $\alpha$ , and IL-6 plasma levels in myelofibrosis cases, suggesting that it can be used to reduce inflammation in COVID-19 patients. In a pilot case series, a low starting dose of ruxolitinib was shown to improve clinical scores of patients without major signs of toxicity (132). Several other studies have suggested that ruxolitinib is beneficial to hospitalized COVID-19 patients, with indications that it can dampen the hyperinflammatory state in patients (133-135). However, Novartis has reported that ruxolitinib did not improve clinical outcomes in hospitalized COVID-19 patients in their phase 3 trial (136). Notably, a study suggests that the combination of ruxolitinib and steroids is beneficial to patients with COVID-19 pneumonia (137). Whether this combination is an effective COVID-19 treatment will have to be verified in larger studies.

Baricitinib, another JAK1/2 inhibitor, has been reported to significantly reduce the fatality rate and ICU admission rate; accelerate viral clearance; and increase discharge rates in

COVID-19 patients with moderate pneumonia, compared to standard-of-care (138). The NIAID-sponsored ACTT-2 phase 3 trial for baricitinib in combination with RDV suggests that the combination shortens the median recovery time and reduces the 28-day mortality of hospitalized COVID-19 patients; in particular, the combination reduced the time to recovery of patients under non-invasive oxygen support from 18 days (RDV only) to 10 days (139). Several trials to evaluate the COVID-19 treatment benefits of baricitinib (e.g., NCT04421027, NCT04373044, NCT04640168) have already been registered.

One potential drawback to the use of JAK1/2 inhibitors against COVID-19 is their ability to target several types of cytokines, some of which (i.e., IFNs) are needed for viral clearance. Thus, other JAK inhibitors that can selectively target certain cytokines are also being considered. Tofacitinib, a potent inhibitor of JAK3, which is not involved in the IFN $\gamma$  pathway, is already being evaluated in phase 2 trials for COVID-19 (e.g., NCT04415151, NCT04469114). Likewise, fedratinib a JAK2 inhibitor, is expected to not disrupt the type I IFN pathways and has already been seen to reduce cytokine production by Th17 cells *in vitro*, suggesting that it can be used for COVID-19 treatment (140).

## ANTI-INFLAMMATORY AGENTS

### Corticosteroids

Corticosteroids were initially not recommended for COVID-19 treatment based on existing data on MERS-CoV and SARS-CoV wherein corticosteroids delayed viral clearance; under the assumption that disease severity is associated with high viremia, the use of corticosteroids in COVID-19 was hypothesized to lead to severe disease and viral sepsis (141). However, given the current evidence that inflammation plays a primary role in COVID-19 progression, anti-inflammatory drugs were deemed viable candidates for the treatment of severe COVID-19 (Table 2).

A controlled, open-label trial (RECOVERY) has shown that a 10-day course of dexamethasone reduced the 28-day mortality among COVID-19 patients who were receiving respiratory support (142). Moreover, dexamethasone reduced the risk of progression to invasive ventilation in patients receiving oxygen support. Notably, improvements were not observed among patients who did not receive respiratory support. These findings suggest that dexamethasone is beneficial to COVID-19 patients in later stages of infection, where pulmonary and systemic inflammatory damage is present. Although another trial (COVID-19 Dexamethasone) shows that while dexamethasone failed to significantly reduce in mortality of COVID-19 patients with moderate or severe ARDS, dexamethasone significantly increased the number of days alive and the number of days the patients were free of mechanical ventilation (143).

Due to the announcement of the RECOVERY findings, enrollment for corticosteroid trials were halted, but a few trials have reported their results. A randomized clinical study shows that hydrocortisone did not significantly improve outcomes in terms of mortality and persistent mechanical ventilation in critical COVID-19 cases, but the study may have been underpowered due to premature termination of enrolment (144). The REMAP-CAP randomized clinical trial, on the other hand, suggested probable superiority of a fixed dose and shock-dependent dosing of hydrocortisone in patients with severe COVID-19, although definitive conclusions could not be made (145). In light of the RECOVERY findings, the WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) working group pooled



data from 7 randomized controlled studies and performed meta-analysis to evaluate the effects of corticosteroids (dexamethasone, hydrocortisone, and methylprednisolone) in critically ill COVID-19 patients. The REACT meta-analysis associated the use of systemic corticosteroids with lower 28-day mortality among COVID-19 patients, leading to the WHO's strong recommendation to use corticosteroids in severe and critical COVID-19 patients and to a conditional recommendation to use corticosteroids in non-severe cases (146,147). The benefits and risks of corticosteroids in non-severe COVID-19 patients; the long-term effects of corticosteroid use in COVID-19 survivors; and the optimal timing of corticosteroid administration will still have to be evaluated in future studies.

## PERSPECTIVES AND CONCLUSIONS

The COVID-19 pandemic has spurred global cooperation for the speedy evaluation of drug and vaccine candidates. In a short span of time, several therapeutic candidates have already been tested, discontinued, reconsidered, or recommended based on the results of collaborative efforts between research institutes, clinical practitioners, and manufacturing companies. However, the current efforts still leave much to be desired. For example, the conflicting results of the WHO Solidarity and RECOVERY trials on RDV emphasize the need for standardized study designs and clinical outcomes to obtain coherent and conclusive evidence in large clinical studies.

Additionally, stratification of patients based on the different phases of COVID-19 is important in determining the optimal timepoint for any intervention. As we have presented, COVID-19 treatment candidates can be grouped based on modes of action (**Fig. 1**) and target stages in COVID-19 progression (**Tables 1 and 2**). The early stages of COVID-19 can be targeted using agents that promote viral clearance, which include antivirals (e.g. nucleoside analogs), approved drugs with non-antiviral indications but with antiviral potential (e.g. statins, CQ/HCQ, camostat mesylate, and nafamostat mesylate), IFNs, and NABs. The middle stages of COVID-19, which is characterized by the decline in viral replication and the start of the hyperinflammatory response, can be targeted using agents that can dampen the inflammatory response, such as cytokine inhibitors, JAK inhibitors, and corticosteroids. Finally, the late stages of COVID-19, which is characterized by hyperinflammation, thrombosis, and other critical manifestations, can be managed using anti-inflammatory and anticoagulatory (e.g. nafamostat mesylate, camostat mesylate) agents.

Understandably, because of the initial surge in hospital burden early into the COVID-19 pandemic, most of the therapeutic approaches, including antivirals and potential antivirals, were tested on hospitalized patients. However, this may explain why most of the candidates failed to show COVID-19 treatment benefits; antivirals and IFNs are expected to be beneficial early into the course of the disease, where viral replication is at its peak, and would be less helpful in alleviating inflammation and other complications that arise in later stages of COVID-19. This may also be the reason why corticosteroids, which target a stage of COVID-19 that coincides with patient hospitalization, are, thus far, the only treatment with strong conclusive evidence. Recently, trials have been directed to COVID-19 outpatients and to mild-to-moderate COVID-19 patients. Some of the agents (e.g. CQ/HCQ, LPVr) are also being tested as prophylaxis for individuals with high risks of exposure to SARS-CoV-2 (e.g. healthcare workers). Various combinations of the candidates are also being looked into for potential synergistic effects. Hopefully, the results of all these studies will reveal early

treatments that will accelerate viral clearance and prevent COVID-19 progression to reduce the hospital burden, morbidity, and mortality associated with SARS-CoV-2 infection.

Although SARS-CoV-2 vaccines have been granted emergency-use authorization in various countries, several months are needed for the global vaccine roll out and to reach the desired level of community immunity. Furthermore, long-term data are needed to ascertain whether vaccination confers long-term protection or will have to be frequently administered (e.g., every few years). Thus, prophylactic and therapeutic agents are expected to fill in the gap in virus control measures left by the ongoing vaccination efforts. Clinical evaluations of candidates for COVID-19 treatment therefore remain invaluable to the management of the SARS-CoV-2 pandemic. Hopefully, the learnings from this pandemic, especially the organization of rapid but thorough clinical evaluations for pharmaceutical interventions and the effective strategies in discovering and developing antiviral treatments, will arm us for future large viral outbreaks.

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