Immune Netw. 2021 Feb;21(1):e7
https://doi.org/10.4110/in.2021.21.e7
pISSN 1598-2629·eISSN 2092-6685

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Review Article

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COVID-19 Antiviral and Treatment Candidates: Current Status

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OPEN ACCESS

Received: Jan 10, 2021
Revised: Jan 27, 2021
Accepted: Jan 31, 2021

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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

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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.

Author Contributions

Conceptualization: Kim JK, Espano E; Formal analysis: Espano E, Kim D, Kim JK; Funding acquisition: Kim JK, Park SK; Writing - original draft: Espano E, Kim D, Kim J, Kim JK; Writing - review & editing: Kim JK, Park SK.

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 (≤81%), with fever, cough, dyspnea, and anosmia as the most common presentations (7). The disease can then progress to the inflammatory or severe phase (≤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-α, IL2, IL-7, IL-1β, 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.

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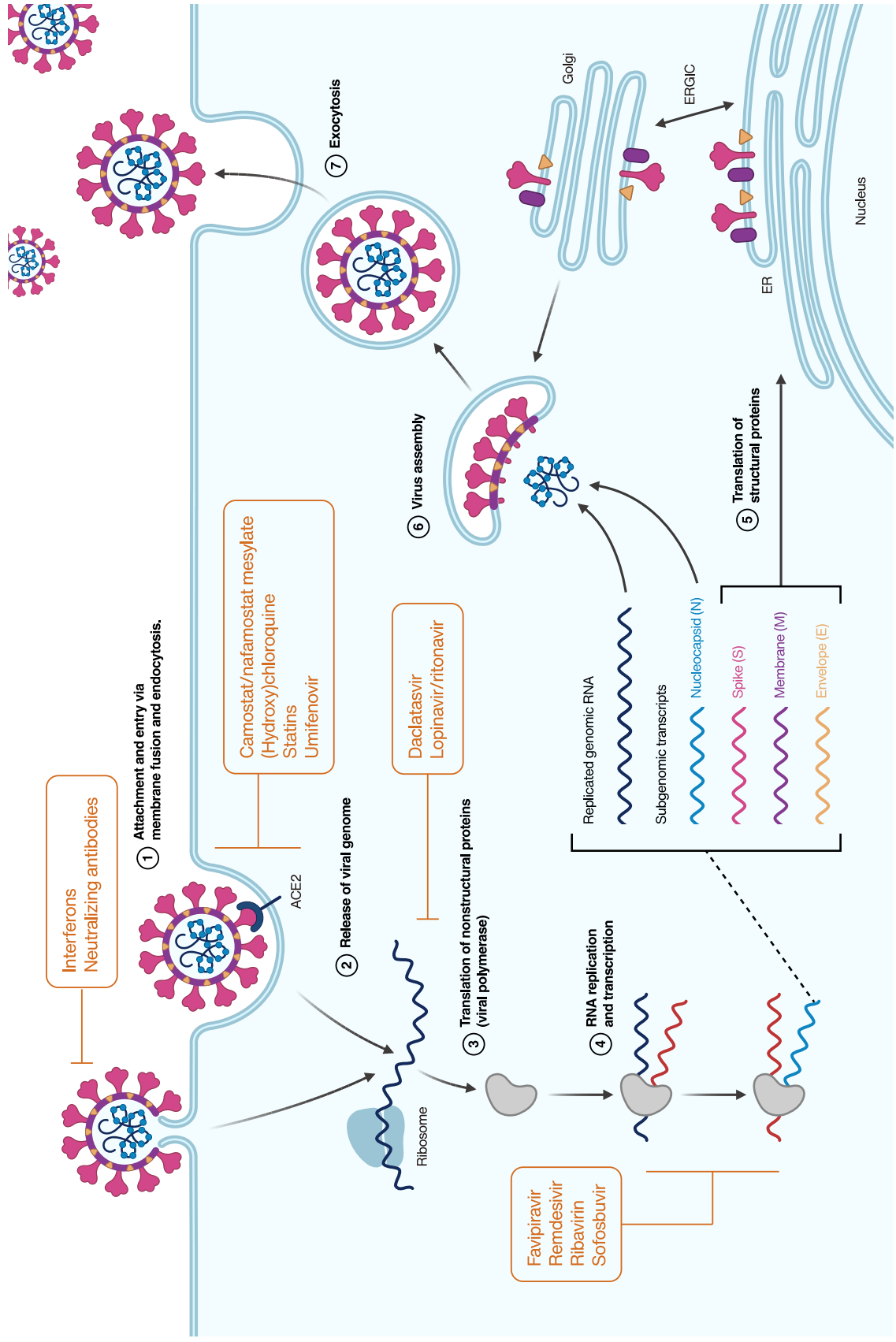

Figure 1. The SARS-CoV-2 replication cycle and the known and potential targets of antivirals and other agents. The SARS-CoV-2 S protein binds ACE2 on the host cell surface, and the S protein is primed through cleavage by transmembrane protease, serine 2 to facilitate entry into the host through membrane fusion or endocytosis. The genomic RNA is uncoated in the cytosol and then translated into polyproteins 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.

https://doi.org/10.4110/in.2021.21.e7

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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
Direct-acting antivirals			
RDV	Early (potential)	Adenosine analog viral RdRp inhibitor	· RECOVERY trial (phase 3) shows improved clinical outcomes in hospitalized patients
	Middle (demonstrated)		· WHO Solidarity trial (phase 3) suggests no benefits for hospitalized patients
			· Approved by the US-FDA
			· Ongoing phase 2/3 trials for COVID-19 outpatients, pediatric patients, and combinatorial therapy
			· Ongoing phase 1 trial for inhaled RDV formulation for early-stage COVID-19
Lopinavir+ritonavir	Early (potential)	HIV protease inhibitor (approved)	· Does not benefit hospitalized patients
		Potential CoV protease inhibitor	· Ongoing phase 2/3 trials as prophylaxis or for early-stage COVID-19
Ribavirin	Early (potential)	Guanosine analog	· Monotherapy does not benefit COVID-19 patients
		Inhibits GTP synthesis	· Ongoing phase 1 trial for aerosolized ribavirin in hospitalized patients
		Viral mutagenesis	· Ongoing phase 2/3 trial for combination with IFNs and other agents
		Immunomodulatory activity	
SOF+DCV	Early (demonstrated)	Hepatitis C virus (approved)	· Phase 2/3 randomized controlled trials suggest treatment benefits of SOF+DCV on severe COVID-19
	Middle (demonstrated)	SOF may bind SARS-CoV-2 RdRp	· Ongoing phase 2/3 trials for SOF alone, with DCV or with other agents
		DCV may bind SARS-CoV-2 protease	
Favipiravir	Early (demonstrated)	Influenza virus emergency drug (Japan)	· Open-labeled trial shows improved therapeutic responses and accelerated viral clearance
		Purine analog	· Ongoing trials for various degrees of COVID-19 severity
		Viral RdRp inhibitor	
Umifenovir	Early (potential)	Influenza treatment and prophylaxis (China and Japan)	· Mixed results for COVID-19 treatment
		Viral endocytosis inhibitor	· Ongoing phase 4 trials for COVID-19 treatment
		Inhibitor of viral genome replication	
Potential antivirals with non-antiviral indications			
CQ, HCQ	Early (potential)	Anti-malaria	· No benefits for hospitalized COVID-19 patients
		Anti-rheumatoid arthritis (HCQ)	· Ongoing phase 1 trials as prophylaxis for COVID-19
		Viral endocytosis inhibitor *in vitro*	· Ongoing phase 2 trials for mild to moderate COVID-19
Statins	Early (potential)	Anti-cholesterol	· Continuous use or use prior to infection associated with less severe COVID-19 in retrospective studies
	Middle (potential)	Evidence for antiviral activity *in vitro*	
		Anti-inflammatory effects	
Camostat mesylate, nafamostat mesylate	Early (potential)	Acute pancreatitis	· Camostat mesylate under phase 2 trials for varying degrees of COVID-19 severity
	Late (potential)	Anticoagulatory effects	· Nafamostat mesylate under phase 2/3 trials for varying degrees of COVID-19 severity
		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.

https://doi.org/10.4110/in.2021.21.e7

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 ($3CL^{pro}$) (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

https://doi.org/10.4110/in.2021.21.e7

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-β1b 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-β1b 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-α, LPVr+IFN-α, and ribavirin+LPVr+IFN-α 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 $3CL^{pro}$ (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-α2b significantly improved clinical symptoms and CT scans of patients with COVID-19 compared to treatment with IFN-α2b 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.

https://doi.org/10.4110/in.2021.21.e7

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-α subtypes, IFN-β, IFN-ε, IFN-κ, IFN-ω, IFN-δ, IFN-ζ, and IFN-τ), type II (IFN-γ), and type III (IFN-λ 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-α2b and IFN-β1 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-α2b in addition to standard treatment (LPVr and CQ) increased the likelihood of recovery and survival among hospitalized COVID-19 patients (101). Remarkably, adding IFN-β1b 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-β1 treatment is not beneficial to hospitalized COVID-19 patients (22). In contrast to this, however, nebulized IFN-β1a 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	• Type I IFNs exhibit treatment benefits in multiple small trials • WHO Solidarity trial shows that IFN-β1 treatment does not benefit hospitalized COVID-19 patients • Ongoing phase 2 trials for different stages of infection and varying degrees of severity • Ongoing phase 3 trial for combination with remdesivir
CP	Early (potential)	Viral neutralization	• Inconclusive results from small trials • Randomized placebo-controlled trial shows no treatment benefits for hospitalized patients with COVID-19 pneumonia • Ongoing phase 2/3 trials for hospitalized COVID-19 patients • Emergency use authorization (USA)
Monoclonal Abs	Early (demonstrated)	Viral neutralization	• Eli-Lilly's LY-CoV555 accelerates viral clearance and lowers hospitalization rates. It has been granted emergency use authorization by the US-FDA • Eli-Lilly's LY-CoV555 and LY-CoV016 cocktail in phase 2/3 evaluation for mild-to-moderate COVID-19 • 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 • Regeneron's REGN-COV2 is undergoing phase 2/3 evaluation for COVID-19 outpatients and hospitalized patients • Phase 1 trial for Celltrion's CT-P59 shows accelerated recovery in patients with mild COVID-19 • Celltrion's CT-P59 is undergoing phase 2/3 trials for COVID-19 outpatients
Cytokine inhibitors			
Tocilizumab	Middle to late (demonstrated)	IL-6 receptor	• COVIDOSE (phase 2) suggests improved outcomes in hospitalized patients • EMPACTA (phase 3) suggests lower likelihood of progression to mechanical ventilation • Randomized, double-blind placebo-controlled study shows no reduction in mortality and progression to mechanical ventilation • Ongoing phase 3 trial in combination with remdesivir
Sarilumab	Middle to late (potential)	IL-6 receptor	• No benefits seen in phase 3 trials (halted)
Siltuximab	Middle to late (potential)	IL-6	• Phase 2 of SISCO study suggests reduced mortality in COVID-19 ARDS patients • Ongoing phase 3 trials for severe COVID-19
Olokizumab	Middle to late (potential)	IL-6	• Pending results for a phase 2/3 trial for severe COVID-19
Mavrilimumab	Middle to late (potential)	GM-CSF receptor α	• Phase 2 placebo-controlled trial suggests reduced mortality and shorter duration of mechanical ventilation in severe COVID-19 patients • Ongoing phase 2/3 trials for severe COVID-19
Anakinra	Middle to late (potential)	IL-1	• Retrospective study reports dampened inflammation and improved respiratory function in severe COVID-19 • Prospective study reports reduced progression to mechanical ventilation and reduced mortality in severe COVID-19 • Ongoing phase 2/3 trials for severe COVID-19
JAK inhibitors			
Ruxolitinib	Middle to late (potential)	JAK1/2	• Case series, retrospective, and randomized controlled trials suggest improved outcomes in severe COVID-19 • Novartis phase 3 trial reports no benefits to hospitalized COVID-19 patients
Baricitinib	Middle to late (potential)	JAK1/2	• Associated with improved clinical outcomes in severe COVID-19 • Combination with RDV is associated with clinical improvement and faster recovery • Ongoing phase 2/3 trials for moderate and severe COVID-19
Tofacitinib	Middle to late (potential)	JAK3	• Ongoing phase 2 trials for moderate and severe COVID-19
Fedratinib	Middle to late (potential)	JAK2	• Not yet being evaluated for COVID-19
Anti-inflammatory agents			
Corticosteroids (dexamethasone, hydrocortisone, methylprednisolone)	Middle to late (demonstrated)	Anti-inflammatory	• Reduced likelihood of progression to mechanical ventilation and reduced mortality in severe COVID-19 across several studies • WHO strong recommendation for systemic corticosteroids in severe COVID-19

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

https://doi.org/10.4110/in.2021.21.e7

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-CSFRα, 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-α, 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 IFNγ 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

https://doi.org/10.4110/in.2021.21.e7

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.

ACKNOWLEDGEMENTS

This work was supported by Korea University Research Grants (K1826621, K2005541 and K2023291). We thank Younsik Kim for the illustration.

REFERENCES

1. Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, Wang W, Song H, Huang B, Zhu N, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet* 2020;395:565-574.
PUBMED | CROSSREF
2. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, Si HR, Zhu Y, Li B, Huang CL, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature* 2020;579:270-273.
PUBMED | CROSSREF
3. The Johns Hopkins Coronavirus Resource Center (CRC). COVID-19 dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU) 2020 [Internet]. Available at https://coronavirus.jhu.edu/map.html [accessed on 30 December 2020].
4. Lauer SA, Grantz KH, Bi Q, Jones FK, Zheng Q, Meredith HR, Azman AS, Reich NG, Lessler J. The incubation period of coronavirus disease 2019 (COVID-19) from publicly reported confirmed cases: estimation and application. *Ann Intern Med* 2020;172:577-582.
PUBMED | CROSSREF
5. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DSC, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 2020;382:1708-1720.
PUBMED | CROSSREF
6. He X, Lau EHY, Wu P, Deng X, Wang J, Hao X, Lau YC, Wong JY, Guan Y, Tan X, et al. Temporal dynamics in viral shedding and transmissibility of COVID-19. *Nat Med* 2020;26:672-675.
PUBMED | CROSSREF
7. Lippi G, Sanchis-Gomar F, Henry BM. COVID-19: unravelling the clinical progression of nature's virtually perfect biological weapon. *Ann Transl Med* 2020;8:693.
PUBMED | CROSSREF
8. Henry BM, Vikse J, Benoit S, Favaloro EJ, Lippi G. Hyperinflammation and derangement of renin-angiotensin-aldosterone system in COVID-19: a novel hypothesis for clinically suspected hypercoagulopathy and microvascular immunothrombosis. *Clin Chim Acta* 2020;507:167-173.
PUBMED | CROSSREF
9. Ragab D, Salah Eldin H, Taeimah M, Khattab R, Salem R. The COVID-19 cytokine storm; what we know so far. *Front Immunol* 2020;11:1446.
PUBMED | CROSSREF

10. Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19): a review. *JAMA* 2020;324:782-793.
PUBMED | CROSSREF

11. Abou-Ismail MY, Diamond A, Kapoor S, Arafah Y, Nayak L. The hypercoagulable state in COVID-19: incidence, pathophysiology, and management. *Thromb Res* 2020;194:101-115.
PUBMED | CROSSREF

12. Carfì A, Bernabei R, Landi FGemelli Against COVID-19 Post-Acute Care Study Group. Persistent symptoms in patients after acute COVID-19. *JAMA* 2020;324:603-605.
PUBMED | CROSSREF

13. Ahmed M, Advani S, Moreira A, Zoretic S, Martinez J, Chorath K, Acosta S, Naqvi R, Burmeister-Morton F, Burmeister F, et al. Multisystem inflammatory syndrome in children: a systematic review. *EClinicalMedicine* 2020;26:100527.
PUBMED | CROSSREF

14. Siegel D, Hui HC, Doerffler E, Clarke MO, Chun K, Zhang L, Neville S, Carra E, Lew W, Ross B, et al. Discovery and synthesis of a phosphoramidate prodrug of a pyrrolo[2,1-f][triazin-4-amino] adenine C-nucleoside (GS-5734) for the treatment of Ebola and emerging viruses. *J Med Chem* 2017;60:1648-1661.
PUBMED | CROSSREF

15. Gordon CJ, Tchesnokov EP, Woolner E, Perry JK, Feng JY, Porter DP, Götte M. Remdesivir is a direct-acting antiviral that inhibits RNA-dependent RNA polymerase from severe acute respiratory syndrome coronavirus 2 with high potency. *J Biol Chem* 2020;295:6785-6797.
PUBMED | CROSSREF

16. Mulangu S, Dodd LE, Davey RT Jr, Tshiani Mbaya O, Proschan M, Mukadi D, Lusakibanza Manzo M, Nzolo D, Tshomba Oloma A, Ibanda A, et al. A randomized, controlled trial of Ebola virus disease therapeutics. *N Engl J Med* 2019;381:2293-2303.
PUBMED | CROSSREF

17. Malin JJ, Suárez I, Priesner V, Fätkenheuer G, Rybniker J. Remdesivir against COVID-19 and other viral diseases. *Clin Microbiol Rev* 2020;34:e00162-e00120.
PUBMED | CROSSREF

18. Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, Shi Z, Hu Z, Zhong W, Xiao G. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) *in vitro*. *Cell Res* 2020;30:269-271.
PUBMED | CROSSREF

19. Wang Y, Zhang D, Du G, Du R, Zhao J, Jin Y, Fu S, Gao L, Cheng Z, Lu Q, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. *Lancet* 2020;395:1569-1578.
PUBMED | CROSSREF

20. Grein J, Ohmagari N, Shin D, Diaz G, Asperges E, Castagna A, Feldt T, Green G, Green ML, Lescure FX, et al. Compassionate use of remdesivir for patients with severe COVID-19. *N Engl J Med* 2020;382:2327-2336.
PUBMED | CROSSREF

21. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, Hohmann E, Chu HY, Luetkemeyer A, Kline S, et al. Remdesivir for the treatment of COVID-19 - final report. *N Engl J Med* 2020;383:1813-1826.
PUBMED | CROSSREF

22. WHO Solidarity Trial ConsortiumPan H, Peto R, Henao-Restrepo AM, Preziosi MP, Sathiyamoorthy V, Abdool Karim Q, Alejandria MM, Hernández García C, Kieny MP, et al. Repurposed antiviral drugs for COVID-19 - interim WHO Solidarity trial results. *N Engl J Med* 2020. doi: 10.1056/NEJMoa2023184.
PUBMED | CROSSREF

23. Corbett AH, Lim ML, Kashuba ADM. Kaletra (lopinavir/ritonavir). *Ann Pharmacother* 2002;36:1193-1203.
PUBMED | CROSSREF

24. Kumar Y, Singh H, Patel CN. *In silico* prediction of potential inhibitors for the main protease of SARS-CoV-2 using molecular docking and dynamics simulation based drug-repurposing. *J Infect Public Health* 2020;13:1210-1223.
PUBMED | CROSSREF

25. Chu CM, Cheng VCC, Hung IFN, Wong MML, Chan KH, Chan KS, Kao RYT, Poon LLM, Wong CLP, Guan Y, et al. Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. *Thorax* 2004;59:252-256.
PUBMED | CROSSREF

26. Park SY, Lee JS, Son JS, Ko JH, Peck KR, Jung Y, Woo HJ, Joo YS, Eom JS, Shi H. Post-exposure prophylaxis for Middle East respiratory syndrome in healthcare workers. *J Hosp Infect* 2019;101:42-46.
PUBMED | CROSSREF

27. Ullrich S, Nitsche C. The SARS-CoV-2 main protease as drug target. *Bioorg Med Chem Lett* 2020;30:127377.
PUBMED | CROSSREF

28. Wang Z, Chen X, Lu Y, Chen F, Zhang W. Clinical characteristics and therapeutic procedure for four cases with 2019 novel coronavirus pneumonia receiving combined Chinese and Western medicine treatment. *Biosci Trends* 2020;14:64-68.
PUBMED | CROSSREF

29. Kim JY, Jeon S, Shin HY, Kim MJ, Seong YM, Lee WJ, Choe KW, Kang YM, Lee B, Park SJ. Case of the index patient who caused tertiary transmission of coronavirus disease 2019 in Korea: the application of lopinavir/ritonavir for the treatment of COVID-19 pneumonia monitored by quantitative RT-PCR. *J Korean Med Sci* 2020;35:e88.
PUBMED | CROSSREF

30. Li Y, Xie Z, Lin W, Cai W, Wen C, Guan Y, Mo X, Wang J, Wang Y, Peng P, et al. Efficacy and safety of lopinavir/ritonavir or arbidol in adult patients with mild/moderate COVID-19: an exploratory randomized controlled trial. *Med (N Y)* 2020;1:105-113.e4.
PUBMED | CROSSREF

31. Horby PW, Mafham M, Bell JL, Linsell L, Staplin N, Emberson J, Palfreeman A, Raw J, Elmahi E, Prudon B, et al. Lopinavir-ritonavir in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet* 2020;396:1345-1352.
CROSSREF

32. World Health Organization. "Solidarity" clinical trial for COVID-19 treatments [Internet]. Available at https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-clinical-trial-for-covid-19-treatments [accessed on 10 September 2020].

33. Leyssen P, Balzarini J, De Clercq E, Neyts J. The predominant mechanism by which ribavirin exerts its antiviral activity *in vitro* against flaviviruses and paramyxoviruses is mediated by inhibition of IMP dehydrogenase. *J Virol* 2005;79:1943-1947.
PUBMED | CROSSREF

34. Crotty S, Cameron CE, Andino R. RNA virus error catastrophe: direct molecular test by using ribavirin. *Proc Natl Acad Sci U S A* 2001;98:6895-6900.
PUBMED | CROSSREF

35. Rigopoulou EI, Abbott WGH, Williams R, Naoumov NV. Direct evidence for immunomodulatory properties of ribavirin on T-cell reactivity to hepatitis C virus. *Antiviral Res* 2007;75:36-42.
PUBMED | CROSSREF

36. Stockman LJ, Bellamy R, Garner P. SARS: systematic review of treatment effects. *PLoS Med* 2006;3:e343.
PUBMED | CROSSREF

37. Morgenstern B, Michaelis M, Baer PC, Doerr HW, Cinatl J Jr. Ribavirin and interferon-β synergistically inhibit SARS-associated coronavirus replication in animal and human cell lines. *Biochem Biophys Res Commun* 2005;326:905-908.
PUBMED | CROSSREF

38. Falzarano D, de Wit E, Rasmussen AL, Feldmann F, Okumura A, Scott DP, Brining D, Bushmaker T, Martellaro C, Baseler L, et al. Treatment with interferon-α2b and ribavirin improves outcome in MERS-CoV-infected rhesus macaques. *Nat Med* 2013;19:1313-1317.
PUBMED | CROSSREF

39. Omrani AS, Saad MM, Baig K, Bahloul A, Abdul-Matin M, Alaidaroos AY, Almakhlafi GA, Albarrak MM, Memish ZA, Albarrak AM. Ribavirin and interferon alfa-2a for severe Middle East respiratory syndrome coronavirus infection: a retrospective cohort study. *Lancet Infect Dis* 2014;14:1090-1095.
PUBMED | CROSSREF

40. Arabi YM, Shalhoub S, Mandourah Y, Al-Hameed F, Al-Omari A, Al Qasim E, Jose J, Alraddadi B, Almotairi A, Al Khatib K, et al. Ribavirin and interferon therapy for critically ill patients with Middle East respiratory syndrome: a multicenter observational study. *Clin Infect Dis* 2020;70:1837-1844.
PUBMED | CROSSREF

41. Tong S, Su Y, Yu Y, Wu C, Chen J, Wang S, Jiang J. Ribavirin therapy for severe COVID-19: a retrospective cohort study. *Int J Antimicrob Agents* 2020;56:106114.
PUBMED | CROSSREF

42. Hung IFN, Lung KC, Tso EYK, Liu R, Chung TWH, Chu MY, Ng YY, Lo J, Chan J, Tam AR, et al. Triple combination of interferon beta-1b, lopinavir-ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial. *Lancet* 2020;395:1695-1704.
PUBMED | CROSSREF

43. Huang YQ, Tang SQ, Xu XL, Zeng YM, He XQ, Li Y, Harypursat V, Lu YQ, Wan Y, Zhang L, et al. No statistically apparent difference in antiviral effectiveness observed among ribavirin plus interferon-alpha, lopinavir/ritonavir plus interferon-alpha, and ribavirin plus lopinavir/ritonavir plus interferon-alpha in patients with mild to moderate coronavirus disease 2019: results of a randomized, open-abeled prospective study. *Front Pharmacol* 2020;11:1071.
PUBMED | CROSSREF

44. Guedj J, Dahari H, Rong L, Sansone ND, Nettles RE, Cotler SJ, Layden TJ, Uprichard SL, Perelson AS. Modeling shows that the NS5A inhibitor daclatasvir has two modes of action and yields a shorter estimate of the hepatitis C virus half-life. *Proc Natl Acad Sci U S A* 2013;110:3991-3996.
PUBMED | CROSSREF

45. Stedman C. Sofosbuvir, a NS5B polymerase inhibitor in the treatment of hepatitis C: a review of its clinical potential. *Therap Adv Gastroenterol* 2014;7:131-140.
PUBMED | CROSSREF

46. Ferreira AC, Reis PA, de Freitas CS, Sacramento CQ, Villas Bôas Hoelz L, Bastos MM, Mattos M, Rocha N, Gomes de Azevedo Quintanilha I, da Silva Gouveia Pedrosa C, et al. Beyond members of the *Flaviviridae* family, sofosbuvir also inhibits chikungunya virus replication. *Antimicrob Agents Chemother* 2019;63:e01389-e18.
PUBMED

47. Elfiky AA. Anti-HCV, nucleotide inhibitors, repurposing against COVID-19. *Life Sci* 2020;248:117477.
PUBMED | CROSSREF

48. Jácome R, Campillo-Balderas JA, Ponce de León S, Becerra A, Lazcano A. Sofosbuvir as a potential alternative to treat the SARS-CoV-2 epidemic. *Sci Rep* 2020;10:9294.
PUBMED | CROSSREF

49. Jockusch S, Tao C, Li X, Chien M, Kumar S, Morozova I, Kalachikov S, Russo JJ, Ju J. Sofosbuvir terminated RNA is more resistant to SARS-CoV-2 proofreader than RNA terminated by Remdesivir. *Sci Rep* 2020;10:16577.
PUBMED | CROSSREF

50. Bahadur Gurung A, Ajmal Ali M, Lee J, Abul Farah M, Mashay Al-Anazi K. Structure-based virtual screening of phytochemicals and repurposing of FDA approved antiviral drugs unravels lead molecules as potential inhibitors of coronavirus 3C-like protease enzyme. *J King Saud Univ Sci* 2020;32:2845-2853.
PUBMED | CROSSREF

51. Sacramento CQ, Fintelman-Rodrigues N, Temerozo JR, da Silva Gomes Dias S, Ferreira AC, Mattos M, Pão CR, de Freitas CS, Soares VC, Bozza FA, et al. The *in vitro* antiviral activity of the anti-hepatitis C virus (HCV) drugs daclatasvir and sofosbuvir against SARS-CoV-2. *bioRxiv* 2020. doi: 10.1101/2020.06.15.153411.
CROSSREF

52. Sadeghi A, Ali Asgari A, Norouzi A, Kheiri Z, Anushirvani A, Montazeri M, Hosamirudsai H, Afhami S, Akbarpour E, Aliannejad R, et al. Sofosbuvir and daclatasvir compared with standard of care in the treatment of patients admitted to hospital with moderate or severe coronavirus infection (COVID-19): a randomized controlled trial. *J Antimicrob Chemother* 2020;75:3379-3385.
PUBMED | CROSSREF

53. Eslami G, Mousaviasl S, Radmanesh E, Jelvay S, Bitaraf S, Simmons B, Wentzel H, Hill A, Sadeghi A, Freeman J, et al. The impact of sofosbuvir/daclatasvir or ribavirin in patients with severe COVID-19. *J Antimicrob Chemother* 2020;75:3366-3372.
PUBMED | CROSSREF

54. Roozbeh F, Saeedi M, Alizadeh-Navaei R, Hedayatizadeh-Omran A, Merat S, Wentzel H, Levi J, Hill A, Shamshirian A. Sofosbuvir and daclatasvir for the treatment of COVID-19 outpatients: a double-blind, randomized controlled trial. *J Antimicrob Chemother* 2020. doi: 10.1093/jac/dkaa501.
PUBMED | CROSSREF

55. Furuta Y, Takahashi K, Kuno-Maekawa M, Sangawa H, Uehara S, Kozaki K, Nomura N, Egawa H, Shiraki K. Mechanism of action of T-705 against influenza virus. *Antimicrob Agents Chemother* 2005;49:981-986.
PUBMED | CROSSREF

56. Mendenhall M, Russell A, Juelich T, Messina EL, Smee DF, Freiberg AN, Holbrook MR, Furuta Y, de la Torre JC, Nunberg JH, et al. T-705 (favipiravir) inhibition of arenavirus replication in cell culture. *Antimicrob Agents Chemother* 2011;55:782-787.
PUBMED | CROSSREF

57. Delang L, Segura Guerrero N, Tas A, Quérat G, Pastorino B, Froeyen M, Dallmeier K, Jochmans D, Herdewijn P, Bello F, et al. Mutations in the chikungunya virus non-structural proteins cause resistance to favipiravir (T-705), a broad-spectrum antiviral. *J Antimicrob Chemother* 2014;69:2770-2784.
PUBMED | CROSSREF

58. Borrego B, de Ávila AI, Domingo E, Brun A. Lethal mutagenesis of rift valley fever virus induced by favipiravir. *Antimicrob Agents Chemother* 2019;63:e00669-e19.
PUBMED | CROSSREF

59. de Ávila AI, Gallego I, Soria ME, Gregori J, Quer J, Esteban JI, Rice CM, Domingo E, Perales C. Lethal mutagenesis of hepatitis C virus induced by favipiravir. *PLoS One* 2016;11:e0164691.
PUBMED | CROSSREF

60. Escribano-Romero E, Jiménez de Oya N, Domingo E, Saiz JC. Extinction of West Nile virus by favipiravir through lethal mutagenesis. *Antimicrob Agents Chemother* 2017;61:e01400-e01417.
PUBMED | CROSSREF

61. Shannon A, Selisko B, Le NTT, Huchting J, Touret F, Piorkowski G, Fattorini V, Ferron F, Decroly E, Meier C, et al. Rapid incorporation of Favipiravir by the fast and permissive viral RNA polymerase complex results in SARS-CoV-2 lethal mutagenesis. *Nat Commun* 2020;11:4682.
PUBMED | CROSSREF

62. Kaptein SJF, Jacobs S, Langendries L, Seldeslachts L, Ter Horst S, Liesenborghs L, Hens B, Vergote V, Heylen E, Barthelemy K, et al. Favipiravir at high doses has potent antiviral activity in SARS-CoV-2-infected hamsters, whereas hydroxychloroquine lacks activity. *Proc Natl Acad Sci U S A* 2020;117:26955-26965.
PUBMED | CROSSREF

63. Cai Q, Yang M, Liu D, Chen J, Shu D, Xia J, Liao X, Gu Y, Cai Q, Yang Y, et al. Experimental treatment with favipiravir for COVID-19: an open-label control study. *Engineering (Beijing)* 2020;6:1192-1198.
PUBMED | CROSSREF

64. Chen C, Zhang Y, Huang J, Yin P, Cheng Z, Wu J, Chen S, Zhang Y, Chen B, Lu M, et al. Favipiravir versus arbidol for COVID-19: a randomized clinical trial. *medRxiv* 2020. doi: 10.1101/2020.03.17.20037432.
CROSSREF

65. Doi Y, Hibino M, Hase R, Yamamoto M, Kasamatsu Y, Hirose M, Mutoh Y, Homma Y, Terada M, Ogawa T, et al. A prospective, randomized, open-label trial of early versus late favipiravir therapy in hospitalized patients with COVID-19. *Antimicrob Agents Chemother* 2020;64:e01897-e20.
PUBMED | CROSSREF

66. Kadam RU, Wilson IA. Structural basis of influenza virus fusion inhibition by the antiviral drug Arbidol. *Proc Natl Acad Sci U S A* 2017;114:206-214.
PUBMED | CROSSREF

67. Pécheur EI, Borisevich V, Halfmann P, Morrey JD, Smee DF, Prichard M, Mire CE, Kawaoka Y, Geisbert TW, Polyak SJ. The synthetic antiviral drug arbidol inhibits globally prevalent pathogenic viruses. *J Virol* 2016;90:3086-3092.
PUBMED | CROSSREF

68. Shi L, Xiong H, He J, Deng H, Li Q, Zhong Q, Hou W, Cheng L, Xiao H, Yang Z. Antiviral activity of arbidol against influenza A virus, respiratory syncytial virus, rhinovirus, coxsackie virus and adenovirus *in vitro* and *in vivo*. *Arch Virol* 2007;152:1447-1455.
PUBMED | CROSSREF

69. Wei XF, Gan CY, Cui J, Luo YY, Cai XF, Yuan Y, Shen J, Li ZY, Zhang WL, Long QX, et al. Identification of compounds targeting hepatitis B virus core protein dimerization through a split luciferase complementation assay. *Antimicrob Agents Chemother* 2018;62:e01302-e01318.
PUBMED | CROSSREF

70. Wang X, Cao R, Zhang H, Liu J, Xu M, Hu H, Li Y, Zhao L, Li W, Sun X, et al. The anti-influenza virus drug, arbidol is an efficient inhibitor of SARS-CoV-2 *in vitro*. *Cell Discov* 2020;6:28.
PUBMED | CROSSREF

71. Lian N, Xie H, Lin S, Huang J, Zhao J, Lin Q. Umifenovir treatment is not associated with improved outcomes in patients with coronavirus disease 2019: a retrospective study. *Clin Microbiol Infect* 2020;26:917-921.
PUBMED | CROSSREF

72. Xu P, Huang J, Fan Z, Huang W, Qi M, Lin X, Song W, Yi L. Arbidol/IFN-α2b therapy for patients with corona virus disease 2019: a retrospective multicenter cohort study. *Microbes Infect* 2020;22:200-205.
PUBMED | CROSSREF

73. Nojomi M, Yassin Z, Keyvani H, Makiani MJ, Roham M, Laali A, Dehghan N, Navaei M, Ranjbar M. Effect of Arbidol (umifenovir) on COVID-19: a randomized controlled trial. *BMC Infect Dis* 2020;20:954.
PUBMED | CROSSREF

74. Devaux CA, Rolain JM, Colson P, Raoult D. New insights on the antiviral effects of chloroquine against coronavirus: what to expect for COVID-19? *Int J Antimicrob Agents* 2020;55:105938.
PUBMED | CROSSREF

75. Hashem AM, Alghamdi BS, Algaissi AA, Alshehri FS, Bukhari A, Alfaleh MA, Memish ZA. Therapeutic use of chloroquine and hydroxychloroquine in COVID-19 and other viral infections: a narrative review. *Travel Med Infect Dis* 2020;35:101735.
PUBMED | CROSSREF

76. Khan M, Santhosh SR, Tiwari M, Lakshmana Rao PV, Parida M. Assessment of *in vitro* prophylactic and therapeutic efficacy of chloroquine against Chikungunya virus in vero cells. *J Med Virol* 2010;82:817-824.
PUBMED | CROSSREF

77. Gautret P, Lagier JC, Parola P, Hoang VT, Meddeb L, Mailhe M, Doudier B, Courjon J, Giordanengo V, Vieira VE, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Int J Antimicrob Agents* 2020;56:105949.
PUBMED | CROSSREF

78. RECOVERY Collaborative GroupHorby P, Mafham M, Linsell L, Bell JL, Staplin N, Emberson JR, Wiselka M, Ustianowski A, Elmahi E, et al. Effect of hydroxychloroquine in hospitalized patients with COVID-19. *N Engl J Med* 2020;383:2030-2040.
PUBMED | CROSSREF

79. Gorabi AM, Kiaie N, Bianconi V, Jamialahmadi T, Al-Rasadi K, Johnston TP, Pirro M, Sahebkar A. Antiviral effects of statins. *Prog Lipid Res* 2020;79:101054.
PUBMED | CROSSREF

80. Takahashi T, Suzuki T. Function of membrane rafts in viral lifecycles and host cellular response. *Biochem Res Int* 2011;2011:245090.
PUBMED | CROSSREF

81. Fecchi K, Anticoli S, Peruzzu D, Iessi E, Gagliardi MC, Matarrese P, Ruggieri A. Coronavirus interplay with lipid rafts and autophagy unveils promising therapeutic targets. *Front Microbiol* 2020;11:1821.
PUBMED | CROSSREF

82. Diamantis E, Kyriakos G, Quiles-Sanchez LV, Farmaki P, Troupis T. The anti-inflammatory effects of statins on coronary artery disease: an updated review of the literature. *Curr Cardiol Rev* 2017;13:209-216.
PUBMED | CROSSREF

83. Mansur A, Steinau M, Popov AF, Ghadimi M, Beissbarth T, Bauer M, Hinz J. Impact of statin therapy on mortality in patients with sepsis-associated acute respiratory distress syndrome (ARDS) depends on ARDS severity: a prospective observational cohort study. *BMC Med* 2015;13:128.
PUBMED | CROSSREF

84. Zhang XJ, Qin JJ, Cheng X, Shen L, Zhao YC, Yuan Y, Lei F, Chen MM, Yang H, Bai L, et al. In-hospital use of statins is associated with a reduced risk of mortality among individuals with COVID-19. *Cell Metab* 2020;32:176-187.e4.
PUBMED | CROSSREF

85. De Spiegeleer A, Bronselaer A, Teo JT, Byttebier G, De Tré G, Belmans L, Dobson R, Wynendaele E, Van De Wiele C, Vandaele F, et al. The effects of ARBs, ACEis, and statins on clinical outcomes of COVID-19 infection among nursing home residents. *J Am Med Dir Assoc* 2020;21:909-914.e2.
PUBMED | CROSSREF

86. Daniels LB, Sitapati AM, Zhang J, Zou J, Bui QM, Ren J, Longhurst CA, Criqui MH, Messer K. Relation of statin use prior to admission to severity and recovery among COVID-19 inpatients. *Am J Cardiol* 2020;136:149-155.
PUBMED | CROSSREF

87. Moeller R, Zapatero-Belinchon FJ, Lasswitz L, Kirui J, Brogden G, Gunesch AP, Pietschmann T, Wichmann D, Kluge S, Gerold G. Effect of statins on SARS-CoV-2 infection. *medRxiv* 2021. doi: 10.1101/2020.07.13.20152272.
CROSSREF

88. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, Schiergens TS, Herrler G, Wu NH, Nitsche A, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell* 2020;181:271-280.e8.
PUBMED | CROSSREF

89. Hoffmann M, Schroeder S, Kleine-Weber H, Müller MA, Drosten C, Pöhlmann S. nafamostat mesylate blocks activation of SARS-CoV-2: new treatment option for COVID-19. *Antimicrob Agents Chemother* 2020;64:e00754-e20.
PUBMED | CROSSREF

90. Lee ST, Cho H. The use of nafamostat mesilate as an anticoagulant during continuous renal replacement therapy for children with a high risk of bleeding. *J Korean Soc Pediatr Nephrol* 2014;18:98-105.

91. Choi JY, Kang YJ, Jang HM, Jung HY, Cho JH, Park SH, Kim YL, Kim CD. Nafamostat mesilate as an anticoagulant during continuous renal replacement therapy in patients with high bleeding risk: a randomized clinical trial. *Medicine (Baltimore)* 2015;94:e2392.
PUBMED | CROSSREF

92. Blanco-Melo D, Nilsson-Payant BE, Liu WC, Uhl S, Hoagland D, Møller R, Jordan TX, Oishi K, Panis M, Sachs D, et al. Imbalanced host response to SARS-CoV-2 drives development of COVID-19. *Cell* 2020;181:1036-1045.e9.
PUBMED | CROSSREF

93. Hadjadj J, Yatim N, Barnabei L, Corneau A, Boussier J, Smith N, Péré H, Charbit B, Bondet V, Chenevier-Gobeaux C, et al. Impaired type I interferon activity and inflammatory responses in severe COVID-19 patients. *Science* 2020;369:718-724.
PUBMED | CROSSREF

94. Zhang Q, Bastard P, Liu Z, Le Pen J, Moncada-Velez M, Chen J, Ogishi M, Sabli IKD, Hodeib S, Korol C, et al. Inborn errors of type I IFN immunity in patients with life-threatening COVID-19. *Science* 2020;370:eabd4570.
PUBMED | CROSSREF

95. Bastard P, Rosen LB, Zhang Q, Michailidis E, Hoffmann HH, Zhang Y, Dorgham K, Philippot Q, Rosain J, Béziat V, et al. Autoantibodies against type I IFNs in patients with life-threatening COVID-19. *Science* 2020;370:eabd4585.
PUBMED | CROSSREF

96. Vanderheiden A, Ralfs P, Chirkova T, Upadhyay AA, Zimmerman MG, Bedoya S, Aoued H, Tharp GM, Pellegrini KL, Manfredi C, et al. Type I and Type III interferons restrict SARS-CoV-2 infection of human airway epithelial cultures. *J Virol* 2020;94:e00985-e20.
PUBMED | CROSSREF

97. Zhou Z, Ren L, Zhang L, Zhong J, Xiao Y, Jia Z, Guo L, Yang J, Wang C, Jiang S, et al. Heightened innate immune responses in the respiratory tract of COVID-19 patients. *Cell Host Microbe* 2020;27:883-890.e2.
PUBMED | CROSSREF

98. Fu W, Liu Y, Xia L, Li M, Song Z, Hu H, Yang Z, Wang L, Cheng X, Wang M, et al. A clinical pilot study on the safety and efficacy of aerosol inhalation treatment of IFN-κ plus TFF2 in patients with moderate COVID-19. *EClinicalMedicine* 2020;25:100478.
PUBMED | CROSSREF

99. Wang N, Zhan Y, Zhu L, Hou Z, Liu F, Song P, Qiu F, Wang X, Zou X, Wan D, et al. Retrospective multicenter cohort study shows early interferon therapy is associated with favorable clinical responses in COVID-19 patients. *Cell Host Microbe* 2020;28:455-464.e2.
PUBMED | CROSSREF

100. Davoudi-Monfared E, Rahmani H, Khalili H, Hajiabdolbaghi M, Salehi M, Abbasian L, Kazemzadeh H, Yekaninejad MS. A randomized clinical trial of the efficacy and safety of interferon β-1a in treatment of severe COVID-19. *Antimicrob Agents Chemother* 2020;64:e01061-e20.
PUBMED | CROSSREF

101. Pereda R, González D, Rivero HB, Rivero JC, Pérez A, López LDR, Mezquia N, Venegas R, Betancourt JR, Domínguez RE. Therapeutic effectiveness of interferon-α2b against COVID-19: the cuban experience. *J Interferon Cytokine Res* 2020;40:438-442.
PUBMED | CROSSREF

102. Rahmani H, Davoudi-Monfared E, Nourian A, Khalili H, Hajizadeh N, Jalalabadi NZ, Fazeli MR, Ghazaeian M, Yekaninejad MS. Interferon β-1b in treatment of severe COVID-19: a randomized clinical trial. *Int Immunopharmacol* 2020;88:106903.
PUBMED | CROSSREF

103. Monk PD, Marsden RJ, Tear VJ, Brookes J, Batten TN, Mankowski M, Gabbay FJ, Davies DE, Holgate ST, Ho LP, et al. Safety and efficacy of inhaled nebulised interferon beta-1a (SNG001) for treatment of SARS-CoV-2 infection: a randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet Respir Med* 2021;9:196-206.
PUBMED | CROSSREF

104. Focosi D, Anderson AO, Tang JW, Tuccori M. Convalescent plasma therapy for COVID-19: state of the art. *Clin Microbiol Rev* 2020;33:e00072-e20.
PUBMED | CROSSREF

105. Erkurt MA, Sarici A, Berber İ, Kuku İ, Kaya E, Özgül M. Life-saving effect of convalescent plasma treatment in COVID-19 disease: clinical trial from eastern Anatolia. *Transfus Apher Sci* 2020;59:102867.
PUBMED | CROSSREF

106. Li L, Zhang W, Hu Y, Tong X, Zheng S, Yang J, Kong Y, Ren L, Wei Q, Mei H, et al. Effect of convalescent plasma therapy on time to clinical improvement in patients with severe and life-threatening COVID-19: a randomized clinical trial. *JAMA* 2020;324:460-470.
PUBMED | CROSSREF

107. Simonovich VA, Burgos Pratx LD, Scibona P, Beruto MV, Vallone MG, Vázquez C, Savoy N, Giunta DH, Pérez LG, Sánchez MDL, et al. A randomized trial of convalescent plasma in COVID-19 severe pneumonia. *N Engl J Med* 2020. doi: 10.1056/NEJMoa2031304.
PUBMED | CROSSREF

108. Wang C, Li W, Drabek D, Okba NMA, van Haperen R, Osterhaus ADME, van Kuppeveld FJM, Haagmans BL, Grosveld F, Bosch BJ. A human monoclonal antibody blocking SARS-CoV-2 infection. *Nat Commun* 2020;11:2251.
PUBMED | CROSSREF

109. Wan J, Xing S, Ding L, Wang Y, Gu C, Wu Y, Rong B, Li C, Wang S, Chen K, et al. Human-IgG-neutralizing monoclonal antibodies block the SARS-CoV-2 infection. *Cell Reports* 2020;32:107918.
PUBMED | CROSSREF

110. Wu Y, Wang F, Shen C, Peng W, Li D, Zhao C, Li Z, Li S, Bi Y, Yang Y, et al. A noncompeting pair of human neutralizing antibodies block COVID-19 virus binding to its receptor ACE2. *Science* 2020;368:1274-1278.
PUBMED | CROSSREF

111. Brouwer PJM, Caniels TG, van der Straten K, Snitselaar JL, Aldon Y, Bangaru S, Torres JL, Okba NMA, Claireaux M, Kerster G, et al. Potent neutralizing antibodies from COVID-19 patients define multiple targets of vulnerability. *Science* 2020;369:643-650.
PUBMED | CROSSREF

112. Chen P, Nirula A, Heller B, Gottlieb RL, Boscia J, Morris J, Huhn G, Cardona J, Mocherla B, Stosor V, et al. SARS-CoV-2 neutralizing antibody LY-CoV555 in outpatients with COVID-19. *N Engl J Med* 2021;384:229-237.
PUBMED | CROSSREF

113. Weinreich DM, Sivapalasingam S, Norton T, Ali S, Gao H, Bhore R, Musser BJ, Soo Y, Rofail D, Im J, et al. REGN-COV2, a neutralizing antibody cocktail, in outpatients with COVID-19. *N Engl J Med* 2021;384:238-251.
PUBMED | CROSSREF

114. Celltrion. Celltrion presents efficacy and safety data for potential COVID-19 treatment candidate CT-P59 in patients with mild symptoms [Internet]. Available at https://www.celltrionhealthcare.com/en-us/board/newsdetail?modify_key=409 [accessed on 29 December 2020].

115. Del Valle DM, Kim-Schulze S, Huang HH, Beckmann ND, Nirenberg S, Wang B, Lavin Y, Swartz TH, Madduri D, Stock A, et al. An inflammatory cytokine signature predicts COVID-19 severity and survival. *Nat Med* 2020;26:1636-1643.
PUBMED | CROSSREF

116. Guaraldi G, Meschiari M, Cozzi-Lepri A, Milic J, Tonelli R, Menozzi M, Franceschini E, Cuomo G, Orlando G, Borghi V, et al. Tocilizumab in patients with severe COVID-19: a retrospective cohort study. *Lancet Rheumatol* 2020;2:e474-e484.
PUBMED | CROSSREF

117. Biran N, Ip A, Ahn J, Go RC, Wang S, Mathura S, Sinclaire BA, Bednarz U, Marafelias M, Hansen E, et al. Tocilizumab among patients with COVID-19 in the intensive care unit: a multicentre observational study. *Lancet Rheumatol* 2020;2:e603-e612.
PUBMED | CROSSREF

118. Xu X, Han M, Li T, Sun W, Wang D, Fu B, Zhou Y, Zheng X, Yang Y, Li X, et al. Effective treatment of severe COVID-19 patients with tocilizumab. *Proc Natl Acad Sci U S A* 2020;117:10970-10975.
PUBMED | CROSSREF

119. Klopfenstein T, Zayet S, Lohse A, Balblanc JC, Badie J, Royer PY, Toko L, Mezher C, Kadiane-Oussou NJ, Bossert M, et al. Tocilizumab therapy reduced intensive care unit admissions and/or mortality in COVID-19 patients. *Med Mal Infect* 2020;50:397-400.
PUBMED | CROSSREF

120. Strohbehn GW, Heiss BL, Rouhani SJ, Trujillo JA, Yu J, Kacew AJ, Higgs EF, Bloodworth JC, Cabanov A, Wright RC, et al. COVIDOSE: a phase II clinical trial of low-dose tocilizumab in the treatment of noncritical COVID-19 pneumonia. *Clin Pharmacol Ther* 2020. doi: 10.1002/cpt.2117.
PUBMED | CROSSREF

121. Salama C, Han J, Yau L, Reiss WG, Kramer B, Neidhart JD, Criner GJ, Kaplan-Lewis E, Baden R, Pandit L, et al. Tocilizumab in patients hospitalized with COVID-19 pneumonia. *N Engl J Med* 2021;384:20-30.
PUBMED | CROSSREF

122. Stone JH, Frigault MJ, Serling-Boyd NJ, Fernandes AD, Harvey L, Foulkes AS, Horick NK, Healy BC, Shah R, Bensaci AM, et al. Efficacy of tocilizumab in patients hospitalized with COVID-19. *N Engl J Med* 2020;383:2333-2344.
PUBMED | CROSSREF

123. Tsai A, Diawara O, Nahass RG, Brunetti L. Impact of tocilizumab administration on mortality in severe COVID-19. *Sci Rep* 2020;10:19131.
PUBMED | CROSSREF

124. Sanofi. Sanofi provides update on Kevzara (sarilumab) phase 3 trial in severe and critically ill COVID-19 patients outside the U.S. [Internet]. Available at https://www.sanofi.com/en/media-room/press-releases/2020/2020-09-01-07-00-00 [accessed on 28 September 2020].

125. Gritti G, Raimondi F, Ripamonti D, Riva I, Landi F, Alborghetti L, Frigeni M, Damiani M, Micò C, Fagiuoli S, et al. IL-6 signalling pathway inactivation with siltuximab in patients with COVID-19 respiratory failure: an observational cohort study. *medRxiv* 2020. doi: 10.1101/2020.04.01.20048561.
CROSSREF

126. Harrison C. Focus shifts to antibody cocktails for COVID-19 cytokine storm. *Nat Biotechnol* 2020;38:905-908.
PUBMED | CROSSREF

127. De Luca G, Cavalli G, Campochiaro C, Della-Torre E, Angelillo P, Tomelleri A, Boffini N, Tentori S, Mette F, Farina N, et al. GM-CSF blockade with mavrilimumab in severe COVID-19 pneumonia and systemic hyperinflammation: a single-centre, prospective cohort study. *Lancet Rheumatol* 2020;2:e465-e473.
PUBMED | CROSSREF

128. Kiniksa. Kiniksa announces data from U.S. investigator-initiated study of mavrilimumab in severe COVID-19 pneumonia and hyperinflammation [Internet]. Available at https://investors.kiniksa.com/news-releases/news-release-details/kiniksa-announces-data-us-investigator-initiated-study [accessed on 23 December 2020].

129. Cavalli G, De Luca G, Campochiaro C, Della-Torre E, Ripa M, Canetti D, Oltolini C, Castiglioni B, Tassan Din C, Boffini N, et al. Interleukin-1 blockade with high-dose anakinra in patients with COVID-19, acute respiratory distress syndrome, and hyperinflammation: a retrospective cohort study. *Lancet Rheumatol* 2020;2:e325-e331.
PUBMED | CROSSREF

130. Huet T, Beaussier H, Voisin O, Jouveshomme S, Dauriat G, Lazareth I, Sacco E, Naccache JM, Bézie Y, Laplanche S, et al. Anakinra for severe forms of COVID-19: a cohort study. *Lancet Rheumatol* 2020;2:e393-e400.
PUBMED | CROSSREF

131. Balkhair A, Al-Zakwani I, Al Busaidi M, Al-Khirbash A, Al Mubaihsi S, BaTaher H, Al Aghbari J, Al Busaidi I, Al Kindi M, Baawain S, et al. Anakinra in hospitalized patients with severe COVID-19 pneumonia requiring oxygen therapy: results of a prospective, open-label, interventional study. *Int J Infect Dis* 2021;103:288-296.
PUBMED | CROSSREF

132. La Rosée F, Bremer HC, Gehrke I, Kehr A, Hochhaus A, Birndt S, Fellhauer M, Henkes M, Kumle B, Russo SG, et al. The Janus kinase 1/2 inhibitor ruxolitinib in COVID-19 with severe systemic hyperinflammation. *Leukemia* 2020;34:1805-1815.
PUBMED | CROSSREF

133. Capochiani E, Frediani B, Iervasi G, Paolicchi A, Sani S, Roncucci P, Cuccaro A, Franchi F, Simonetti F, Carrara D, et al. Ruxolitinib rapidly reduces acute respiratory distress syndrome in COVID-19 disease. Analysis of data collection from RESPIRE protocol. *Front Med (Lausanne)* 2020;7:466.
PUBMED | CROSSREF

134. Cao Y, Wei J, Zou L, Jiang T, Wang G, Chen L, Huang L, Meng F, Huang L, Wang N, et al. Ruxolitinib in treatment of severe coronavirus disease 2019 (COVID-19): a multicenter, single-blind, randomized controlled trial. *J Allergy Clin Immunol* 2020;146:137-146.e3.
PUBMED | CROSSREF

135. Innes AJ, Cook LB, Marks S, Bataillard E, Crossette-Thambiah C, Sivasubramaniam G, Apperley J, Milojkovic D. Ruxolitinib for tocilizumab-refractory severe COVID-19 infection. *Br J Haematol* 2020;190:e198-e200.
PUBMED | CROSSREF

136. Novartis. Novartis provides update on RUXCOVID study of ruxolitinib for hospitalized patients with COVID-19 2020 [Internet]. Available at https://www.novartis.com/news/media-releases/novartis-provides-update-ruxcovid-study-ruxolitinib-hospitalized-patients-covid-19 [accessed on 23 December 2020].

137. D'Alessio A, Del Poggio P, Bracchi F, Cesana G, Sertori N, Di Mauro D, Fargnoli A, Motta M, Giussani C, Moro P, et al. Low-dose ruxolitinib plus steroid in severe SARS-CoV-2 pneumonia. *Leukemia* 2021;35:635-638.
PUBMED | CROSSREF

138. Cantini F, Niccoli L, Nannini C, Matarrese D, Natale MED, Lotti P, Aquilini D, Landini G, Cimolato B, Pietro MAD, et al. Beneficial impact of Baricitinib in COVID-19 moderate pneumonia; multicentre study. *J Infect* 2020;81:647-679.
PUBMED | CROSSREF

139. Kalil AC, Patterson TF, Mehta AK, Tomashek KM, Wolfe CR, Ghazaryan V, Marconi VC, Ruiz-Palacios GM, Hsieh L, Kline S, et al. Baricitinib plus remdesivir for hospitalized adults with COVID-19. *N Engl J Med* 2020. doi: 10.1056/NEJMoa2031994.
PUBMED | CROSSREF

140. Wu D, Yang XO. TH17 responses in cytokine storm of COVID-19: an emerging target of JAK2 inhibitor Fedratinib. *J Microbiol Immunol Infect* 2020;53:368-370.
PUBMED | CROSSREF

141. Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. *Lancet* 2020;395:473-475.
PUBMED | CROSSREF

142. RECOVERY Collaborative Group, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, Staplin N, Brightling C, Ustianowski A, et al. Dexamethasone in hospitalized patients with COVID-19 - preliminary report. *N Engl J Med* 2020. doi: 10.1056/NEJMoa2021436.
PUBMED | CROSSREF

143. Tomazini BM, Maia IS, Cavalcanti AB, Berwanger O, Rosa RG, Veiga VC, Avezum A, Lopes RD, Bueno FR, Silva MVAO, et al. Effect of dexamethasone on days alive and ventilator-free in patients with moderate or severe acute respiratory distress syndrome and COVID-19: the CoDEX randomized clinical trial. *JAMA* 2020;324:1307-1316.
PUBMED | CROSSREF

144. Dequin PF, Heming N, Meziani F, Plantefève G, Voiriot G, Badié J, François B, Aubron C, Ricard JD, Ehrmann S, et al. Effect of hydrocortisone on 21-day mortality or respiratory support among critically ill patients with COVID-19: a randomized clinical trial. *JAMA* 2020;324:1298-1306.
PUBMED | CROSSREF

145. Angus DC, Derde L, Al-Beidh F, Annane D, Arabi Y, Beane A, van Bentum-Puijk W, Berry L, Bhimani Z, Bonten M, et al. Effect of hydrocortisone on mortality and organ support in patients with severe COVID-19: the REMAP-CAP COVID-19 corticosteroid domain randomized clinical trial. *JAMA* 2020;324:1317-1329.
PUBMED | CROSSREF

146. WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group, Sterne JAC, Murthy S, Diaz JV, Slutsky AS, Villar J, Angus DC, Annane D, Azevedo LCP, Berwanger O, et al. Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: a meta-analysis. *JAMA* 2020;324:1330-1341.
PUBMED | CROSSREF

147. World Health Organization. Corticosteroids for COVID-19: living guidance [Internet]. Available at https://apps.who.int/iris/handle/10665/334125 [accessed on 23 September 2020].