NRC Research Press

REVIEW

Current therapies under investigation for COVID-19: potential COVID-19 treatments

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Abstract: In response to the outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), researchers are expeditiously searching for antiviral treatments able to alleviate the symptoms of infection, which can be life-threatening. Here, we provide a general overview of what is currently known about the structure and characteristic features of SARS-CoV-2, some of which could potentially be exploited for the purposes of antiviral therapy and vaccine development. This minireview also covers selected and noteworthy antiviral agents/supportive therapy out of hundreds of drugs that are being repurposed or tested as potential treatments for COVID-19, the disease caused by SARS-CoV-2.

Key words: COVID-19, coronavirus, SARS-CoV-2, SARS-CoV, MERS-CoV.

Résumé : En réaction à flambée de nouveau coronavirus du syndrome respiratoire aigu sévère (SARS-CoV-2), les chercheurs se sont mis de manière expéditive à la recherche de traitements antiviraux permettant d'atténuer les symptômes de l'infection, lesquels pouvant menacer le pronostic vital. Nous proposons ici un aperçu général de ce que l'on sait en ce moment de la structure et des caractéristiques du SARS-CoV-2, dont certaines pourraient être exploitées en vue du développement de traitements antiviraux et de vaccins. Cette courte synthèse couvre aussi des agents antiviraux et des traitements de soutien sélectionnés et dignes de mention parmi des centaines de médicaments en voie d'être reconvertis ou testés comme traitements éventuels contre la COVID-19, la maladie causée par le SARS-CoV-2. [Traduit par la Rédaction]

Mots-clés : COVID-19, coronavirus, SARS-CoV-2, SARS-CoV, MERS-CoV.

SARS-CoV-2

A newly emerged human coronavirus, called Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) (formerly named 2019-nCoV), was first reported in Wuhan, China. It belongs to the Baltimore Group IV classification of viruses, which includes West Nile virus, dengue virus, rhinoviruses, hepacivirus C (hepatitis C virus (HCV)), Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV), and Middle East Respiratory Syndrome Coronavirus (MERS-CoV) (Baltimore 1971). These viruses, which behave in the same way and share a similar genome, use long (10 000 to 30 000 bp) positive-sense, single-stranded RNA as genetic material; the genomic RNA can act as mRNA and be translated into protein by the ribosomes of the host cell (Ahlquist et al. 2003; Nagy and Pogany 2011).

Coronaviruses such as SARS-CoV, which originated in the wet markets of Guangdong Province, China, and migrated to 37 countries, and MERS-CoV, which originated in Saudi Arabia and then rapidly spread to 29 countries, can jump the species barrier and then cause outbreaks in immune-naïve human populations characterized by high morbidity (Su et al. 2016; Coleman et al. 2016). Both SARS-CoV and MERS-CoV originated in bats; SARS-CoV spread to humans through raccoon dogs and civet cats, and MERS-CoV spread to humans through camels as an intermediate animal host (Dyall et al. 2014; Coleman et al. 2016). The case fatality rate associated with SARS-CoV was around 10% with over 8000 documented cases, and the case fatality rate associated with MERS-CoV has been around 34% with over 2500 documented cases (Dyall et al. 2014; Coleman et al. 2016). The emergence of highly infectious and potentially fatal pathogens such as SARS-CoV and MERS-CoV, and most recently SARS-CoV-2, suggests a pressing need for development of effective antiviral agents that can be used for current and impending coronavirus epidemics or pandemics.

Human coronaviruses are characterized by two groups of proteins: structural proteins (Spike (S), Envelope (E), Nucleocapsid (N), and Membrane (M)) and nonstructural proteins (named nsp1–nsp16). These proteins are required at different stages of the virus replication cycle and many are potential targets for therapy or vaccine development (Snijder et al. 2016; Elfiky et al. 2017). Multiple nsps come together to form a replicase–transcriptase complex, with RNA-dependent RNA polymerase (RdRp) (nsp12) as the primary replicase–transcriptase protein (Snijder et al. 2016). RdRp is an essential enzyme in the life cycle of RNA viruses such as coronaviruses and HCV; this protein is among several (nsp7–nsp16) that direct coronavirus RNA synthesis (Snijder et al. 2016).

Nsp1 has garnered significant attention as a possible factor determining virulence of coronaviruses and is a potential target for

Received 27 May 2020. Accepted 24 June 2020.

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Table 1. Selected panel of drugs under investigation as therapies for COVID-19.

Drug	Activity/mechanism
Corticosteroids	Reduce lung inflammation
Lopinavir + ritonavir	Inhibit chymotrypsin-like protease-3
Darunavir + cobicostat	Inhibit chymotrypsin-like protease 3
Chloroquine/hydroxychloroquine	Inhibit viral entry/viral trafficking
Ribavirin	Immunomodulation/guanosine nucleoside analog
Nitazoxanide	Enhances host immune response/inhibits viral replication
Oseltamivir	Inhibits neuraminidase
Niclosamide	Inhibits viral entry/viral replication
Remdesivir	Inhibits RNA-dependent RNA polymerase/adenosine nucleotide analog
Favilavir	Inhibits RNA-dependent RNA polymerase
Nafamostat	Inhibits spike glycoprotein-mediated membrane fusion
Umifenovir	Inhibits influenza membrane fusion
Sarilumab	Inhibits IL-6 receptor
Tocilizumab	Inhibits IL-6 receptor

coronavirus vaccine development due to its role in downregulation of the immune response of the host (Narayanan et al. 2015). Studies investigating nsp2 and nsp3 identify these proteins as features distinguishing SARS-CoV-2 from SARS-CoV, with nsp2 possibly contributing to SARS-CoV-2 being more contagious (Angeletti et al. 2020). Nsp3 is the largest encoded protein of the coronavirus genome that is a vital constituent of the replication/transcription complex (Lei et al. 2018). Papain-like protease (PLpro) cleaves the N terminus of the replicase polyprotein to release nsp1, nsp2, and nsp3, an important step related to viral replication, and it also functions in antagonizing the host's innate immunity (Harcourt et al. 2004; Chen et al. 2014; Li et al. 2016). Nsp3, nsp4, and nsp6 have been implicated in membrane rearrangement (Hagemeijer et al. 2014; EA and Jones 2019), and the activity of the nsp5 protease (chymotrypsin-like protease 3 (3CL-pro)) is required during viral replication and mediates maturation of the nsps, necessary for the virus life cycle (Perlman and Netland 2009). Replication of the genomic RNA of SARS-CoV involves replicase proteins that are processed by PLpro and 3Clpro, which makes these proteases attractive targets for therapy for SARS-like coronaviruses.

SARS-CoV-2 is a member of the *Betacoronavirus* genus, like SARS-CoV and MERS-CoV, and shares 80% RNA sequence identity with SARS-CoV, with >90% sequence identity shared between the RdRp of the two viruses at the nucleotide level (Morse et al. 2020; Lu et al. 2020*b*). SARS-CoV-2 and MERS-CoV, by contrast, share around 50% sequence identity (Lu et al. 2020*b*).

Although SARS-CoV and MERS-CoV modulate transcriptional changes differently in host cells, their viral replication kinetics are similar (Josset et al. 2013). The SARS-CoV virion, or infective form of the virus outside the host cell, undergoes receptor-mediated endocytosis, a mode of viral entry that involves its spike protein (S) glycoprotein binding to angiotensin-converting enzyme 2 (ACE2), a cell surface receptor on lung AT2 alveolar epithelial cells (Li et al. 2003). Within the endosomal compartment, cleavage of the S protein by cathepsin L produces a fusion-competent glycoprotein rendering the S2 domain accessible (Simmons et al. 2005). Acidification of the endosomal compartment triggers S-mediated fusion of the viral and endosomal membranes, allowing the viral genome to escape into the cytoplasm where it can be expressed. The entry of the MERS-CoV virion is similar, with endocytosis preceding via S binding to dipeptidyl peptidase 4 (DPP4) followed by trafficking to the site of fusion of the virion and endosomal membrane in a manner dependent on the host cell protease furin (Burkard et al. 2014). The activation of S by proteases is a critical step in viral infectivity, and such proteases are potential therapeutic targets, as are various kinases involved in virion entry.

In the case of SARS-CoV-2, the receptor binding domain (RBD) of the S protein on its surface binds to the ACE2 receptor on the host cell surface to gain entry (Cao et al. 2020*b*). This is followed by formation of a viral RNA replicase–transcriptase complex that leads to production of RNA negative strands, which are translated into structural proteins; new viral particles are made through assembly of RNA and structural proteins, and through exocytosis, SARS-CoV-2 leaves the host cell (Cao et al. 2020*b*).

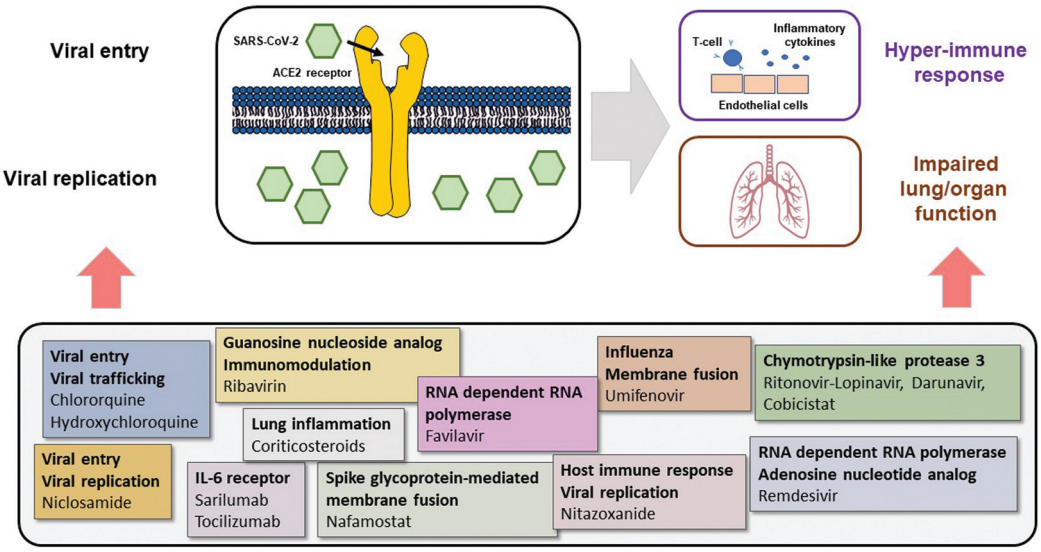
Current treatment approaches for COVID-19

Due to the high mortality rates associated with COVID-19, the disease caused by SARS-CoV-2, approved, yet unproven, therapies have been readily utilized that are based on treatments previously used for SARS-CoV and MERS-CoV, including broad-spectrum antibiotics, the nucleoside inhibitor ribavirin, the protease inhibitors lopinavir–ritonavir, interferons (IFNs), mycophenolic acid, and corticosterioids; these agents are administered alone or in combination with other agents (Table 1). A summary of selected therapies under investigation for SARS-CoV-2 is shown in Fig. 1.

Hundreds of international COVID-19 clinical trials are ongoing and an increasing number of trials testing existing and experimental agents are being commenced at a high rate. The aforementioned drugs are currently under investigation in many of the current trials as well as novel therapies in development, such as vaccines, including vaccines against MERS-CoV, convalescent plasma from recovered COVID-19 patients, anti-SARS-CoV-2 monoclonal antibodies, and antibody-based and small molecule approaches to reducing inflammatory conditions and cytokine storm through IL-6 inhibition. Trials are also being conducted that test combinations of agents, including therapies with Traditional Chinese Medicines (TCM) (NCT04306497, NCT04251871, NCT04285190, NCT04278963, NCT04279197, and NCT04310865).

Some agents have limitations for COVID-19 treatment due to various factors that may make them challenging to use for SARS-CoV-2-infected patients as therapeutics. For instance, although corticosteroids, which reduce lung inflammation, have been extensively used for treatment of SARS-CoV, MERS-CoV, and most recently SARS-CoV-2 disease (Stockman et al. 2006; Arabi et al. 2018; Huang et al. 2020), the World Health Organization has advised clinicians against using corticosteroids given their lack of efficacy and potential adverse side effects (delayed viral clearance, inhibition of host immune response, hyperglycemia, avascular necrosis, and psychosis) (Stockman et al. 2006; Li et al. 2004; Lee et al. 2004*a*, 2004*b*; Xiao et al. 2004; Russell et al. 2020). Despite this, there are numerous ongoing COVID-19 trials that are investigating interferons and corticosteroids (www.ClinicalTrials.gov). Of note, dexamethasone has recently been shown in a large trial called RECOVERY (NCT04381936) to reduce deaths due to COVID-19 by around one third in severely ill patients on ventilators (Ledford 2020).

Fig. 1. Selected drugs under investigation for activity against SARS-CoV-2. [Colour online.]



IFNs have potential prophylactic as well as early therapeutic activity due to their ability to compensate for virally diminished IFN production or function (Prokunina-Olsson et al. 2020). IFNs, often used in combination with ribavirin, had up to recently been considered limited in terms of therapeutic potential for COVID-19 due to toxicity as well as mixed results from studies involving patients with other coronaviruses (Mo and Fisher 2016; Arabi et al. 2020). However, there are data now in support of using IFN-lambda for COVID-19 and trials are currently ongoing (Prokunina-Olsson et al. 2020). Type III IFNs (IFN-lambda 1–4) can be prophylactic in the early phase of SARS-CoV-2 infection, with antiviral response limited to epithelial cells; this would diminish proinflammatory and other adverse effects caused by type I IFNs (IFN-alpha/beta) (Prokunina-Olsson et al. 2020).

Attractive protease targets for coronavirus therapy include the deubiquitylating enzyme PLpro, which is involved in host immune response evasion, and 3CLpro (Ratia et al. 2006; Bekes et al. 2015; Baez-Santos et al. 2015). Both are deemed important for SARS-CoV replication and function to process the viral polyprotein in a regulated manner (Baez-Santos et al. 2015). It should be noted that the papain-like protease domain/deubiquitylating enzyme activity has been found to be a virulence trait that varies among SARS-CoV and SARS-related CoVs (Niemeyer et al. 2018).

Protease inhibitors lopinavir and ritonavir (both approved for Human Immunodeficiency Virus (HIV)) target 3CLpro (Anand et al. 2003). There are in vitro data suggesting that lopinavir exhibits antiviral activity against SARS-CoV-2 (Choy et al. 2020). However, in a randomized, controlled, open label trial involving hospitalized SARS-CoV-2-infected patients suffering from severe COVID-19, lopinavir and ritonavir did not lead to clinical benefit beyond standard care (Lu et al. 2020*a*; Cao et al. 2020*a*). That said, the combination of lopinavir–ritonavir with pneumonia-targeting adjuvant drugs, as compared with the adjuvant drugs alone, led to more clinical benefit and the combination was well tolerated (Ye et al. 2020), and a clinical trial testing a triple combination of lopinavir–ritonavir, ribavirin, and interferon-beta1b in patients with mild to moderate COVID-19 showed a shortening of duration of hospitalization and viral shedding (NCT04276688). There are currently a number of ongoing COVID-19 clinical trials investigating lopinavir/ritonavir (www.ClinicalTrials.gov).

Darunavir and cobicistat have been approved for HIV and target 3CLpro (Kakuda et al. 2015; Khan et al. 2020); they are under investigation for COVID-19 in clinical trials in China (NCT04252274) and Italy (NCT04368351). There are, however, currently no in vitro data or clinical data in support of this drug combination as a therapeutic for SARS-CoV-2-infected patients.

The antimalarial drugs chloroquine and hydroxychloroquine were approved by the United States Food and Drug Administration (FDA) for limited emergency use as a treatment for COVID-19 (Lenzer 2020). Chloroquine is believed to work at least in part through disruption of viral fusion and entry by raising the endosomic pH slightly (Sinha and Balayla 2020; Wang et al. 2020). Widespread testing of patients with these drugs has ensued in clinical trials conducted by academic institutions and government agencies. Clinical results with chloroquine were reported in China as suggestive of offering clinical benefit compared to controls (Wang et al. 2020; Gao et al. 2020). However, the data were generated in multiple hospitals with varying controls and outcome indicators, and so it is difficult to make interpretations and draw solid conclusions from these reports (Touret and de Lamballerie 2020). A recent observational study of hospitalized COVID-19 patients revealed no link between hydroxychloroquine treatment and either a substantially decreased or increased risk of death or end point of intubation (Geleris et al. 2020). Chloroquine and hydroxychloroquine are currently being investigated in numerous clinical trials in patients with mild, moderate, and severe COVID-19 and are being tested for pre-exposure or post-exposure prophylaxis of SARS-CoV-2 infection (www.ClinicalTrials.gov). Significantly, there is a narrow margin between the therapeutic and toxic doses of these drugs, and life-threatening cardiovascular disorders have historically occurred in association with chloroquine treatment (Frisk-Holmberg et al. 1983).

Ribavirin is a synthetic guanosine analogue that functions as a direct viral agent by abrogating viral RNA synthesis, but it has immunomodulatory function as well (Shiffman 2009). Ribavirin with pegylated interferon-alpha (Peg-INF-alpha) is the standard of care for HCV (Deutsch and Hadziyannis 2008). Robust activity against MERS-CoV has been demonstrated by IFN-alpha2b and ribavirin in MERS-CoV-infected rhesus macaques; however, clinical findings regarding efficacy and safety of ribavirin combined with IFN (either IFN-alpha2a, IFN-alpha2b, or IFN-beta1a) against MERS-CoV are controversial (Falzarano et al. 2013; Zumla et al. 2016; Arabi et al. 2020). Clinical studies thus far suggest that ribavirin is ineffective against COVID-19, and drug-induced anemia could potentially be harmful for patients suffering from respiratory distress (Martinez 2020). There are currently ongoing COVID-19 clinical trials that involve investigation of ribavirin, either as an

intervention or as a control medication (NCT04356677 and NCT04306497) and one that has completed (NCT04276688).

Nitazoxanide is a broad-spectrum antiparasitic and antiviral drug approved for diarrhea treatment that is under consideration for COVID-19 treatment (Simsek Yavuz and Unal 2020; Rossignol 2014). Nitazoxanide functions to enhance host innate immune response and block virus-specific immune evasion strategies (Jasenosky et al. 2019). It has specifically been shown to inhibit Ebola virus replication via effects on protein kinase R and retinoic acid inducible protein 1 (Jasenosky et al. 2019). There are some preclinical studies that demonstrated efficacy against SARS-CoV-2; however, clinical use against other coronaviruses has not demonstrated efficacy (Gamino-Arroyo et al. 2019). The drug has an acceptable safety profile, however a poorly tolerated formulation. There are ongoing COVID-19 trials investigating nitazoxanide (NCT04360356, NCT04361318, NCT04348409, NCT04359680, NCT04343248, NCT04351347, NCT04341493, and NCT04345419).

Oseltamivir (approved for influenza) is an inhibitor of influenza neuraminidase (Li and De Clercq 2020). Neuraminidase inhibitors such as oseltamivir, however, have been found to be ineffective through clinical treatment studies with COVID-19 patients, since coronaviruses do not use neuraminidase for the budding stage of reproduction (Li et al. 2020). Therefore, these drugs are not recommended for clinical application. There are ongoing COVID-19 trials investigating oseltamivir or using it as a standard care control (NCT04303299, NCT04338698, NCT04255017, NCT04261270, NCT04349241, NCT04323345, NCT04348877, NCT04365764, NCT02735707, and NCT04361422).

Niclosamide is an antihelminthic medication used for tapeworm infections, first discovered in the late 1950s (Pearson and Hewlett 1985). It was shown in vitro to inhibit the replication of SARS-CoV (Wu et al. 2004) and has demonstrated broad-spectrum activity as well against MERS-CoV, HCV, Zika virus, and adenovirus (Xu et al. 2020*a*). One limitation of niclosamide is variable oral bioavailability (Andrews et al. 1982). Its production was discontinued in the United States after voluntary withdrawal from the market by Bayer; however, it is available through compounding companies in the United States and is commercially available in other countries including Italy and France (Schweizer et al. 2018). Niclosamide is currently being investigated as a potential treatment of COVID-19 (NCT04345419) (Xu et al. 2020*a*). Its proposed mechanism of action against SARS-CoV-2 is unclear; however, it may involve prevention of viral replication through inhibition of autophagy as well as prevention of viral entry through alteration of endosomal pH (Pindiprolu and Pindiprolu 2020). Of note, despite its discontinuation in the United States, niclosamide is listed on the World Health Organization's List of Essential Medicines (Schweizer et al. 2018).

The broad-spectrum antiviral drug remdesivir (GS-5734) (Gilead Sciences), a nucleotide analog (Tchesnokov et al. 2019), was originally developed as a therapy for Ebola virus, with potent in vitro activity against Ebola viruses and others (EC_{50} values 0.06–0.14 μmol/L) (Cardile et al. 2017). Remdesivir showed efficacy in primate models; however, in a randomized controlled clinical trial for Ebola (PALM clinical trial (NCT03719586)), the rate of mortality for remdesivir-treated patients was found to be inferior to that of monoclonal antibody therapies (Warren et al. 2016; Mulangu et al. 2019). Remdesivir has demonstrated activity against RNA viruses including SARS-CoV and MERS-CoV (Sheahan et al. 2017, 2020; de Wit et al. 2020). Remdesivir displayed much higher potency in vitro against SARS-CoV-2 (EC_{50} = 0.77 μmol/L) than other antiviral agents, such as ribavirin (EC_{50} = 109.5 μmol/L), favilavir (EC_{50} = 61.88 μmol/L), and penciclovir (EC_{50} = 95.96 μmol/L) (Wang et al. 2020).

Studies have demonstrated low efficacy of nucleotide analogs against coronaviruses because of the presence of the virus exonuclease proofreading enzyme. Importantly, remdesivir has been shown to potently inhibit coronaviruses with intact proofreading, and drug resistance has been proven difficult to select (Agostini et al. 2018). In a study involving passage and selection of murine hepatitis virus (MHV) in the presence of the GS-5734 parent nucleoside, two amino acid substitutions in the nsp12 polymerase at residues conserved across coronaviruses were selected that provided low-level resistance to remdesivir that higher nontoxic concentrations could override (Agostini et al. 2018). The resistance mutations were found to decrease the virulence of MHV in vitro and lessened pathogenesis in a SARS-CoV animal model of infection (Agostini et al. 2018).

Remdesivir is currently being investigated as a COVID-19 therapy in international, multisite clinical trials and has shown some promise in patients (Grein et al. 2020). The drug was given on a compassionate-use basis to hospitalized patients afflicted with severe COVID-19 symptoms, and 36/53 (68%) of the patients showed clinical improvement (Grein et al. 2020). These data, however, are anecdotal and derived from compassionate use cases, and the lack of a control arm makes this study difficult to interpret in terms of the direct influence of remdesivir on recovery. The study as published lacks viral load data, which would be needed to know the extent of antiviral activity of redemsivir. In a separate study reporting the success of remdesivir treatment for the first COVID-19 patient in the United States, defined as a mild to moderate case, nasopharyngeal and oropharyngeal swabs showed that the viral load had decreased 4 days prior to remdesivir treatment, which could have occurred as a possible result of the self-limiting nature of SARS-CoV-2, effects of the supportive treatment that had been implemented for days prior to remdesivir treatment, or the patient's immune response (Cao et al. 2020*b*; Holshue et al. 2020). These factors make the definitive role of remdesivir in the patient's recovery in this study unclear.

Numerous controlled trials investigating the safety and efficacy of remdesivir have been carried out and completed or are ongoing (www.ClinicalTrials.gov). In the first randomized, double-blind, placebo-controlled, multicenter trial in China assessing intravenously administered remdesivir in patients with COVID-19 (NCT04257656), there was no statistically significant difference between remdesivir-treated and placebo-treated patients with respect to time to clinical improvement, and there were overall no statistically significant clinical benefits observed for remdesivir beyond standard care (Wang et al. 2020). However, it should be noted that the predetermined sample size of this study was not attained due to the COVID-19 outbreak having been substantially controlled (237 patients were enrolled, with 158 randomly assigned to a remdesivir-treated group and 79 to a placebo-treated group). A larger Phase 3 trial, called the Adaptive COVID-19 Treatment Trial (ACTT) (NCT04280705), has been carried out in the United States and is the first clinical trial launched in the country to evaluate a COVID-19 therapy. It is sponsored by the National Institute of Allergy and Infectious Diseases (NIAID), with an enrollment of over 1000 COVID-19 patients participating internationally. Initial reports of this study's results have been encouraging but modest, with a recovery time for patients shortened from 15 to 11 days (31% improvement) ($p < 0.001$) and a mortality rate of 8% for remdesivir-treated patients and 11.6% for the control group (not statistically significant; $p = 0.059$). As a result of these findings, on 1 May 2020, the FDA issued an emergency approval for remdesivir as a therapy for severely ill patients diagnosed with COVID-19. Approval for this patient population is temporary and formal approval would need to happen at a later date.

Several drugs have either been approved for use against COVID-19 in China or are under consideration for COVID-19 that are approved for other indications in Asia. The National Medical Products Administration of China has approved the antiviral drug favilavir (favipiravir) (Zhejiang Hisun Pharmaceutical), believed to work through inhibition of RdRp (Jin et al. 2013). Currently approved for influenza in China and Japan (Shiraki and Daikoku 2020), it was approved as a therapy for SARS-CoV-2 infection after it demonstrated safety and efficacy in a small trial (Du and Chen

2020; Cai et al. 2020). However, existing evidence in support of favilavir has been criticized by the Italian Pharmaceutical Agency as being preliminary and insufficient. Favilavir is currently under investigation in COVID-19 trials (NCT04336904, NCT04359615, NCT04358549, NCT04349241, NCT04303299, NCT04310228, NCT04333589, NCT04346628, NCT04351295, NCT04356495, and NCT04345419). China also approved tocilizumab (Roche; Actemra), a recombinant humanized IL-6 receptor monoclonal antibody (Sheppard et al. 2017), for treatment of serious COVID-19 complications. A study in China investigating a 5 day treatment with tocilizumab for patients with severe or critical COVID-19 found 15/20 (75%) of patients had lowered their requirement for oxygen supplement following treatment and one patient did not require oxygen therapy (Xu et al. 2020*b*). Safety issues associated with tocilizumab include increased risk of developing serious infections that could be fatal, including tuberculosis and other opportunistic pathogens. Tocilizumab is under investigation in numerous COVID-19 trials (www.ClinicalTrials.gov). In a retrospective review of tocilizumab-treated patients with severe COVID-19 with a 14 day followup, radiological improvement, mitigation of inflammatory markers, and a lessened requirement for ventilatory support were observed (Alattar et al. 2020). However, 92% of the patients experienced at least one adverse event, although it is unclear which of these events are attributable to tocilizumab treatment (Alattar et al. 2020).

Other approved antiviral drugs in Asia include nafamostat, a serine protease inhibitor that decreases formation of fibrin from fibrinogen and also inhibits spike glycoprotein-mediated membrane fusion, and umifenovir (Arbidol), which inhibits influenza membrane fusion, preventing virus–host cell contact, and is approved for influenza in Russia and China (Lu 2020; Li and De Clercq 2020). Umifenovir is currently being investigated in a clinical trial as a treatment for COVID-19 (NCT04352400).

Sarilumab (Kevzara) is a human monoclonal antibody against the IL-6 receptor that is under investigation as a COVID-19 therapy (Kim et al. 2015). Compared with tocilizumab, sarilumab displayed a similar safety, however with less frequency of administration required (every other week instead of weekly) (Raimondo et al. 2017). In a Phase II study (ALIGN), investigating the safety and efficacy of sarilumab, there were no reported cases of tuberculosis (Sieper et al. 2015). However, in a Phase III (MONARCH) trial, there was a similar incidence of infections (28.8% and 27.7%) as well as serious infections (mastitis and infective bursitis, 1.1%) between sarilumab and another IL-6 receptor antibody therapy, adalimumab (Burmester et al. 2017). In Europe, sarilumab is contraindicated in people with active, severe infections. In the United States, there is a boxed warning of potential for serious infections and caution is advised due to incidences of tuberculosis resulting from immune suppression with the drug. There are currently COVID-19 trials that are testing sarilumab (NCT04357808, NCT04315298, NCT04341870, NCT04357860, NCT04327388, NCT04359901, NCT04324073, NCT04322773, and NCT04345289).

A summary of the aforementioned drug treatments under investigation for COVID-19 is provided in Table 1.

Conclusion

Demonstrated and highly efficacious countermeasures against SARS-CoV-2-induced COVID-19 are currently lacking. There are, however, existing agents that are being repurposed and tested extensively and internationally in hundreds of clinical trials as potential treatments for COVID-19. This may also include drugs and treatment approaches that have been previously considered or tested against SARS-CoV and MERS-CoV. Development of clinically effective therapies for COVID-19 is particularly urgent, in light of the conceivable length of time it could take for development of a vaccine that offers enduring protection and that does not worsen the infection. There is promise in small molecule agents with the ability to decrease viral loads in patients and (or) that could mitigate a hyperinflammatory response resulting in severe and potentially fatal disease symptoms. The greatest potential for therapeutic benefit likely lies in the combination of two or more agents, such as has been successfully employed for HIV. This approach — contingent on dosing optimized for safe administration — takes advantage of unique and beneficial properties of different agents that could result in potentiation of drug effects, leading to greater clinical efficacy and a reduced risk of drug resistance.

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