Minireview *Highlight article*

COVID-19: Antiviral agents and enzyme inhibitors/receptor blockers in development

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Impact statement

In the wake of the coronavirus disease 2019 (COVID-19) pandemic that originated in late December 2019, antiviral therapies are urgently needed for better patient outcomes and to reduce the burden on healthcare systems across the world. While the vaccines have been developed to mitigate this crisis, there are significant delays in their distribution and administration due to the holiday season, lack of sufficient hospital staff, and short half-life of messenger RNA vaccines. In this review, we have discussed the antiviral agents that inhibit key enzymes facilitating viral propagation. We now know that viral spike protein is primed by the transmembrane protease, serine 2 (TMPRSS2) enzyme, and it binds to the angiotensin-converting enzyme 2 (ACE2) receptor for entry into the host cell. TMPRSS2 and ACE2 blockers have been outlined here as potential strategies to prevent viral entry into cells.

Abstract

Novel 2019 coronavirus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) and coronavirus disease 2019 (COVID-19), the respiratory syndrome it causes, have shaken the world to its core by infecting and claiming the lives of many people since originating in December 2019 in Wuhan, China. World Health Organization and several states have declared a pandemic situation and state of emergency, respectively. As there is no treatment for COVID-19, several research institutes and pharmaceutical companies are racing to find a cure. Advances in computational approaches have allowed the screening of massive antiviral compound libraries to identify those that may potentially work against SARS-CoV-2. Antiviral agents developed in the past to combat other viruses are being repurposed. At the same time, new vaccine candidates are being developed and tested in preclinical/clinical settings. This review provides a detailed overview of select repurposed drugs, their mechanism of action, associated toxicities, and major clinical trials involving these agents.

Keywords: COVID-19, severe acute respiratory syndrome coronavirus 2, remdesivir, hydroxychloroquine, angiotensin-converting enzyme 2, lopinavir

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Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in a seafood market located in Wuhan, China in December 2019 and is the cause of novel coronavirus disease 2019 (COVID-19).[1] Within a short span of 10 months, >106 million people were infected and >2.3 million died due to the virus worldwide.[2] Having descended from bats, SARS-CoV-2 possesses similarities with bat coronaviruses, SARS-CoV, and Middle East respiratory syndrome coronavirus (MERS-CoV), in that order, with possible involvement of a seemingly unknown intermediate host.[3,4]

Early, rapid sequencing of the viral genome allowed the identification of possible drug targets and prompted subsequent efforts to develop potential intervention strategies. According to Clinicaltrials.gov and World Health Organization (WHO) Trial Registry Network, over 3700 clinical trials in total (including interventional and observational studies) are currently ongoing at various hospitals across the world (Figure 1). In this review, we discuss select interventional strategies against COVID-19, mechanism of action/adverse effects of drugs, and relevant clinical trials. Some classes of agents described here include (1) antiviral agents that may improve survival odds for a patient, (2) receptor blockers that may prevent viral entry into the host cell, and (3) corticosteroids that may reduce inflammatory response by the body, thereby lowering the risk of lung injury.[5]

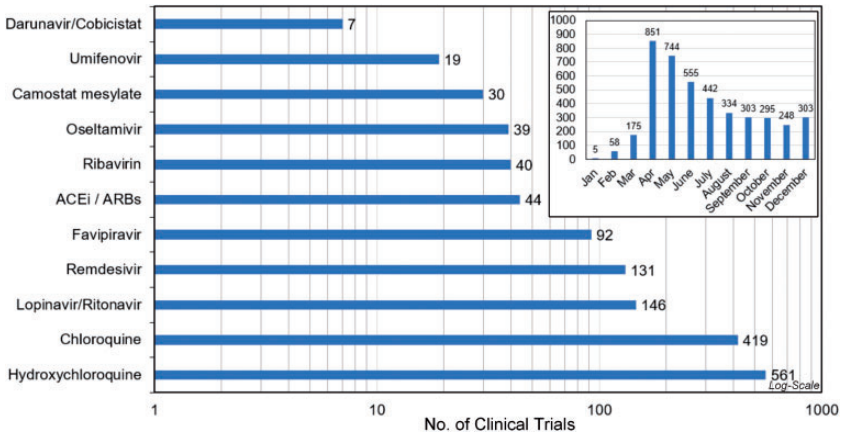

Figure 1. Clinical trials involving pharmacological treatments against COVID-19. Clinical trials posted on clinicaltrials.gov were sorted by month based on the "First posted" date. The logarithmic scale shows the number of ongoing clinical trials for each repurposed drug. (A color version of this figure is available in the online journal.)
ACEi: angiotensin-converting enzyme inhibitor; ARBs: angiotensin II receptor blockers.

Antiviral agents

Remdesivir

Remdesivir interferes with viral RNA replication by serving as a nucleotide monophosphate analog and inhibiting RNA-dependent RNA polymerase (RdRP) activity.[6] Originally developed during the Ebola outbreak, remdesivir (GS-5734) has shown profound activity against RNA viruses such as SARS-CoV and MERS-CoV.[7,8] Upon remdesivir treatment, reduced lung viral titers and lung damage were observed in rhesus macaque and murine models of MERS-CoV.[9,10] Remdesivir became a popular treatment option for viral infection due to its extremely low half-maximal effective concentration (EC_{50}) against Ebola (86 nM; in macrophages),[11] and now against SARS-CoV-2 (0.77 μM; in *in vitro* models).[12,13]

Clinical trials to determine the safety and efficacy of remdesivir in COVID-19 patients have been completed and demonstrated efficacy. The federally funded Adaptive COVID-19 Treatment Trial (ACTT-1) (NCT04280705; Table 1) assessed the potential of remdesivir to reduce the time to recovery in COVID-19 patients.[6] The patients in the treated group were administered a 200-mg loading dose and subsequent daily doses of 100 mg intravenously. After 10 days of following this regime, the time to recovery was found to be 11 days in the treated group as opposed to 15 days in the placebo group.[6] Given the demonstrated efficacy, subsequent trials of antiviral therapies were evaluated on the background of remdesivir treatment.[14] An additional trial (NCT04292899; Table 1) showed 5-day treatment was equivalent to 10-day treatment of remdesivir in hospitalized COVID-19 patients.[15] Other clinical trials tested variable doses of remdesivir (3–225 mg) and reported a half-life of >35 h within the cell, without any evident toxicity.[16] An international study with over 11,000 patients led by the WHO Solidarity Trial Consortium looked to evaluate 4 separate antiviral therapies in hospitalized COVID-19 patients and found no benefit in mortality of any of the treatments in this intention-to-treat trial though it was not well-structured to assess clinical improvement.[17] With the additional review of adverse events observed such as anemia, acute kidney injury, pyrexia, hyperglycemia, and elevated aminotransferase levels, the U.S. Food and Drug Administration (FDA) ultimately issued an emergency use authorization (EUA) for the use of remdesivir in patients over the age of 12 for the treatment of COVID-19 requiring hospitalization on 22 October 2020, becoming the first therapy approved for the treatment of COVID-19.

Chloroquine/hydroxychloroquine

For decades, chloroquine (CQ) and hydroxychloroquine (HCQ) were used to treat diseases like rheumatoid arthritis, malaria, and systemic lupus erythematosus (SLE).[18] Although these relatively inexpensive agents are known to play a role in the reduction of proinflammatory cytokine secretion, endosomal acidification, preventing glycosylation and binding of angiotensin-converting enzyme 2 (ACE2) to the viral spike protein, and autophagy inhibition in host cells,[19,20] they did not have much success against SARS-CoV and MERS-CoV. Interestingly, CQ was found to be effective against other viruses such as Zika, human immunodeficiency virus (HIV), dengue virus (DENV), West Nile virus (WNV) infection, influenza virus, and Japanese encephalitis virus (JEV), due to its ability to inhibit pH-dependent steps in the viral replication cycle.[21–24]

There is a paucity of data pertaining to the benefit of CQ for impacting SARS-CoV-2 infection. A few studies have observed growth inhibition of SARS-CoV-2 in response to CQ.[13,25] A study conducted in China suggested improved viral clearance and slower disease progression when COVID-19 patients were treated with CQ.[26] HCQ showed better *in vitro* antiviral activity against SARS-CoV-2 than CQ at 24 h, as evidenced by lower EC_{50} values for HCQ.[25] Enhanced virologic clearance was reported in COVID-19 patients (70%) on the sixth day when they were administered a 200-mg dose of HCQ orally thrice a day compared to those in the control group (12.5%). Combinatorial therapy with azithromycin imparted additional benefit (100%) compared to that observed with monotherapy (57%).[27] These studies however had a small starting sample size ($n = 36$) that became even smaller due to a halt in the

Table 1. Overview of select COVID-19 treatments in clinical development.

Class	Intervention	Mechanism of action	Clinical trial identifier[a]
Antiviral agents	Remdesivir	RNA-dependent RNA polymerase inhibitor	NCT04431453, NCT04409262, NCT04280705
	Chloroquine/ hydroxychloroquine	Viral entry blockade by preventing host cell surface receptor glycosylation, reduction of cytokine secretion, endosomal acidification, autophagy inhibition	NCT04308668, NCT04303507, ChiCTR2000031174
	Lopinavir/Ritonavir	Aspartic protease inhibitor	ChiCTR2000031196, NCT04350684
	Ribavirin	RNA-dependent RNA polymerase inhibitor	NCT04254874, ChiCTR2000029308
	Umifenovir	Prevents membrane fusion by disrupting interaction between viral spike protein and ACE2 receptor	NCT04260594, NCT04254874, ChiCTR2000029993
	Darunavir/Cobicistat	Aspartic protease inhibitor	NCT04252274, ChiCTR2000029541
	Favipiravir	RNA-dependent RNA polymerase inhibitor	NCT04359615, ChiCTR2000030254
	Oseltamivir	Neuraminidase inhibitor	NCT04261270, ChiCTR2000029603
Enzyme inhibitors/ receptor blockers	Camostat mesylate	Viral entry blockade via TMPRSS2 inhibition	NCT04353284, NCT04355052
	ACEi/ARBs	Elevation of ACE2 expression	NCT04351581, NCT04357535, NCT01597635, NCT04382950

RNA: ribonucleic acid; ACE2: angiotensin-converting enzyme 2; TMPRSS2: transmembrane protease, serine 2; ACEi: angiotensin-converting enzyme inhibitor; ARBs: angiotensin II receptor blockers.
[a]clinicaltrials.gov/chictr.org.cn.

treatment of some patients (6) experiencing adverse events, lack of safety outcomes, disparities in basal viral loads among treatment arms, and toxicities associated with combination therapies, making it difficult to make significant conclusions of efficacy. On the contrary, a similar study showed no change in viral clearance when a double dose (400 mg) of HCQ was administered daily to patients in the treatment group, while the control group received standard of care.[28] A clinical trial (NCT04308668; Table 1) assessing the postexposure prophylactic potential of HCQ revealed no difference in the incidence of COVID-19 between the group of people exposed to a known case of COVID-19 and treated with HCQ, and those receiving placebo.[29] A large randomized controlled trial evaluating HCQ with and without azithromycin in hospitalized COVID-19 patients[30] found no improvement in an ordinal scale with HCQ or HCQ with azithromycin, while in the RECOVERY trial, HCQ was found to have no impact on mortality or rate of mechanical ventilation.[31]

SLE and malaria patients can display adverse events such as retinopathy, QTc prolongation, neuropsychiatric effects, and hypoglycemia, upon administration of CQ/HCQ and require monitoring of these adverse events while on CQ/HCQ.[32] Patients taking QT-interval prolonging medications and severely ill patients are particularly prone to arrhythmia when treated with CQ/HCQ, generating potential concern for harm with CQ/HCQ treatment.[33]

FDA issued an EUA for CQ/HCQ based on a few studies showing that the drugs improve viral clearance and decrease viral shedding. This EUA has since been revoked because the above findings could not be reproduced in randomized controlled trials.[34]

Lopinavir/ritonavir

Originally developed to fight HIV, FDA-approved lopinavir/ritonavir combination is a potent inhibitor of aspartic proteases key to viral propagation, thereby resulting in the production of non-functional and immature virions.[35] The two drugs are complementary to each other in that ritonavir inhibits an enzyme called cytochrome P450 3A4 (CYP3A4), which is involved in the lopinavir metabolism in the liver.[36] Lopinavir/ritonavir is primarily excreted via feces with minimal urinary excretion. While lopinavir rarely crosses the placenta, ritonavir can increase the incidence of placental transfer. Studies have reported developmental defects in fetuses upon treatment of pregnant rats with high doses of these drugs.[37] Currently, there is a dearth of adequate data relating to the use of lopinavir/ritonavir in pregnant women, and therefore, the drugs should only be administered in light of significant benefit compared to risks.

A limited amount of *in vitro* data suggests that lopinavir possesses antiviral activity against SARS-CoV, MERS-CoV, human coronavirus hCoV-229E,[38] and SARS-CoV-2.[39] Most clinical studies conducted at the time were either observational or retrospective and, therefore, inconclusive. Molecular docking analyses involving lopinavir/ritonavir revealed that these drugs can strongly bind to SARS-CoV-2 protease.[40] However, a previous study using lopinavir/ritonavir failed to demonstrate satisfactory outcomes for severe COVID-19 patients. Patients were administered 400 and 100 mg of lopinavir and ritonavir, respectively, two times a day over the course of 14 days. No difference was observed in the incidence of death, time to improvement, or the viral clearance in the group receiving lopinavir/ritonavir plus standard care compared to that receiving standard care alone.[41] Combination of lopinavir–ritonavir with interferon beta-1b has shown benefit in a small, randomized control trial for MERS.[42] The WHO Solidarity trial found no improvement in mortality for COVID-19 patients treated with lopinavir/ritonavir.[17] Drug delivery during an earlier stage of the viral life cycle may be necessary since studies involving delayed treatment showed no improvement in clinically significant outcomes.[43,44] Adverse reactions have been reported by many studies[41,45,46] and

include gastrointestinal discomfort, skin eruptions, QT prolongation, liver injury as well as pancreatitis.

Darunavir and cobicistat

Like lopinavir/ritonavir, the darunavir/cobicistat combination belongs to the class of protease inhibitors and is known to have lesser adverse reactions compared to the former.[47] Being a structural analog of ritonavir, cobicistat has a similar mechanism of action to ritonavir in that it also inhibits CYP3A, CYP2D6, p-glycoprotein, and drug transporters such as organic anion transport protein (OATP1B1) and OATP1B3.[47] While cobicistat has not shown an antiviral effect *in vitro*, darunavir worked well against SARS-CoV-2. However, clinically relevant data are currently unavailable.

A randomized Phase III clinical trial is currently ongoing to compare the efficacy of darunavir/cobicistat plus standard of care with the standard of care alone (NCT04252274; Table 1). Various outcomes including the rate of viral clearance on the seventh day and critical illness as well as mortality rate at two weeks are recorded. Another randomized controlled trial evaluating the safety and efficacy of darunavir/cobicistat with the standard of care consisting of thymosin α1 in adults is underway in Wuhan (ChiCTR2000029541; Table 1). Outcomes such as mortality, length of stay in the hospital/ICU, improvement of disease symptoms and lung CT findings, etc. will be evaluated. Some commonly observed adverse effects include nausea, diarrhea, headache, and muscle spasms.[47]

Favipiravir

Similar to remdesivir, favipiravir (T-705) inhibits the activity of RdRP, a pivotal enzyme in the viral replication process, by acting as a guanine analog.[48] Favipiravir has shown activity against RNA viruses such as influenza, Ebola, Lassa, rabies,[48,49] and more recently, SARS-CoV-2 at the preclinical level, although dosing regimens need to be adjusted depending upon the type of infection.[13] The drug has been licensed to treat influenza in several countries including Japan.

Lower concentrations of favipiravir have been reported to inhibit influenza, while higher doses are needed to treat COVID-19 and Ebola.[50] A loading dose of 2400–3000 mg twice a day and a subsequent dose of 1200–1800 mg twice a day have been suggested for administration. Pharmacokinetic values for the half-life period lie between 4.8 and 5.6 h.[49] Incidence and severity of adverse reactions (such as nausea, vomiting, uric acid elevation in serum) are much lower in favipiravir-treated patients than those treated with lopinavir/ritonavir.[51] Randomized controlled trials are underway to determine the potential of favipiravir to effectively treat COVID-19, in combination with other drugs such as HCQ (NCT04359615; Table 1). The efficacy of favipiravir, when administered with umifenovir, was determined in a clinical trial (ChiCTR2000030254; Table 1). No significant differences were found in the rate of clinical recovery in the two groups on day 7. While the latency was shortened for pyrexia and cough, there was no difference in the rate of oxygen therapy or mechanical ventilation.[52] These data support further investigation with RCTs of the efficacy of favipiravir for the treatment of COVID-19. Of late, Glenmark Pharmaceuticals has launched a Phase III clinical trial to test the efficacy of favipiravir in treating COVID-19 patients. The results of the trial are highly anticipated by August 2020.

Ribavirin

Ribavirin interferes with viral replication by inhibiting the RdRP enzyme. While commonly used for treating hepatitis C, ribavirin has shown a reduction in the mortality rate when administered in combination with lopinavir/ritonavir and a corticosteroid to SARS-CoV patients suffering from acute respiratory distress syndrome (ARDS) but only at high doses (e.g. 1200–2400 mg thrice a day orally).[53] Although a similar combination involving ribavirin, lopinavir/ritonavir, and an interferon-α did not prove effective against MERS-CoV,[54,55] reduction in blood viral titers was observed.[56] No differences in antiviral activity were observed with various routes of drug administration.[57] Ribavirin has demonstrated the inhibition of viral replication in SARS-CoV-2 *in vitro* models established by the Bojkova group.[58] The study revealed the ability of the virus to reprogram key intracellular pathways and opened new avenues in terms of identifying small molecule inhibitors targeting these pathways, thereby inhibiting viral replication.[58] Multiple clinical trials to evaluate the efficacy of ribavirin and interferon-α in COVID-19 patients are underway (NCT04254874, ChiCTR2000029308; Table 1).

Ribavirin administration at high doses was associated with adverse reactions such as hemolytic anemia, transaminase elevations as well as liver toxicity[59] and safety issues such as the need for blood transfusions.[60] Ribavirin is not recommended for use in pregnant women as it is known to cause birth defects.[61]

Umifenovir

Umifenovir or arbidol hydrochloride disrupts the interaction between viral spike protein and the ACE2 receptor, thereby preventing the process of membrane fusion.[62] Originally developed in Russia, umifenovir has shown efficacy in the prevention and cure of influenza.[63] Additionally, the antiviral agent has demonstrated activity against a range of viruses, including Zika, WNV, adenovirus, hepatitis B, hantavirus, and respiratory syncytial virus.[64] Preclinical data demonstrated inhibition of SARS-CoV reproduction in cultured cells in response to arbidol and ribavirin.[65]

The recommended dosing regimen for influenza consists of oral administration of 200 mg arbidol three times a day. This regimen is currently being tested in combination with conventional treatment in a clinical trial involving ~380 COVID-19 patients (NCT04260594; Table 1). Evidence also suggests that a nine-day arbidol treatment reduces mortality and increases discharge rates in COVID-19 patients in Wuhan, China compared to the control group.[66] Umifenovir is currently under investigation to determine its potential as a monotherapy or combination

therapy candidate (NCT04254874, ChiCTR2000029993; Table 1).

Oseltamivir

Oseltamivir inhibits neuraminidase, a crucial enzyme facilitating the release of newly formed virions via the removal of sialic acid residues holding the viral particles on the host cell surface.[67] It has shown broad activity against various strains of influenza.[68,69] If administered early following the onset of symptoms, oseltamivir can reduce the overall duration and severity of the disease. Oseltamivir should be converted to its carboxylate form to be active.[70]

While oseltamivir has not shown antiviral activity *in vitro*, multiple clinical trials are evaluating its efficacy in combination with other agents such as favipiravir, ritonavir, CQ, and ASC09F (NCT04261270, ChiCTR2000029603; Table 1). Patient comorbidities and contraindications should be considered while deciding the optimal dosing regimen. There is an indication that oseltamivir may prove useful as a COVID-19 treatment due to its ability to bind to viral protease.[40] Oseltamivir-associated adverse reactions include nausea, vomiting, skin reactions, neuropsychiatric effects in children,[71] and sometimes even death.[72]

Enzyme inhibitors/receptor blockers

Camostat mesylate

Camostat mesylate, a serine protease inhibitor commonly prescribed for pancreatitis in Japan and South Korea, has previously been shown to prevent the viral spread mediated by a serine protease in a mouse model of SARS-CoV infection and may potentially have a similar role in MERS-CoV pathogenesis.[73] More recently, it was demonstrated that the transmembrane protease, serine 2 (TMPRSS2) is involved in SARS-CoV-2 spike protein priming.[74] They also reported the blockade of the SARS-CoV-2 entry into the lung cells by camostat mesylate via TMPRSS2 inhibition.[74] Camostat mesylate (600 mg total, thrice a day) may reduce the severity of COVID-19 in patients.[75] The drug is safe for oral administration. Adverse effects associated with camostat mesylate include lightheadedness, pruritus, and increased appetite/thirst.[76] Multiple clinical trials are ongoing to determine the efficacy with which camostat mesylate reduces the viral burden in the upper respiratory tract in COVID-19 patients as a monotherapy (NCT04353284; Table 1).

ACE inhibitors, angiotensin II receptor blockers, and recombinant ACE2

SARS-CoV-2 infects the host cell upon binding of viral spike protein to ACE2.[74] Binding and internalization of viral-ACE2 complex lead to increased ACE2 cleavage from cell membrane. Decreased ACE2 causes an increase in angiotensin II by ACE and a lower rate of conversion of angiotensin II (vasoconstrictor, proinflammatory, profibrotic) and a decrease in angiotensin$_{1-7}$ (vasodilator, anti-inflammatory, antifibrotic) exacerbating lung injury.[77] *In vivo* studies in mice have shown ACE2 to be protective in acid-induced lung injury.[78] ACE inhibitors (ACEi) and angiotensin II receptor blockers (ARBs), medications to treat hypertension, have been shown to elevate ACE2 expression[79,80] and could be protective in SARS-CoV-2 infection. However, ACE2 may act as a double-edged sword as the increased ACE2 expression could increase viral entry into the host cells.

A multitude of retrospective studies has looked at the impact of ACEi/ARBs on the risk of SARS-CoV-2 infection, COVID-19 disease severity, and COVID-19 mortality, the overwhelming majority finding no effect of ACEi/ARB use. Two recent randomized controlled trials looked at continued or switching ACEi/ARB use upon hospitalization with COVID-19 and found no impact on hospitalization outcomes.[81,82] Adverse events associated with ACEi/ARBs include cough, angioedema, hypotension, hyperkalemia, and acute kidney injury.[83]

Recombinant ACE2 (rACE2) therapy has previously shown promise in reducing angiotensin II and IL-6 levels in ARDS patients.[84] The absence of antibodies and adverse events was reported following the intravenous administration of the protein (NCT01597635; Table 1). The effect of similar therapy in COVID-19 patients remains to be seen though a case report suggested the potential benefit of the use of rACE2 with improvement in outcome and decrease in inflammatory cytokines and viral load in association rACE2.[85] However, clinical trials are ongoing to evaluate the potential of rACE2 therapy (NCT04382950; Table 1) in COVID-19 outcomes.

Corticosteroids

Corticosteroids such as methylprednisolone, hydrocortisone, and dexamethasone are being used to treat COVID-19 due to their role as immunosuppressants. Historically, the role of corticosteroids has been debated. Observational studies conducted to determine their efficacy in treating viral infections indicate the association between deregulated viral clearance and complications in SARS-CoV and MERS-CoV, and higher secondary infection rates as well as mortality in influenza.[86] More recently, a COVID-19 study from Wuhan showed reduced mortality risk with methylprednisolone in patients with ARDS. Similarly, dexamethasone reduced mortality with a 6-mg dose administered for 10 days in COVID-19 patients on oxygen support, while no mortality benefit was observed in those who did not need it.[87] Hydrocortisone showed a similar mortality benefit.[88] Corticosteroid treatment is usually accompanied by adverse reactions such as psychosis and muscle weakness. In addition, steroids are prothrombotic, as evidenced by the autopsy of COVID-19 patients.[87] Their use at higher doses (>6 mg/day) and for longer than two weeks should be carefully weighed, as it could lead to increased mortality.[88]

Conclusions

COVID-19 pandemic has led to several challenges across the world. It has challenged the scientific community to understand the pathogenesis of SARS-CoV-2 to inform

potential therapeutic targets. It has challenged the medical community to characterize COVID-19 illness and mechanisms of disease to suggest hopeful therapeutic approaches. The ability of the scientific and medical communities to come together to build upon previous knowledge and apply it to the current pandemic has allowed for rapid evaluation of a number of developed medications. In some cases, this has brought promise (remdesivir), while in others, it allowed us to discount previously hopeful therapies (HCQ/CQ). Currently, remdesivir remains the only antiviral compound approved by FDA and can be combined with baricitinib to treat hospitalized COVID-19 patients, both adults and $\geq$ 2-year-old children. Despite the development of efficacious vaccines, repurposed therapeutics to improve outcomes in COVID-19 remain important, given ongoing challenges with the vaccine distribution.

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MPJ, AV, and ABP contributed to the conception, writing, and discussion of this review manuscript. MPJ, AV, and ABP wrote the initial draft of the manuscript. The final version of the manuscript was approved by all authors.

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SUPPLEMENTAL MATERIAL

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