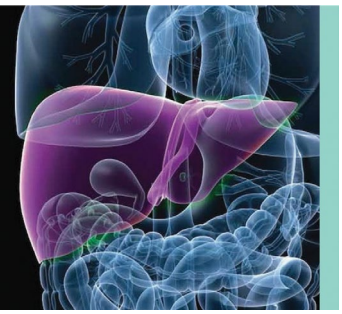

Potential Treatments for SARS-CoV-2 Infection

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Currently, there are no established treatments for severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) infection that causes coronavirus infectious disease 2019 (COVID-19). However, remdesivir was recently granted Emergency Use Authorization for treatment of severe disease by the US Food and Drug Administration (FDA) pending completion of ongoing studies. In addition, a number of repurposed drugs, as well as novel agents, are under investigation (see https://clinicaltrials.gov/ct2/results?cond=COVID-19).

SARS-COV-2 VIRUS

SARS-CoV-2 is a single-stranded, enveloped RNA virus that shares 80% genome homology with the severe acute respiratory syndrome (SARS; CoV-1) virus. The majority of deaths from COVID-19 are due to severe pneumonia with multiorgan failure that develops more frequently in the elderly and those with medical comorbidities.[1] SARS-CoV-2, like other coronaviruses, infects the epithelium of the nasopharynx and lung, and is highly transmissible from person to person via respiratory droplets and secretions. *In vitro* studies demonstrate that SARS-CoV-2 infects human tissues by binding of the Spike glycoprotein to the angiotensin-converting enzyme type 2 (ACE2) receptor (Fig. 1). The ACE2 receptor is highly expressed in the vascular endothelium and tissues of the lung, heart, kidney, and small intestine. ACE2 is also expressed to a greater extent in cholangiocytes versus hepatocytes.[2]

COVID-19 has variable clinical manifestations ranging from asymptomatic acute infection to a mild-to-moderate flu-like illness. However, a substantial minority (5%-10%) of patients go on to acquire severe infection with systemic symptoms of myalgias, pneumonia, and weakness. Hospitalized subjects with SARS-CoV-2 are considered to have mild-to-moderate disease, whereas those

Abbreviations: ACE-2, angiotensin-converting enzyme type 2; ALT, alanine aminotransferase; ARB, angiotensin receptor blocker; ARDS, acute respiratory distress syndrome; AST, aspartate aminotransferase; AZT, azithromycin; COVID-19, coronavirus infectious disease 2019; CQ, chloroquine; CRP, C-reactive protein; DDI, drug-drug interaction; FDA, US Food and Drug Administration; GFR, glomerular filtration rate; HBV, hepatitis B virus; HCQ, hydroxychloroquine; ICU, intensive care unit; IL-6, interleukin-6; IV, intravenous; LOS, length of stay; NIH, National Institutes of Health; NSAID, nonsteroidal anti-inflammatory drug; RCT, randomized controlled trial; SARS, severe acute respiratory syndrome; SARS-CoV-2, severe acute respiratory syndrome coronavirus type 2; SC, subcutaneous; ULN, upper limit of normal.

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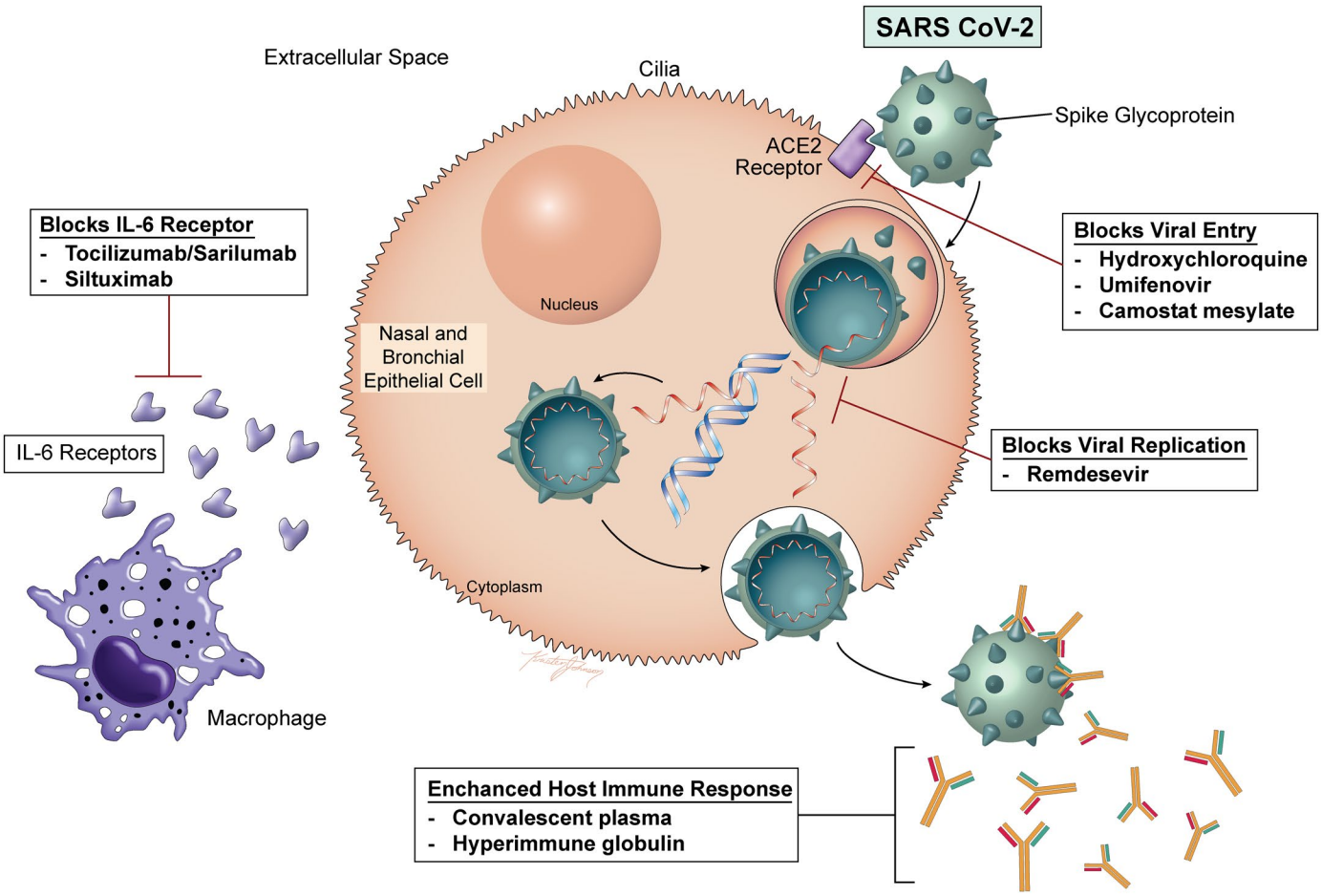

FIG 1 Molecular targets of potential SARS-CoV-2 treatments. The spike structural protein of SARS-CoV-2 binds to the ACE2 receptor. Once inside the cell, viral proteins are synthesized and intracellular RNA is amplified via an RNA-dependent RNA polymerase. ACE inhibitors and ARBs, as well as HCQ, umifenovir, and camostat, may reduce viral particle entry and uptake by endosomes. Remdesivir, a potent nucleotide analogue, is believed to act as an intracellular chain terminator. After exocytosis from the infected cell, the host immune response is activated and characterized by high levels of IL-6, IL-1, and tumor necrosis factor. Drugs such as tocilizumab that block the IL-6 signaling pathway can dampen the overly exuberant host immune response. Convalescent plasma may work by binding to SARS-CoV-2 viral particles or helping clear infected cells.

who require supplemental oxygen, pressors, or intensive care unit (ICU) care are considered to have severe disease. Progression to acute respiratory distress syndrome (ARDS) is believed to be mediated, in part, by an overly exuberant host immune response (i.e., high serum ferritin, C-reactive protein [CRP], interleukin-6 [IL-6] levels) and may also be exacerbated by endothelitis from viral infection of the vascular endothelium.

Elevated serum aminotransferase levels are noted in 20% to 40% of patients with SARS-CoV-2 and are associated with increased mortality.[3] In addition, patients with preexisting liver disease, particularly cirrhosis, have a higher rate of hospitalization and mortality when compared with comorbidity-matched control subjects.[4] However, clinical jaundice is uncommon and is believed to be caused by cholestasis of sepsis in ICU patients rather than direct effects of the virus or by idiosyncratic drug toxicity in most cases.

ANTIVIRALS

Ongoing studies are attempting to prevent primary infection in health care workers and other individuals at high risk, as well as treat hospitalized patients with moderate-to-severe COVID-19 (Table 1). Study designs include randomized controlled trials (RCTs) and adaptive designs with varying primary endpoints that include infection rates, time to illness recovery, length of stay

TABLE 1. SELECTED TREATMENTS FOR SARS-COV-2

Agent (Route/Mechanism)	Target Population (Study Endpoint)	Efficacy Data	Safety Issues
Antiviral agents			
Remdesivir (IV/nucleotide analogue)	Mild to severe (time to improvement)	*In vitro* and animal models Cohort study showed clinical improvement and reduced mortality NIH RCT: 31% faster recovery, reduced mortality China RCT: no benefit Emergency Use Authorization granted by FDA as additional studies are awaited	Well tolerated in Ebola Few DDIs anticipated 20%-30% reversible AST/ALT elevations Nausea/vomiting, rash *Contraindicated:* GFR < 30 mL/min AST/ALT > 5× ULN
HCQ (+/– AZT) (oral/host proteins)	Mild to severe (hospital LOS) (symptom duration)	Three RCTs with mixed results regarding clinical improvement, radiological findings, and viral clearance Largest RCT (n = 150): improved CRP/leukopenia, higher adverse events in HQC arm, no difference in viral clearance by PCR NIH and FDA recommend only in carefully monitored setting	Nausea/vomiting Hypoglycemia QT prolongation (↑ with AZT) Safer than CQ *Contraindicated:* QT > 500 ms Cardiomyopathy Glucose-6-phosphate dehydrogenase deficiency Pregnancy/breast-feeding
CQ (+/– AZT) (oral/host proteins)	Mild to moderate (hospital LOS) (symptom duration)	RCT (n = 81) of high-versus low-dose CQ: stopped early due to higher mortality in high-dose CQ group (all received AZT); no difference in viral clearance Weaker *in vitro* effects versus HCQ	Same as above Higher risk for QT prolongation, DDIs, toxicities
Immunomodulators			
Tocilizumab (IV/monoclonal IL-6 receptor antagonist)	Severe respiratory failure +/– ↑ IL-6 (% requiring mechanical ventilation/FiO_2/ mortality) (pulmonary function)	RCT ongoing One uncontrolled study (n = 21) showed clinical improvement and reduced LOS	Single versus repeated dosing Opportunistic infections
Sarilumab (Kevzara) (SC/monoclonal anti-IL-6 antibody)		Preliminary data showed no benefit versus placebo RCT ongoing	HBV reactivation
Siltuximab (IV/monoclonal anti-IL-6 antibody)		RCT ongoing	1%-5% cytopenias 20%-40% AST/ ALT elevation ALF (rare) *Contraindicated:* Absolute neutrophil count < 2,000 Platelets < 100,000 ALT > 5× ULN
Convalescent plasma (IV)	Severe respiratory failure (safety, feasibility, mortality, clinical improvement)	Data from salvage therapy in SARS/MERS showed clinical improvement Chinese case series (n = 15) showed reduced mortality and no adverse events	Transfusion reactions (transfusion-related acute lung injury, anaphylaxis) Donor-related infections Hypervolemia Impaired host antibody response

(LOS), and mortality. Serial quantitative SARS-CoV-2 RNA levels from secretions may prove to be a useful prognostic and/or efficacy biomarker, but further studies using standardized preprocedural sample acquisition and analytical methods are needed.

Remdesivir

Remdesivir is an intravenously (IV) administered nucleotide analogue with broad activity against many RNA viruses. *In vitro* and animal studies have demonstrated potent antiviral efficacy against SARS-CoV-2 as a chain terminator (Fig. 1). The drug is typically given as a loading dose followed by 7 to 10 days of daily infusions. Remdesivir is largely eliminated by the kidney and contraindicated if glomerular filtration rate (GFR) is < 30 mL/min due to potential vehicle accumulation.[5]

A compassionate use study of remdesivir demonstrated that 36 of 53 inpatients (68%) had an objective improvement in their oxygenation status, and 57% of the intubated patients were successfully extubated during a median follow-up of 18 days.[6] The most common adverse events were serum aminotransferase elevations (23%), diarrhea (9%), and rash (4%). Currently, the National Institutes of Health (NIH) is conducting an adaptive, double-blind RCT of remdesivir versus placebo for 10 days in 1037 patients with a primary efficacy endpoint of time to recovery defined as hospital discharge or no longer requiring supplemental oxygen. Preliminary interim results show that patients who received remdesivir had a 31% faster recovery time than placebo (11 versus 16 days; $P < 0.001$) and a potential mortality benefit (8% versus 11.6%; $P = 0.059$). However, another study of 237 Chinese patients demonstrated no improvement in time to recovery (21 versus 23 days) or 28-day mortality (14% versus 13%).[7] Furthermore, the rate of viral load decline was similar in both groups, but the incidence rate of aminotransferase elevations was numerically lower in the remdesivir group (5% versus 12%). An ongoing open-label RCT of various remdesivir dosing regimens in 6000 patients with severe disease is eagerly awaited.[8]

Hydroxychloroquine/Chloroquine

Hydroxychloroquine (HCQ) is an orally administered antimalaria drug with immunomodulatory properties that has a better safety profile than chloroquine (CQ). Based on *in vitro* studies, HCQ may interfere with endosomal uptake and processing of SARS-CoV-2 (Fig. 1). Three small RCTs involving 30, 62, and 22 patients had mixed results with regard to viral clearance and clinical and/or radiological improvements.[9] Since then, another open-label RCT of 150 Chinese patients with mild-to-moderate disease that used higher doses of HCQ demonstrated no difference in viral clearance or improvement in CRP, but adverse events were more common in the HCQ arm (30% versus 9%).[10] Other studies are exploring HCQ/CQ with azithromycin (AZT), but there are increasing reports of potential cardiac toxicity, including QT prolongation.[11,12] It is currently recommended that this combination of drugs not be administered outside of a carefully monitored clinical trial setting.[13]

OTHER ANTIVIRAL AGENTS

Other approved drugs being tested include favipiravir and umifenovir with efficacy in influenzae; nitazoxanide, which is approved for cryptosporidium; and camostat, which is used for pancreatitis in Japan.[1] The human immunodeficiency virus protease inhibitor, lopinavir-ritonavir, had no demonstrable efficacy in a large RCT and is currently not recommended.[14]

IMMUNOMODULATORS

The pathophysiology of severe disease and multiorgan failure in COVID-19 is believed to result from a dysregulated immune response, or cytokine storm. Numerous immunomodulators are under investigation for patients with severe, life-threatening disease, but available data indicate no demonstrable benefit from corticosteroids.[15] As a result, initiation of high-dose corticosteroids is not recommended for hospitalized patients with COVID-19 without ARDS.[15]

IL-6 Blockade

Tocilizumab, sarilumab, and siltuximab are parenterally administered monoclonal antibodies that target the IL-6 signaling pathway. Uncontrolled data with these agents have shown promising results with rapid clinical improvement and decreased LOS.[16] However, a preliminary report showed no benefit in an RCT of sarilumab versus placebo.[17] Known side effects of these agents include an increased risk for opportunistic infection, hepatitis B virus (HBV) reactivation, cytopenias, and elevated aminotransferase levels in 20% to 40% of treated patients, including rare instances of acute liver failure.

Convalescent Plasma

Antibodies from patients who have recovered from COVID-19 may help improve free viral clearance and infected host cell clearance (Fig. 1). Convalescent plasma was used as salvage therapy in other coronavirus outbreaks, including SARS and Middle East Respiratory Syndrome (MERS), with a reduction in mortality and minimal adverse events in observational studies.[18] Small case series demonstrate reduced mortality in patients with COVID-19, but the optimal donor, volume, and frequency of plasma administration are unknown.[19] In addition, vaccines derived from the SARS-CoV-2 spike glycoprotein and/or nucleoproteins are under development to prevent primary infection, but these studies will likely take 12 months or more to complete.

CONCOMITANT MEDICATIONS

Chronic nonsteroidal anti-inflammatory drug (NSAID) use can lead to up-regulation of ACE2 receptors, which has raised concerns regarding more severe SARS-CoV-2 infection (Table 2). Although there is no causal evidence showing adverse outcomes in patients with COVID-19 receiving NSAIDs, the World Health Organization and FDA do not recommend for or against the use of NSAIDs until further studies are completed.[15] Acetaminophen is an effective analgesic that can be safely used in patients with COVID-19 as long as the total dose does not exceed 2 to 3 g/day.

ACE Inhibitors

These antihypertensive medications are used by many older adults with underlying hypertension and diabetes mellitus who are at greater risk for adverse outcomes with COVID-19. There are mixed reports whether these drugs may increase the expression of the ACE2 receptor or whether angiotensin receptor blockers (ARBs) may block viral entry. Current recommendations are to continue these drugs in patients with a medical indication while therapeutic clinical trials of ARBs are being undertaken.[15,20]

TABLE 2. COMMONLY USED MEDICATIONS IN PATIENTS WITH SARS-COV-2 INFECTION

Concomitant Drug	Safety Issues
Acetaminophen	Preferred analgesic for fevers and myalgias 2 to 3 grams maximal dose per day
NSAID	ACE2 receptor upregulation Concern for new onset or worsening kidney injury
ACE inhibitor/ARB	Theoretically may block viral entry Recommend continuation in patients with diabetes or hypertension No role at this time to start for antiviral effects
Heparin	Many patients have elevated D-dimer levels and may be hypercoagulable with endothelitis SQ Heparin for deep vein thrombosis prophylaxis is recommended for hospitalized patients Role of therapeutic anticoagulation not established

SUMMARY

A number of promising antiviral, immunomodulatory, and biological approaches are being tested in patients with SARS-CoV-2 infection. Individuals with preexisting liver disease and transplant recipients appear to be at increased risk for poor outcomes. Mild serum aminotransferase elevations are frequently seen in hospitalized patients and are associated with poorer outcomes. The completion of ongoing studies to improve the diagnosis, prognosis, and treatment of afflicted patients, as well as primary prevention studies using novel vaccines, is eagerly awaited.

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