Potential Treatments for SARS CoV-2 infection

Sameer K. Berry, MD, Robert J. Fontana, MD

Division of Gastroenterology and Hepatology, University of Michigan Medical School, Ann Arbor, MI

Corresponding author:

Robert J. Fontana

Professor of Medicine

3912 Taubman Center

Ann Arbor, MI 48109

Tel: 734-936-4780

Fax: 734-936-7392

Email

rfontana@med.umich.edu

sameber@med.umich.edu

Abbreviations

ACE-2	Angiotensin-converting enzyme 2
ALT	Alanine aminotransferase
ARB	Angiotensin receptor blockers
CoVID-19	Coronavirus Infectious Disease 2019
CQ	Chloroquine
CRP	C-reactive protein
GFR	Glomerular filtration rate
HCQ	Hydroxychloroquine
NSAID	Non-steroidal anti-inflammatory drug

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/CLD.969

IL-6	Interleukin-6
RCT	Randomized controlled trial
SARS-CoV2	Severe acute respiratory Syndrome Coronavirus-2

Word count = 1,420

Introduction:

Currently there are no established treatments for Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-Co-V2) infection that causes Coronavirus Infectious Disease 2019 (COVID-19). However, remdesivir was recently granted emergency use approval for treatment of severe disease by the FDA pending completion of ongoing studies. In addition, a number of repurposed drugs as well as novel agents are under investigation (seehttps://clinicaltrials.gov/ct2/results?cond=COVID-19).

The SARS-CoV-2 virus

SARS-CoV-2 is a single stranded, enveloped RNA virus that shares 80% genome homology to the 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 co-morbidities (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 **(Figure 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 to 10%) go on to develop severe infection with systemic symptoms of myalgias, pneumonia, and weakness. Hospitalized subjects with SARS CoV-2 are considered to have mild/moderate disease while those requiring supplemental oxygen, pressors or ICU care are considered to have severe disease. Progression to 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 20-40% of SARS CoV-2 patients and associated with increased mortality (3). In addition, patients with pre-existing liver disease and particularly cirrhosis have a higher rate of hospitalization and mortality when compared to co-morbidity matched controls (4). However, clinical jaundice is uncommon and believed to be due to cholestasis of sepsis in ICU patients rather than direct effects of the virus or from idiosyncratic drug toxicity in most cases.

Antivirals

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

Remdesivir

Remdesivir is an intravenously 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 (**Figure 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) < 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 NIH is conducting an adaptive, double-blind, RCT of remdesivir vs. 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 vs. 16 days, p<0.001) and a potential mortality benefit (8% vs. 11.6% p=0.059). However, another study of 237 Chinese patients demonstrated no improvement in time to recovery (21 vs 23 days) nor 28-day mortality (14% vs 13%) (7). Furthermore, the rate of viral load decline was similar in both groups but the incidence of aminotransferase elevations was numerically lower in the remdisivir group (5% vs 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 anti-malaria 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 **(Figure 1**). Three small RCTs involving 30, 62, and 22 patients had mixed results with regards to viral clearance and clinical/radiological improvements (9). Since then, another open-label RCT of 150 Chinese patients with mild/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% vs. 9%) (10). Other studies are exploring HCQ/CQ with azithromycin (AZT) but there are increasing reports of potential cardiac toxicity including Q-T 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 favipravir and umifenovir with efficacy in influenzae, nitazoxanide which is approved for cryptosporidium, and camestata which is used for pancreatitis in Japan (1). The HIV 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 indicates no demonstrable benefit from corticosteroids (15). As a result, initiation of high dose corticosteroids is not recommended for hospitalized COVID-19 patients 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 length-of-stay (16). However, a preliminary report showed no benefit in an RCT of sarilumab vs placebo (17). Known side effects of these agents include an increased risk of opportunistic infection, 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 (**Figure 1**). Convalescent plasma was used as salvage therapy in other coronavirus outbreaks including SARS and MERS with a reduction in mortality and minimal adverse events in observational studies (18). Small case series demonstrate reduced mortality in COVID-19 patients 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 non-steroidal anti-inflammatory drug (NSAID) use can lead to upregulation of ACE2 receptors which has raised concerns regarding more severe SARS Co-V2 infection (**Table 2**). Although, there is no causal evidence showing adverse outcomes in COVID-19 patients receiving NSAIDs, the WHO 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 COVID-19 patients as long as the total dose does not exceed 2 to 3 grams per day.

ACE inhibitors

These antihypertensive medications are used by many older individuals with underlying hypertension and diabetes mellitus who are at greater risk for adverse outcomes with COVID-19. There are mixed reports as to whether these drugs may increase 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 ARB's are being undertaken (15, 20).

Summary

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

References

1. Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19): A Review. JAMA - Journal of the American Medical Association. 2020 published online April 13; 2020;
2. Zhang C, Shi L, Wang FS. Liver injury in COVID-19: management and challenges. The Lancet Gastroenterology and Hepatology. 2020; 5:428–430.
3. Sultan S, Altayar O, Siddique SM, Davitkov P, Feuerstein JD, Lim JK et al. AGA Institute rapid Review of the GI and Liver manifestations of COVID-19, meta-analysis of International data, and recommendations for the consultative Management of patients with COVID-19. Gastroenterology May 1st 2020.
4. Singh S, Khan A. Clinical Characteristics and outcomes of COVID-19 Amongst patients with pre-existing liver disease in the United States: A multi-center Research Network Study. Clin Gastro Hep May 3rd 2020; https://doi.org/10.1053/j.gastro.2020.04.064.
5. Mulangu S, Dodd LE, Davey RT, Mbaya OT, Proschan M, Mukadi D, et al. A randomized, controlled trial of Ebola virus disease therapeutics. NEJM. 2019; 381:2293–2303.

6. Grein J, Ohmagari N, Shin D, Diaz G, Asperges E, Castagna A, et al. Compassionate Use of Remdesivir for Patients with Severe Covid-19. NEJM. Published online April 10th, 2020;
7. Wang Y, Zhang D, Du G, Du R, Zhao J, Jin Y, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. The Lancet [Internet]. 2020 [cited 2020 Apr 30];0. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0140673620310229
8. Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants With Severe Coronavirus Disease (COVID-19) - Full Text View - ClinicalTrials.gov [Internet]. [cited 2020 Apr 30];Available from: https://clinicaltrials.gov/ct2/show/NCT04292899?term=remdesivir&cntry=US&draw=2&rank=2
9. Alexander PE, Debono VB, Mammen MJ, Iorio A, Aryal K, Deng D, et al. COVID-19 research has overall low methodological quality thus far: case in point for chloroquine/hydroxychloroquine. Journal of Clinical Epidemiology [Internet]. 2020 [cited 2020 Apr 30]; Available from: https://doi.org/10.1016/j.jclinepi.2020.04.016
10. Tang W, Cao Z, Han M, Wang Z, Chen J, Sun W, et al. Hydroxychloroquine in patients with COVID-19: an open-label, randomized, controlled trial. medRxiv. 2020;2020.04.10.20060558.
11. Gautret P, Lagier J-C, Parola P, Hoang VT, Meddeb L, Mailhe M, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. International Journal of Antimicrobial Agents. 2020;105949.
12. Chorin E, Dai M, Shulman E, Wadhwani L, Bar Cohen R, Barbhaiya C, et al. The QT Interval in Patients with SARS-CoV-2 Infection Treated with Hydroxychloroquine/Azithromycin. medRxiv [Internet]. 2020 [cited 2020 Apr 30];2020.04.02.20047050. Available from: http://medrxiv.org/content/early/2020/04/03/2020.04.02.20047050.abstract
13. FDA cautions against use of hydroxychloroquine or chloroquine for COVID-19 outside of the hospital setting or a clinical trial due to risk of heart rhythm problems | FDA [Internet]. [cited 2020 Apr 30]; Available from: https://www.fda.gov/drugs/drug-safety-and-availability/fda-cautions-against-use-hydroxychloroquine-or-chloroquine-covid-19-outside-hospital-setting-or

14. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, et al. A Trial of Lopinavir–Ritonavir in Adults Hospitalized with Severe Covid-19. NEJM [Internet]. 2020 [cited 2020 Apr 30] 2001282. Available from: http://www.nejm.org/doi/10.1056/NEJMoa2001282

15. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19 [Internet]. [cited 2020 Apr 30]; Available from: https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/

16. Xu X, han M, Li T, Sun W, Wang D, Fu B, et al. Effective treatment of severe COVID-19 patients with toclizumab. PNAS 2020; April 29th, 2020; https://doi.org/10.1073/pnas.2005615117

17. Regeneron and Sanofi Provide Update on U.S. Phase 2/3 Adaptive-Designed Trial of Kevzara® (sarilumab) in Hospitalized COVID-19 Patients | Regeneron Pharmaceuticals Inc. [Internet]. [cited 2020 Apr 30]; Available from: https://investor.regeneron.com/news-releases/news-release-details/regeneron-and-sanofi-provide-update-us-phase-23-adaptive

18. Chen L, Xiong J, Bao L, Shi Y. Convalescent plasma as a potential therapy for COVID-19. The Lancet Infectious Diseases. 2020; 20:398–400.

19. Shen C, Wang Z, Zhao F, Yang Y, Li J, Yuan J, et al. Treatment of 5 Critically Ill Patients with COVID-19 with Convalescent Plasma. JAMA - Journal of the American Medical Association. 2020;

20. Mehra MR, Desai SS, Kuy W, et al. Cardiovascular disease, drug therapy, and mortality in Covid-19. NEJM 2020; May 1st, 2020.

Figure 1- Molecular targets of potential SARS CoV-2 treatments

Legend: 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 ARB's as well as hydroxychloroquine, 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. Following exocytosis from the infected cell, the host immune response is activated and characterized by high levels of IL-6, IL-1 and TNF. Drugs such as toclizumab 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.

Agent (route/ mechanism)	Target population (Study Endpoint)	Efficacy data	Safety issues
Antiviral agents			
Remdesivir (IV/ nucleotide analogue)	Mild-severe (Time to improvement)	In vitro & animal models Cohort study showed clinical improvement & 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 tolerate in Ebola. Few DDI anticipated. 20-30% reversible AST/ALT elevations. Nausea/vomiting, rash *Contraindicated:* GFR < 30 ml/min AST/ALT > 5x ULN
Hydroxychloroquine (+/- Azithromycin) (oral/ host proteins)	Mild-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 & FDA recommends only in carefully monitored setting	Nausea/vomiting Hypoglycemia QT prolongation (↑ with azithromycin) Safer than CQ *Contraindicated:* QT > 500 ms Cardiomyopathy G6PD Deficiency Pregnancy/breast-feeding
Chloroquine (+/- Azithromycin) (oral/ host proteins)	Mild-moderate (Hospital LOS) (Symptom duration)	RCT (n=81) of high vs low-dose CQ: stopped early due to higher mortality in high dose CQ group (all received azithromycin). No difference in viral clearance Weaker in-vitro effects vs HCQ	Same as above Higher risk of QT prolongation, DDI, toxicities.
Immunomodulators			
Tocilizumab	Severe.	RCT ongoing	Single vs repeated dosing

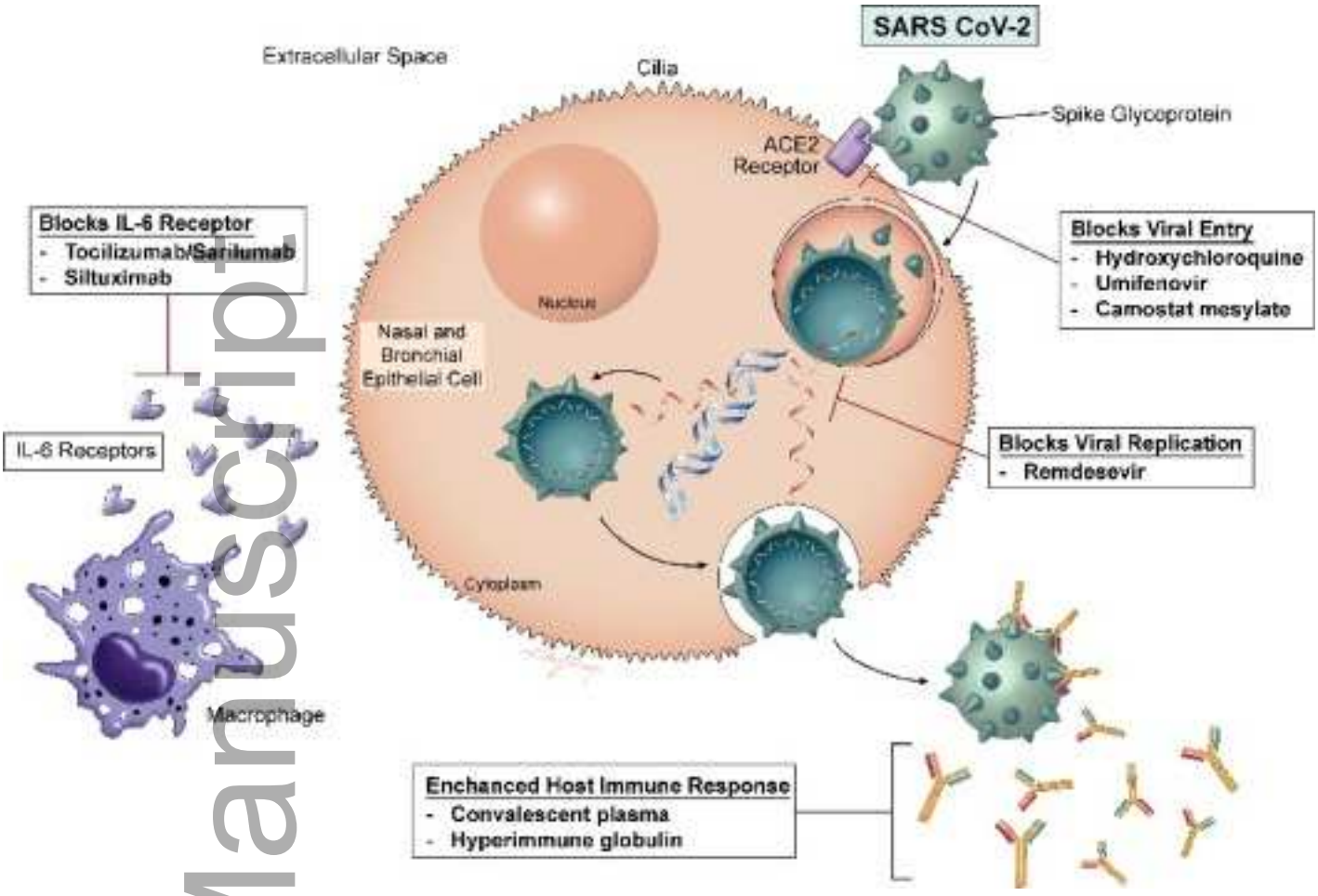
ANC = absolute neutrophil count DDI= drug-drug interaction LOS = length of stay RCT= randomized controlled trial ULN = upper limit of normal

(IV/ monoclonal IL-6 receptor antagonist)	Respiratory failure +/- ↑ IL-6. (% requiring mechanical ventilation / FIO_2 / mortality) (Pulmonary function)	One uncontrolled study (n=21) showed clinical improvement and reduced LOS	Opportunistic infections HBV reactivation 1-5% Cytopenias 20-40% AST/ ALT elevation ALF (rare) *Contraindicated:* ANC < 2,000 Platelets < 100,000 ALT > 5x ULN
Sarilumab (Kevzara) (SC/ monoclonal anti-IL-6 ab)		Preliminary data showed no benefit vs. placebo RCT ongoing	
Siltuximab (IV/ monoclonal anti IL-6 ab)		RCT ongoing	
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 (TRALI, anaphylaxis) Donor-related infections Hypervolemia Impaired host Ab response

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 inhibitors/ ARB	Theoretically may block viral entry Recommend continuation in diabetic or hypertensive patients. No role at this time to start for antiviral effects
Heparin	Many patients have elevated D-dimer levels and may be hypercoaguable with endothelitis SQ Heparin for DVT prophylaxis is recommended for hospitalized patients Role of therapeutic anti-coagulation not established.

ACE= angiotensin converting enzyme ARB= angiotensin receptor blocker NSAID = nonsteroidal anti-inflammatory drug SQ= subcutaneous



cld_969_f1.tif