Potential specific therapies in COVID-19

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Abstract: COVID-19 has grown into a global pandemic that has strained healthcare throughout the world. There is a sense of urgency in finding a cure for this deadly virus. In this study, we reviewed the empiric options used in common practice for COVID-19, based on the literature available online, with an emphasis on human experiences with these treatments on severe acute respiratory syndrome-associated coronavirus (SARS-COV-1) and other viruses. Convalescent blood products are the most promising potential treatment for use in COVID-19. The use of chloroquine or hydroxychloroquine (HCQ), remdesivir, and tocilizumab are some of the other promising potential therapies; however, they are yet to be tested in randomized clinical trials (RCTs). The use of lopinavir-ritonavir did not prove beneficial in a large RCT. The use of corticosteroids should be avoided in COVID-19 pneumonia unless used for other indications, based on the suggestion of harm in patients with SARS-COV-1 and Middle Eastern Respiratory Syndrome (MERS) infection.

The reviews of this paper are available via the supplemental material section.

Keywords: convalescent blood products, coronavirus, corticosteroids convalescent sera, favipiravir, IL-6, interferons, lopinavir-ritonavir, MERS, novel virus, remdesivir, ribavirin, SARS-COV-1, tocilizumab

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Introduction

As the COVID-19 pandemic spreads throughout the world, there is an urgent call for effective treatments. We review the potential therapies for COVID-19 with an emphasis on experience with severe acute respiratory syndrome-associated coronavirus (SARS-COV-1) (COVID-19 has about 80% nucleotide similarity to SARS-COV-1)[1] and other viruses. Convalescent blood products, other antivirals such as chloroquine phosphate, hydroxychloroquine (HCQ), favipiravir, remdesivir, interferon, and ribavirin, and immune modulators such as tocilizumab, are considered as therapies for the novel coronavirus COVID-19. Evidence has accumulated against other medications such as lopinavir-ritonavir and steroids, which are likely not beneficial in COVID-19 treatment. Here, we review the evidence that has led to the interest in these therapies against the novel COVID-19 infection (Table 1).

Convalescent blood products

Convalescent blood products are derived from the serum or whole blood of patients who have recovered from the infection and are the source of antibodies that can neutralize the pathogens.[32] The various forms of convalescent blood products include convalescent serum or whole blood, pooled human immunoglobulin, high titer immunoglobulin, and polyclonal or monoclonal antibodies.[33] In a meta-analysis that included eight studies with 1703 patients infected with Spanish influenza, convalescent sera were effective in reducing mortality (16% *versus* 37%).[2] In another meta-analysis that included 32 studies with SARS-COV-1 and severe influenza, convalescent plasma transfusion was associated with a statistically significant decrease in mortality [odds ratio (OR), 0.25; 95% confidence interval (CI), 0.14–0.45].[3] In a non-randomized observational study in Hong Kong, 80 SARS-COV-1 patients were treated with convalescent plasma. Higher day 22 discharge rate was observed in patients who were treated with convalescent plasma prior to day 14 of illness (58.3% *versus* 15.6%; $p < 0.001$). The mortality rates in the two groups were 6.3% and 21.9%, respectively ($p = 0.08$).[34] In another retrospective, non-randomized study on 40 SARS-COV-1 patients who did not improve with

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Table 1. Summary of the potential specific therapies of COVID-19.

Medication	Dose (for CrCl >60), Route	Safety, adverse events	Human clinical studies in viruses other than COVID-19	Human clinical studies in COVID-19
Convalescent blood products	The dose is adjudicated based on the titer of antibody in the convalescent serum	Well tolerated, antibody-dependent enhancement of infection; susceptibility to other viral infections, transfusion-related lung injury, thrombotic events	Mortality improvement with convalescent sera in Spanish flu,[2] H1N1 flu infection,[3] and no mortality benefit in Ebola infection.[4] Monoclonal antibodies mAb114 and REGN-EB3 were superior to remdesivir in reducing mortality in Ebola infection[5]	In a case-series of five critically ill intubated, convalescent plasma transfusion was associated with clinical improvement in all five patients, a decrease in viral load, resolution of ARDS in four patients, extubation and discharge in three patients.[6] In another study of 10 severe COVID-19 patients, the transfusion led to the improvement in clinical symptoms in 3 days, and the disappearance of viremia along with radiological improvement in 7 days[7]
Chloroquine phosphate/HCQ	No optimal dosage defined. Chloroquine 500 mg oral daily (South Korea) 5–10 days, HCQ 600mg daily[8] 5–10 days HCQ 400mg daily for 5 days[9]	Diarrhea, QT prolongation Monitoring for QT prolongation and cardiovascular effects, especially if combined with azithromycin. A rare side effect of retinopathy in the long term and high dose use. HCQ is the less toxic form of chloroquine phosphate.	Two clinical trials of HIV-1 at 800mg/day HCQ dose decreased viral load and IL-6.[10,11] Another clinical trial in HIV 1 patients with HCQ 400 mg/day did not reduce viral load or change in immune activation[12]	Zhejiang RCT 30 patient, randomized to HCQ + conventional treatment *versus* conventional treatment; no difference in the nasopharyngeal viral carriage (87% *versus* 93% on day 7)[13] Wuhan RCT 62 patients, randomized to HCQ *versus* control; shortened time to clinical recovery and increased resorption of pneumonia in HCQ arm (80.6% *versus* 54.8%)[9]
Favipiravir	1600 mg orally twice a day on the 1st day, 600 mg orally twice a day starting 2nd day onward.[14] Duration: 4–7 days	Well tolerated, GI side effects, transaminitis, increased uric acid, psychiatric symptoms[14]	The nonrandomized clinical trial in EBOLA virus patients showed a lack of efficacy in patients with high viremia; however, it may be useful in patients with relatively low viral load[15]	Preliminary non-peer reviewed preprinted results from a randomized clinical trial on 240 patients suggests improved 7-day clinical recovery and more effective reduction in the incidence of fever and cough compared with arbidol; however, no difference in oxygen requirement or non-invasive ventilation rate noted[14]
Remdesivir	200 mg IV on the first day followed by 100 mg Duration: 5–10 days	Concern for GI side effect; nausea, vomiting, diarrhea, and elevated transaminases	Randomized clinical trial in Ebola infection did not show any mortality benefit.[5]	The compassionate use of remdesivir on 61 patients, clinical improvement was observed in 68% (36 out of 53) of the patients. RCT results awaited[16]
Lopinavir/Ritonavir	400/100mg oral two times daily(HIV dose)	Diarrhea, GI disturbances, rash	Favorable clinical response in a non-randomized clinical trial on SARS–COV 1 patients[17]	Data from the randomized clinical trial did not show any benefit[18]

(Continued)

Table 1. (Continued)

Medication	Dose (for CrCl >60), Route	Safety, adverse events	Human clinical studies in viruses other than COVID-19	Human clinical studies in COVID-19
INF-α-2a and Ribavirin	Peg INF-alpha-2a; 180 µg subcutaneously per week for 2 weeks Ribavirin 2000 mg orally loading dose then 1200 mg every 8 h for 4 days, then 600 mg PO every 8 h for 4–6 days (dose used for MERS)[19]	Unfavorable side effect profile: significant depressive symptoms (21–58%),[20] anemia (34%), flu-like symptoms (22%) and GI symptoms (19.4%)[21]	In a multicenter observational study of 349 critically ill MERS patients, interferon and ribavirin combination were not associated with any benefit in mortality or viral clearance.[19] A retrospective observational study of 32 MERS patients, mortality with interferon α2a was 85% *versus* 64% with interferon β1a.[22] Retrospective cohort study 44 MERS patients, interferon-alfa-2a and ribavirin, was associated with improved survival at 14 days but not at 28 days[19]	No clinical trial data available
Corticosteroids	–	Unfavorable side effect profile. Hypertension, hyperglycemia, osteoporosis, psychosis	Systemic review in SARS-COV-1 reported harm associated with corticosteroids use[23] delayed viral clearance (RCT),[24] psychosis,[25] diabetes,[26] and avascular necrosis.[27] Corticosteroid use was associated with delayed clearance of viral RNA in MERS-CoV infection[28]	Recommended against use in COVID-19 pneumonia unless indicated for other reasons[29,30]
Tocilizumab	50–60 kg: 400 mg as a single intravenous infusion 60–85 kg: 600 mg as a single intravenous infusion 85 kg: 800 mg as a single intravenous infusion. Repeat the dose in 12 h if no improvement observed	Elevated liver enzymes	No randomized clinical trial available	A retrospective observational study of 20 patients; 75% of the patients had improvement in oxygen requirement, 90.5% of the patients had radiological improvement on CT scan, CRP decreased significantly, and the lymphocytes count initially decreased and then improved[31] RCT results pending

ARDS, acute respiratory distress syndrome; COVID-19, severe acute respiratory syndrome coronavirus 2; CRP, C-reactive protein; CT, computed tomography; GI, gastrointestinal; HCQ, hydroxychloroquine; HIV-1, human immunodeficiency virus-1; IL-6, interleukin six; INF-α-2a, interferon-alpha-2a; MERS, Middle Eastern respiratory syndrome; RCT, randomized clinical trial; SARS-COV-1, severe acute respiratory syndrome coronavirus 1.

ribavirin and 1.5 g pulsed methylprednisolone, the patients were assigned to receive convalescent plasma or further pulsed steroids. Patients who received plasma had shorter hospital stay (adjusted discharge rate 77.8% *versus* 23%, *p* = 0.004) and lower mortality (0% *versus* 23.8%, p < 0.049).[35] In the H1N1 influenza pandemic, in a prospective cohort study, treatment with convalescent plasma reduced respiratory viral load and mortality (20% *versus* 54.8%).[36] The convalescent plasma was tested in the Ebola epidemic in a non-randomized study of 84 patients with confirmed Ebola. It did not improve mortality (31% *versus* 38%, risk difference, −7% points; 95% CI, −18 to 4).[4] However, the authors later reported that the titers of anti-Ebola virus antibodies were low in many donations, and that the effectiveness of higher titer antibodies convalescent sera needed to be tested.[37] Significant mortality reduction was noted with the use of the monoclonal antibody MAb114 [35.1% *versus* 49.7% (control), *p* = 0.007] and the triple monoclonal antibody REGN-AB3 [33.5% *versus* 51.3% (control), *p* = 0.002] compared with remdesivir and the control arm in a large randomized clinical trial (RCT) of 681 patients.[5] In a case-series of five critically ill intubated patients of COVID-19, who had a high viral load despite being previously treated with various antivirals and steroids, convalescent plasma was administered between 10 and 22 days of admission. The plasma transfusion was associated with clinical improvement, normalization of body temperature, and decrease in viral load in all the patients. Three out of five patients were extubated and discharged.[6] In another observational study of 10 severe COVID-19 patients, no serious side-effects were observed with the transfusion of convalescent plasma. The transfusion led to the improvement in clinical symptoms in 3 days and the disappearance of viremia along with radiological improvement in 7 days.[7] As the pandemic spreads, convalescent plasma will become an important potential therapy in the treatment of critically ill COVID-19 patients.[38] The development of monoclonal and polyclonal antibodies against COVID-19 is an area of active research.[38] In a non-peer reviewed pre-printed study from the Netherlands, 47D11 monoclonal antibody was reported to cross-neutralize COVID-19 and SARS- COV-1 by binding to its conserved epitope.[39]

Convalescent blood products have a long track record of safety; however, they can increase the risk of antibody dependant enhancement of infection (ADE), a phenomenon that can make a person susceptible to infection with other viruses in the presence of antibodies.[40] Transfusion-related acute lung injury is also an important risk factor.[41] Thrombotic events are rare, but life-threatening complications associated with the transfusion of immunoglobulins.[42]

Chloroquine phosphate and HCQ

Chloroquine phosphate is known to inhibit COVID-19,[43] SARS COV-1,[44,45] and influenza A and B virus *in vitro*,[46,47] and HIV-1 in patients.[48,49] Multiple mechanisms for the antiviral activity of chloroquine have been proposed.[50] Increased intracellular zinc levels with zinc ionophores that allow the entry of zinc into the cells have been shown to inhibit RNA-dependent RNA polymerase, an RNA synthesizing enzyme that is critical for the pathogenesis of positive-stranded RNA viruses.[51] The intracellular zinc levels are limited primarily by cell membrane structure, as demonstrated by the observation that the addition of zinc chloride only slightly increases intracellular zinc levels.[52] Chloroquine, however, is a zinc ionophore and significantly increases intracellular zinc levels.[52] In a study reported by the United States Centers for Disease Control and Prevention (CDC), chloroquine appears to interfere with the terminal glycosylation of the angiotensin-converting enzyme 2 (ACE 2),[45] in addition to the elevation in endosomal pH. ACE 2 is the receptor used by the SARS-COV virus to gain entry into cells. The authors concluded that the drug had a possible prophylactic and therapeutic use against SARS-COV-1 cell cultures.[45] HCQ is the less toxic derivative of chloroquine. In a recent *in vitro* study, it was found to be more potent than chloroquine against COVID-19.[53]

In early clinical trials on HIV-1 patients, the use of HCQ monotherapy at 800 mg/day (equivalent to 500 mg/day chloroquine) resulted in decreased viral load.[10,11] However, when it was used at 400 mg/day in another clinical trial,[12] it did not show any effect on viral load or immune activation. Attention should be paid to the dosing of HCQ, if used at all, for its antiviral effect.[54] Chloroquine failed to improve survival in mice and hamster models infected with Ebola virus.[55] In an unpublished news report from China, chloroquine demonstrated encouraging results in COVID-19 patients.[56] Based on these preliminary

results, a chloroquine sulfate 500 mg twice-daily dose was approved in China,[57] and chloroquine 500 mg once-daily dose was recommended in South Korea for critically ill or old patients.[58] In a recent French open-label non-RCT reported by Gautret *et al.*, a total of 26 patients receiving HCQ 600 mg daily (6 patients received azithromycin) were compared with 16 control patients. On day 6, all the patients treated with HCQ 600 mg daily and azithromycin did not have the virus detected, *versus* 57.1% in patients treated with HCQ only and 12.5% in the control group ($p < 0.005$).[8] In a follow-up study by the same French group on 80 COVID-19 patients treated with HCQ and azithromycin without a control arm, the virus was not detected in 83% on day 7 and 93% of the patients on day 8.[59] In another prospective French study, 11 patients were treated with HCQ and azithromycin in the absence of control. Out of 10 patients, 8 had virus detected on days 5 or 6 since initiation of treatment.[60] Any conclusion from these studies is limited in the absence of a randomized control arm and a lack of clear clinical data. In a randomized control trial from Zhejiang by Chen *et al.*, 30 patients were randomized to HCQ 400 mg daily for 5 days with conventional treatment to the control arm. No significant difference in nasopharyngeal viral carriage was noted in the two arms on day 7; however, the use of other antivirals may have confounded the results.[13] The study was not powered to detect any difference in clinical outcomes due to its small sample size. In another RCT from Wuhan, Chen *et al.* randomized HCQ 400 mg daily for 5 days to control arm in 62 COVID-19 patients. Shortened temperature recovery time, cough remission time, and increased absorption of pneumonia (80.6 *versus* 54.8%) were observed with HCQ treatment.[9] The data cannot be extrapolated to critically ill patients as only mildly severe COVID-19 (SpO2 > 93%) patients were recruited in the study.[61] Large prospective clinical trial data in critically ill COVID-19 patients are awaited.

Chloroquine and HCQ have a good safety profile overall. QT prolongation and cardiovascular effects are clinical concerns with high doses of chloroquine. QT prolongation should be monitored, especially if combining with azithromycin. Another rare side effect noted is retinopathy. However, retinal damage has been observed when chloroquine has been used for years in the treatment of autoimmune conditions.[62]

Remdesivir

Remdesivir is considered one of the promising antivirals in the armamentarium against COVID-19.[63] Remdisivir (developmental code GS-5734) is an experimental antiviral drug developed by Gilead Sciences. It is a monophosphoramidate prodrug of an adenosine analog. It has a broad spectrum of antiviral *in vitro* activity against other pathogenic RNA viruses, including Middle Eastern Respiratory Syndrome (MERS) and SARS-COV 1, bat COVs viruses. In the *in vitro* system of human airway epithelial cells, remdesivir inhibits MERS-COV and SARS-COV-1. The mouse model of SARS-COV1 demonstrated that the early administration of remdesivir decreased viral load, improved lung function, and the course of clinical disease.[64] As a nucleotide analog, remdesivir interferes with the activity of RNA polymerase and overcomes the intact exon proofreading ability, thus leading to the premature termination of the transcription.[65] It was effective in the treatment of Rhesus monkeys against EBOLA virus.[66] However, when subsequently tested in a clinical trial conducted during the Kivu Ebola epidemic, the monoclonal antibodies mAb114 and REGN-EB3 were superior to remdesivir in reducing mortality.[5] Remdesivir has been shown to inhibit COVID-19 potently in cell cultures.[43] In the compassionate use of remdesivir on 61 patients, clinical improvement was observed in 68% (36 out of 53) of the patients; however, any derivation of a conclusion is limited because of lack of comparator arm and lack of post-treatment data from 7 patients. Hepatic enzyme elevation was observed in 23% of the patients.[16] It is currently being tested for efficacy against COVID-19 in clinical trials in China.[67,68]

Favipiravir

Favipiravir (Avigan) developed by Fujifilm Toyama Chemical has been effective against various RNA viruses, including influenza virus, arenaviruses, bunyaviruses, West Nile viruses, yellow fever viruses, and foot and mouth viruses.[69] It is effective against the H5N1 influenza virus in a mouse model; mice are poorly sensitive to oseltamivir.[70] Favipiravir is a nucleoside analog that requires intracellular phosphoribosylation to be converted into the active metabolite. The mechanism of action is inhibition of viral RNA-dependent RNA polymerase.[71] In the non-RCT against EBOLA virus disease, where a historic control arm was used to analyze the results, favipiravir was not

effective as a stand-alone treatment in patients with very high viremia; however, it should be further studied in patients with relatively lower viral loads. Favipiravir was well tolerated in clinical trials.[15] Favipiravir is approved in Japan for the treatment of pandemic influenza infections.[72] Based on its broad-spectrum antiviral effect, favipiravir is thought to be a prime candidate for emerging RNA viruses. The bar for developing resistance against favipiravir is high.[72] In non-peer-reviewed preprinted results from a clinical trial of 240 patients randomized for the use of favipiravir or arbidol on hospitalized SARS-COV-1 patients, favipiravir use was associated with the higher 7-day clinical recovery and more effective reduction in the incidence of fever and cough; however, no difference in oxygen requirement or non-invasive ventilation rate was noticed.[14] Favipiravir use was also associated with increased uric acid, psychiatric symptoms, gastrointestinal (GI) adverse effects, and increased liver function tests in 14% of the patients.[14] These results are reminiscent of favipiravir use in the Ebola epidemic, suggesting that favipiravir may not be as effective in severe cases compared with mild cases of COVID-19.

Lopinavir–Ritonavir

Lopinavir is a protease inhibitor that, when combined with ritonavir, improves the mean trough plasma lopinavir concentration. It is approved for the treatment of HIV-infected patients.[73] Adverse effects of lopinavir–ritonavir include diarrhea, GI disturbances, headache, and skin rash.[74] Lopinavir–ritonavir and ribavirin showed an apparent favorable clinical response in 44 SARS-COV-1 patients when compared against 111 historic control ribavirin-treated patients.[17] In a double-blinded RCT on 199 patients infected with COVID-19 in China, lopinavir–ritonavir did not show any benefit beyond standard care (mortality 19.2% *versus* 25.0%; difference, −5.8 percentage points; 95% CI, −17.3 to 5.7).[18] With these results from the clinical trial, lopinavir–ritonavir use should no longer be considered for the treatment of COVID-19, unless in the context of a clinical trial.

Interferons and Ribavirin

Dysregulated immune response, including suppressed levels of interferons, have been observed with the infection of corona viruses.[75–78] Human recombinant interferon inhibits SARS-COV-1

replication *in vitro* .[79–82] In a non-human primate model in the common marmoset, the combination of interferon β1b and lopinavir/ritonavir was associated with better outcomes.[83]

Ribavirin has been used in the past for the treatment of respiratory syncytial virus (RSV), Congo hemorrhagic fever,[84] and hepatitis C.[85] Ribavirin is a guanosine analog and interferes with polymerase inhibition, mRNA capping, and lethal mutagenesis. It has also been used in combination with interferon. The combination of interferon-α2b and ribavirin inhibited MERS-COV *in vitro*.[86] In a preliminary uncontrolled study on patients with SARS-COV-1, nine patients received interferon alfacon-1 with corticosteroids, and three patients were transferred to the ICU; however, none died.[87] In a retrospective cohort study of 44 critically ill MERS patients, 24 patients received interferon-alfa-2a and ribavirin; the therapy was associated with improved survival at 14 days but not at 28 days.[88] In another retrospective study of 32 MERS patients, interferon α2a or interferon β1a were used in combination with ribavirin. The mortality rate in patients who received interferon α2a was 85% compared with 64% in those who received interferon β1a.[22] These results did not suggest benefit with interferon and ribavirin since MERS-COV pneumonia mortality was thought to be around 67%.[89] In a multicenter observational study of 349 patients with critically ill MERS patients, 144 patients received interferon and ribavirin. They were not associated with any benefit in mortality or viral clearance.[19]

The combination of interferon-alpha-2a and ribavirin in the clinical trial led to discontinuation of the medication in up to 27% of the patients receiving therapy for a year.[90] Interferon-alpha-2a and ribavirin have an unfavorable adverse effect profile, including significant depressive symptoms (21–58%),[20] anemia (34%), flu-like symptoms (22%), and GI symptoms (19.4%).[21] Based on mostly unfavorable experiences with MERS epidemics and high side-effect profile, the empiric combination should not be advocated in the absence of any clinical trial results on COVID-19.

Corticosteroids

The idea of the use of steroids was coined in the treatment of acute respiratory distress in the meta-analysis on the effect of steroids in

SARS-COV-1 by Stockman *et al.*; 25 studies were inconclusive, and only 4 studies were conclusive, all of which showed harm with the use of steroid.[23] Corticosteroids use in the first week were associated with delayed viral clearance in a randomized, double-blind placebo trial.[91] The other three studies reported psychosis,[25] diabetes,[26] and avascular necrosis.[27] Corticosteroid use was associated with delayed clearance of viral RNA in MERS-CoV infection.[28] In preliminary data from a retrospective cohort study from China in COVID-19, corticosteroids were used more often in patients who died (48%) than in patients who survived (23%), $p < 0.001$.[92] Based on this evidence, the World Health Organization (WHO) and other experts have recommended against the use of corticosteroid treatment against COVID-19 lung injury unless indicated for other indications.[29,30] In the setting of cytokine storm, immunosuppression with steroids, if tocilizumab is not available, maybe considered.[93]

Tocilizumab

Tocilizumab is a humanized monoclonal antibody used in the treatment of rheumatoid arthritis,[94] juvenile idiopathic arthritis,[95] and cytokine release syndrome.[96] Tocilizumab blocks the interleukin-six (IL-6) receptor. IL-6 is a pro-inflammatory cytokine and can be released in response to viral infections.[97] In a study on 150 patients from Wuhan, China, IL-6, ferritin, and C reactive protein (CRP) were elevated in patients who died in comparison with those who survived.[98] These elevated laboratory markers suggest the possibility of hypercytokinemia in the setting of secondary hemophagocytic lymphohistiocytosis.[93] A viral infection is considered to be the most common trigger of secondary hemophagocytic lymphohistiocytosis.[99] Reports of the hemophagocytic syndrome have been noted in SARS-COV-1,[100] avian influenza,[101] and human influenza.[102,103] Tocilizumab, approved for cytokine release syndrome, is being tested in a clinical trial from China in COVID-19 patients.[104] The use of H score for cytokine storm has been recommended to determine the critical timing of tocilizumab in severe COVID-19 patients.[93] In a retrospective observational pre-printed non-peer reviewed study from China, tocilizumab was used in 20 worsening COVID-19 patients; 75% of the patients had improvement in oxygen requirement, 90.5% of the patients had radiological improvement on computed tomography (CT) scan, CRP decreased significantly, and lymphocyte count initially decreased and then improved.[31] There was no randomized control arm in the study, a lack of data reported on the important inflammatory markers such as ferritin and IL-6, and only two patients were intubated prior to the use of tocilizumab in the study. These biases limit the derivation of any conclusion from the study. Elevated liver enzymes is a common adverse effect associated with tocilizumab.[105] The use of the Janus kinase (JAK) inhibitor baricitinib, which can inhibit clathrin-mediated endocytosis, has also been considered as a potential option for hypercytokinemia.[106]

Conclusion

Convalescent blood products are promising potential therapies for COVID-19. Other antivirals such as chloroquine or HCQ, remdesivir, and immune modulators such as tocilizumab are the other potential therapies for COVID-19 that are being tested in clinical trials. The use of antiretrovirals, such as lopinavir/ritonavir, did not provide any benefit in a RCT. Steroids appear to be harmful based on human experiences with SARS-COV-1 and MERS infection.

Author contribution(s)

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Conflict of interest statement

The authors declare that there is no conflict of interest.

Supplemental material
The reviews of this paper are available via the supplemental material section.

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