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REVIEW

Treatment of SARS-CoV-2 (COVID-19): A safety perspective

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Abstract

The goal of this review is to report a balanced perspective of current evidence for efficacy of treatments for coronavirus disease 2019 (COVID-19) against the historical safety of these treatments as of May 2021. We preselected therapies of interest for COVID-19 based on national guidelines and modified over time. We searched PubMed and Medline for these specific COVID-19 treatments and data related to their efficacy. We also searched for prior randomized controlled trials of each therapy to assess adverse effects, and we obtained the Food and Drug Administration Approval label for this information. Several drugs have been approved for the treatment of COVID-19, and many more are under study. This includes dexamethasone, remdesivir, hydroxychloroquine/chloroquine, lopinvir/ritonavir, interferon or interleukin inhibitors, convalescent plasma and several vitamins and minerals. The strongest evidence for benefit is mortality benefit with dexamethasone in patients with COVID-19 and hypoxemia, although there is a signal of harm if this is started too early. There are several other promising therapies, like interleukin inhibitors and ivermectin. Hydroxy-chloroquine/chloroquine, lopinvir/ritonavir, and convale-scent plasma do not have enough evidence of benefit to outweigh the known risks of these drugs.

Key Words: COVID-19; Coronavirus; SARS-CoV-2; SARS; Drug safety; Pharmacotherapy

Core tip: Coronavirus disease 2019 (COVID-19) has radically changed the approach to healthcare and public health in the last year. Over 100 million people worldwide have

been affected. Dexamethasone appears to be the most efficacious drug for appropriately selected patients with COVID-19 (*i.e.*, those requiring supplemental oxygen). Remdesivir may reduce length of hospitalization with mild side effects. While they do not have enough evidence to be recommended at this time, ivermectin and zinc should be studied further for early illness and interferon and interleukin blockade should be studied for critical illness. Hydroxychloroquine/chloroquine, azithromycin, and vitamins C and D have no evidence of benefit at this time.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is caused by a novel, highly infectious strain of coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Seven coronavirus strains have been shown to infect humans. The first strains of coronaviruses to infect humans were identified in 1960s and were reported to cause common cold like symptoms. Since then, two highly pathogenic strains have been associated with prior pandemics. The first, termed SARS-CoV, was identified in 2003, and reported to cause severe pneumonia and acute respiratory distress syndrome (ARDS)[1]. The other, Middle Eastern Respiratory Syndrome (MERS) Coronavirus was identified in 2012 and is highly virulent and is also known to cause pneumonia, respiratory distress, and renal failure in some cases[2]. SARS-CoV-2, the cause of COVID-19, is the newest of these highly pathogenic coronaviruses.

Due to the worldwide impact and high mortality of this virus, therapeutics for COVID-19 are under ongoing intense investigation. There are currently four drug therapies with approval or emergency use authorization (EUA) under the US Food and Drug Administration (FDA): The antiviral remdesivir with or without barcitinib, convalescent plasma, and the immunotherapies bamlanivimab/etesevimab and casirivimab/imdevimab. The steroid dexamethasone is also a widely used therapy for hospitalized patients. Several other therapies have been studied; some have shown consistent lack of evidence [hydroxychloroquine (HCQ)/chloroquine (CQ) and lopinavir/ritonavir (LPV/RTV)], and some have ongoing research and early promise (serotonin reuptake inhibitors, angiotensin modulators, interleukin inhibitors, interferon treatments, histamine blockers, and vitamin and mineral supplements). There is rapidly evolving evidence on therapeutics for COVID-19, but haste in the research has also led to some disappointments.

Every drug has a potential for adverse effects, which must be weighed against its efficacy. Therefore, the goal of this review is to present a balanced review of efficacy and safety data for the most highly promising COVID-19 therapeutics.

DEXAMETHASONE

Corticosteroids, such as dexamethasone, have been the only drugs to consistently show mortality benefit in COVID-19[3]. Early observational data suggested that steroids were associated with increased mortality and disease severity[4,5], and many guidelines initially discouraged their use[6]. However, the large randomized controlled RECOVERY trial in the UK then showed significant mortality benefit at a 6-mg daily dose in patients requiring supplemental oxygen[7]. Patients with more severe illness benefitted the most, and patients not requiring supplemental oxygen actually showed a signal of harm. Several other studies have confirmed these findings[3]. Therefore, steroids should be reserved for patients requiring supplemental oxygen and not generic outpatients with COVID-19.

In other causes of severe pneumonia, corticosteroids have also shown benefit[8]. Steroids are nonselective immunosuppressants, and their benefit in severe COVID-19 suggests that an inflammatory cascade contributes to severe illness. Hydrocortisone, but not methylprednisolone, is associated with similar benefit but with less robust data

[3,9]. More recent guidelines almost universally endorse the use of dexamethasone in moderate to severe COVID-19 (Table 1)[10].

Corticosteroids have been well studied for many indications, and their side effect profile is well understood. Hyperglycemia and hypernatremia are the most commonly observed side effects, with highly variable rates reported[8,11]. Up to 40% increased odds of stress ulcers and gastrointestinal bleeding can be seen in hospitalized patients using steroids[12,13]. In intensive care patients, steroid-induced myopathy is a well-recognized complication[11,14]; however, there are no great data on the incidence of steroid-induced myopathy. Steroid-induced neuropsychiatric complications are also rare but well recognized[15]. These include psychosis, agitation, mania, and insomnia. Other commonly recognized side effects of corticosteroid use have not been shown to be statistically increased when used for short courses in the hospital. However, large studies, even some using short courses of steroids, have shown an association with these risks. These include decreased bone density and pathological fractures[16], increased risk of infections and sepsis[17,18], glaucoma[19,20], venous thromboembolism[17], hypertension[21], and weight gain[22,23].

A rare, but recognized complication of immunosuppression, particularly with corticosteroids, is *Stronglyoides* hyperinfection/dissemination[24]. This typically occurs in patients with chronic unrecognized asymptomatic infection when given an immunosuppressant, like dexamethasone or other corticosteroids, and it appears to be unrelated to dose or duration of steroid administration[25,26]. Chronic *Strongyloides* infection is more common in patients from tropical regions[27].

Given the mortality benefit demonstrated in several studies, the use of dexamethasone in COVID-19 patients requiring supplemental oxygen is prudent, despite the known side effects. Preventive strategies for these side effects should be observed. This includes appropriate patient selection (*i.e.*, only patients requiring supplemental oxygen), appropriate dosing of steroids (6 mg daily dexamethasone for non-critically ill patients), close monitoring of electrolytes and blood sugar, low threshold for stress ulcer prophylaxis, early mobilization and physical therapy, appropriate deep venous thrombosis prophylaxis, and delirium precautions.

REMDESIVIR

Remdesivir is a broad-spectrum antiviral drug proposed for the treatment of coronavirus and Ebola virus infections. This nucleotide analog is metabolized into an ATP analog in the cells and inhibits viral RNA-dependent RNA polymerase[28-30]. Case reports for remdesivir in Ebola virus infection showed promise[31,32]; however, clinical trial data did not support its efficacy[33] and it was never approved. *In vitro* data showed efficacy for SARS-CoV[34], MERS-CoV[35] and SARS-CoV-2[36].

Of course, these preclinical data fostered interest in the use of remdesivir for patients with COVID-19. Early observational data without a comparison group showed that, among patients who received remdesivir under compassionate use agreement, 68% improved[29]. A small randomized trial showed no benefit[37]. Further randomized trials, though, showed a decrease in hospital length of stay and clinical improvement among hospitalized patients, but no statistical difference in mortality[38,39]. And, later analyses demonstrated that a 5-day course dose was equally as effective as a 10-day course[40]. The FDA approved remdesivir under EUA on May 1, 2020[41], and full approval on October 22, 2020[42].

Interestingly, in the final report of the largest randomized controlled trial, there were more adverse events in the placebo group than the remdesivir group[38]. An elevation in liver enzymes is known to occur in some people[43] and is an indication to cease treatment (when levels reach 10 times the upper limit of normal)[44]. In fact, this was the most common adverse event in the observational compassionate use data, with a rate of 23%[29]. However, only international normal ratio elevation, and not aspartate transaminase, alanine transaminase (ALT) or bilirubin, was increased compared to placebo in the randomized controlled trial[38]. As remdesivir contains sulfobutylether-beta-cyclodextrin sodium, a renally cleared solubilizing preservative, its use in patients with a glomerular filtration rate < 30 mL/min is not recommended, although the clinical significance of its use in patients with renal disease is not known [44]. A single patient receiving loading-dose remdesivir in the Ebola trial had profound hypotension during the infusion ultimately leading to cardiac arrest[33]. This was adjudicated as possibly related to the remdesivir, but it is not clear if it was part of the underlying Ebola virus infection either. Again, hypotension was not shown to be increased in the randomized controlled trial[38].

Table 1 Summary of guideline recommendations for COVID-19 treatment

Organization	Dexamethasone	Hydroxychloroquine	Remdesivir	Convalescent plasma	Tocilizumab
World Health Organization	Strong recommendation to use in patients with severe/critical illness; Conditional recommendation against use in non-severe/critical patients	Strong recommendation against use	Conditional recommendation against use	No recommendation	No recommendation
United States Centers for Disease Control and Prevention/National Institutes of Health	Recommend use in patient requiring supplemental oxygen or mechanical ventilation; Recommend against use in patients not requiring supplemental oxygen	Recommend against	Recommend in hospitalized patients requiring supplemental oxygen; Not routinely recommended for patients requiring mechanical ventilation	Recommends against use in hospitalized patients; No recommendation for non-hospitalized or immunocompromised patients	Recommended for patients requiring mechanical ventilation within 24 h of ICU admission
Infectious Disease Society of America	Suggest against use in hospitalized patients not requiring oxygen; Suggest use for patients with severe disease; Recommend use for patients with critical disease	Recommend against use	Suggest against use in hospitalized patients not requiring oxygen; Suggest use for patients with severe/critical disease	Suggest against use	Conditionally suggest use in severe/critical patients
Surviving Sepsis/Society for Critical Care Medicine	Recommend for patients with severe/critical illness	Recommend against use in patients with severe/critical illness	Recommend to use in severe/critical patients not receiving mechanical ventilation; Recommend against starting in patients receiving mechanical ventilation	Recommend against (outside of clinical trial) for patients with severe/critical illness	No recommendation

While further research is needed, there do appear to be some clinically important outcomes when remdesivir is used in hospitalized patients with COVID-19, namely clinical improvement, but there is no certain mortality benefit. However, its safety profile seems beneficial, especially when patients are selected appropriately. Of course, all drugs carry some risk of allergic or infusion reactions, but these seem exceedingly rare. Therefore, in appropriate hospitalized patients with COVID-19, remdesivir should be considered.

LPV/RTV

LPV/RTV are protease inhibitors that were once drugs of choice in multidrug regimens for treating HIV infection. Several studies have reported efficacy of LPV and RTV along with other compounds for treatment of HIV infection[45-47]. After initial preclinical trials showed *in vitro* efficacy against SARS-CoV[48,49], LPV/RTV treatment along with ribavirin was trialed in patients with SARS-CoV[50] and MERS-CoV[51], but there was no proven evidence in randomized trials. Combination of LPV/RTV was administered to 43 health care workers (HCWs) in South Korea exposed to MERS-CoV. The study reported no incidence of MERS in HCWs receiving the drug as postexposure prophylaxis (PEP); whereas, six HCWs in the non-PEP group showed symptoms of MERS[52].

LPV/RTV was, understandably, of interest for use against SARS-CoV-2. However, an early randomized controlled trial in hospitalized patients showed no difference in either time to clinical improvement or mortality. Therefore, interest in its use in COVID-19 rapidly waned. Several trials since then have confirmed no clinically or statistically significant improvement in patients with COVID-19 receiving LPV/RTV [53-55].

In one randomized trial of LPV/RTV in COVID-19, total adverse events were similar between groups and serious adverse events were more common in the control group[55]. Gastrointestinal side effects (nausea, vomiting, diarrhea and abdominal pain) and leukopenia were more common in the group receiving LPV/RTV. Four serious gastrointestinal events (gastritis and bleeding) were attributed to LPV/RTV. In a retrospective study of LPV/RTV in SARS-CoV infection, mild adverse reactions were

experienced by 11 of 41 patients (27%) in the treatment group: gastrointestinal upset (27%), liver dysfunction (22%), headache (15%) and blurred vision (7%). Only one patient required early discontinuation because of a significant rise in ALT to more than twice the normal level. Anemia occurred in 71% of patients in the treatment group; two of whom required a transfusion[50]. In a small PEP study, nearly all (96%) patients who received LPV/RTV reported at least one symptom, with the most common being diarrhea (41%), nausea (41%), stomatitis (18%) and fever (14%). All patients who received LPV/RTV had hyperbilirubinemia, 45% had anemia, and 40% had leukopenia. Other liver enzymes were normal, and all laboratory values normalized after therapy[52]. There has been a suggestion of bradycardia as related to LPV/RTV[50-56]. In HIV studies, gastrointestinal side effects are most common. Asthenia/malaise, headache, and rash are also reported[57]. With long-term use, metabolic syndrome, high cholesterol and, weight gain have been reported[57]; however, in a short-term randomized controlled trial, 55 patients (52%) in the standard-care group and 65 (68%) in the LPV/RTV group had elevated lipids. Lipid elevations in patients receiving LPV/RTV have led to reports of pancreatitis, rarely fatal, although it is unclear if this is related to LPV/RTV[58.59]. The US FDA also notes the possibility of hepatotoxicity, immune reconstitution syndrome, dysrhythmia, and hyperglycemia, although a causal relationship has not been established for any of these[59].

Given the lack of efficacy in randomized trials COVID-19, and the consistent signal of adverse effects, LPV/RTV cannot be recommended at this time.

HCQ/CQ

HCQ and CQ are drugs primarily used for prevention and treatment of malaria and treatment of other inflammatory conditions, such as rheumatoid arthritis and lupus [30]. The exact mechanism of action of these drugs is poorly understood. Their antimalarial properties are thought to be related to inhibition of blood product degradation, leading to a toxic buildup of heme, which kills the parasites[60]. In rheumatic disease, several immunomodulatory mechanisms have been proposed, but none is definitively accepted[61]. In practice, HCQ is used more commonly than CQ due to its better tolerability, but they are presumed to have a similar efficacy and mechanism of action.

In vitro studies identified antiviral properties of CQ[62], namely inhibition of viral entry into the cell[63,64]. This was confirmed to also be effective *in vitro* against SARS-CoV-2[37,62]. Several early observational studies suggested some clinical benefit of HCQ in COVID-19 and garnered much media and political attention[65-67]. The US FDA initially authorized HCQ under EUA on March 28, 2020[68], but subsequently withdrew it on June 15, 2020 due to lack of efficacy in several controlled trials[69]. To date, there are several large randomized trials (including unpublished data from trials stopped early for futility) that showed no benefit of HCQ in COVID-19: mild illness [70] and PEP[71]. Therefore, it is not recommended for use by most guidelines (Table 1).

HCQ has been associated with several adverse effects such as gastrointestinal distress, headache, allergic reactions, nausea, anxiety, skin rash, fatigue, dizziness, dry mouth, hyperglycemia, loss of appetite, cramps, depression, palpitations, tachycardia, vomiting, chest, and back and joint pain[72]. QT prolongation, hypoglycemia, myopathy, and retinal damage are well known adverse effects documented by the US FDA[73]. Interestingly, QT prolongation, which has previously been thought to be the most common adverse effect, has not been shown to be clinically relevant in all of the large randomized studies in COVID-19. That is, there has been no significant increase in cardiac dysrhythmias, so any QT prolongation is likely insignificant[74,75]. Most of the side effects were gastrointestinal in nature (*e.g.*, nausea, vomiting and diarrhea), followed by neurological (*e.g.*, dizziness, irritability and tinnitus). In randomized studies of HCQ on patients with COVID-19, side effects were nearly always higher in HCQ compared to placebo groups (Supplementary Table 1).

There are also case reports of serious adverse effects of HCQ treatment such as renal phospholipidosis in patient with undifferentiated connective tissue disease[76], cardiomyopathy in rheumatoid arthritis patients[77,78], and psychosis in a patient with Q fever[79] and one with lupus[80]. Psychiatric side effects have been reported and are well accepted, but have not borne out, *per se*, to be significant in large studies [81,82]. This, however, is confounded by the fact that side effects are often bundled and reported as "neuropsychiatric", where neurological symptoms like headache are

paired with psychiatric symptoms like anxiety, depression, and psychosis[82].

CQ is almost universally associated with more intolerance and severe complications than HCQ is[83,84]. Therefore, HCQ should almost universally be chosen over CQ when indicated. However, the randomized clinical evidence for HCQ overwhelmingly shows that it is not effective monotherapy against COVID-19, and the US FDA revoked emergency use authorization of HCQ[69]. Given its proven lack of efficacy on clinically significant outcomes and high rates of intolerance and risk of severe side effects, neither HCQ or CQ should be used in the treatment of patients with COVID-19.

VITAMIN C

Ascorbic acid or vitamin C is a water-soluble vitamin that is known for its anti-inflammatory, antioxidant and immunomodulatory properties[85]. High-dose intravenous vitamin C (often with thiamine) has been purported to improve outcomes in sepsis [86], but several large randomized trials have largely disproven this[87-89]. However, it is still a subject of ongoing research and debate[90], as some randomized trials have shown benefit in secondary outcomes like organ dysfunction or a nonsignificant trend toward reduction in mortality[87,88].

Studies have shown that severe COVID-19 infection is associated with a cytokine storm that in turn triggers immune reaction involving Th1 cells, severe inflammation, and elevated proinflammatory cytokines such as granulocyte–macrophage colony-stimulating factor and interleukin (IL)-6[91]. Vitamin C has known immunomodulatory properties, and is suspected to therefore suppress the cytokine storm[91-93]. It also is a strong antioxidant[92].

In a retrospective controlled study, oral administration of 500–1500 mg ascorbic acid had no effect on mortality and extubation rates in COVID-19 patients[94]. A case study on a COVID-19-positive 74-year-old patient with acute respiratory syndrome and sepsis reported intravenous administration of vitamin C (high dose) led to clinical improvement and rapid recovery of the patient within 5 d[95]. In another case study, a 35-year-old COVID-19 patient with mild symptoms was recommended to take 200 mL herbal tea (ginger and garlic with lemon fruit) over 12 h with daily supplementation of 2000 mg/d vitamin C. Other members of the family were recommended to take vitamin C (adults 1000 mg/d and children 500 mg/d) as prophylaxis. The patient recovered and none of the family members were infected[96]. Despite the initial reports on the beneficial effects of vitamin C for COVID-19 patients, no controlled studies have shown benefit, although no large, well-conducted studies have been completed. There are several ongoing studies of intravenous vitamin C with or without other medications in patients with COVID-19[97-99].

Vitamin C is largely thought to be safe since it is an essential nutrient; however, the doses used in critically ill patients are well above physiological needs. The typical recommended daily allowance in healthy men and women is 75 and 90 mg/d, respectively, with a tolerable upper intake level of 2 g/d[100]. The initial studies utilized 1.5 g intravenously every 6 h[86], but subsequent studies have gone as high as 50 mg/kg (*e.g.*, 3.5 g for a 70-kg patient) every 6 h[101]. The large CITRIS-ALI study found no study-related adverse events at the higher dose. In the VITAMINS trial, which used vitamin C with thiamine and hydrocortisone, two patients in the intervention group had adverse events. One had hyperglycemia, which was likely from the steroids, and one had fluid overload, which was unlikely related to the study interventions[87]. Studies in other populations have confirmed very low risk of side effects[102-104]. One patient had hypokalemia and one had kidney stones in a systematic review of cancer patients receiving vitamin C[103].

There is no great clinical evidence for the use of vitamin C in patients with COVID-19, although it is likely very safe. Further research is needed on its efficacy before it can be routinely recommended, but it might be considered in select cases.

VITAMIN D

Vitamin D is a fat-soluble steroid hormone involved in calcium homeostasis. It also has recognized immunomodulatory effects, with vitamin D deficiency associated with autoimmunity and an increased risk of infections[105]. Deficiency in vitamin D is ubiquitous, with nearly half of Americans having vitamin D deficiency[106]. Deficiency in vitamin D is associated with an increased risk of respiratory infections

[107,108], but, more importantly, supplementation of vitamin D has shown to ameliorate this risk[109]. It is understandable, therefore, that vitamin D has been proposed as a treatment for COVID-19.

In *in vitro* studies, vitamin D has been shown to be a potential mitigating agent for SARS-CoV-2 infection[110]. A case series of four patients also suggested a benefit [111]. Critically ill patients are known to have vitamin D deficiency[112-114]. However, several randomized trials of vitamin D supplementation in critically ill patients with vitamin D deficiency have shown no benefit[115]. In several studies in COVID-19, vitamin D deficiency was associated with critical illness[116-119]. One small study on supplementation in vitamin-D-deficient outpatients with COVID-19 showed that vitamin D reduced viral loads and fibrinogen levels[120]. Another open label, randomized study (*n* = 63) showed that vitamin D supplementation (calcifediol 0.532 mg on day 1 and 0.266 mg on subsequent days) in hospitalized patients reduced the risk of intensive care upgrade compared to standard care[121]. In a larger preprint randomized study (*n* = 240), vitamin D (single dose 200 000 IU cholecalciferol) supplementation did restore vitamin D levels but had no effect on clinical outcomes: hospital length of stay, intensive care unit (ICU) admission, mechanical ventilation, or mortality[122].

The most recognized side effect of vitamin D supplementation is hypercalcemia at very high doses. Associated nausea, pain, neuropsychiatric effects, constipation and fatigue can occur. The recommended daily allowance of vitamin D is 600–800 IU for adults, and the upper tolerable limit is 4000 IU daily in adults. Some patients experience gastrointestinal upset with vitamin D supplementation. There is also an association with an increased risk of urinary tract infections[123]. In the large prior randomized studies on critically ill patients, serious adverse events were rare and similar between vitamin D and placebo groups[115]. In one of these studies (with a single 540 000 IU dose), levels of calcium were shown to be slightly elevated in some patients, but with no difference in clinical outcomes. There were no differences in incidence of renal stones, and a slight nonsignificant increase in falls (7.1% *vs* 5.3%) and fall-related fractures (0.8% *vs* 0.4%) in the vitamin D group. In the other study (with a single 540 000 IU dose followed by 5 monthly 90 000 IU doses), one patient was found to be moderately hypercalcemic and have undiagnosed hyperparathyroidism, and another patient accidentally took all subsequent doses (540 000 IU) in the 1 mo following the study with no adverse event other than elevated vitamin D levels. Study drug discontinuation, fractures and falls were similar between the two groups[115]. Neither of the randomized studies in COVID-19 reported any adverse effects[121,123].

Vitamin D is likely to be safe in reasonable doses. Prior data have shown that a large number of Americans are deficient in vitamin D and critically ill patients are also deficient in vitamin D, but prior data on supplementation in critically ill patients with sepsis have not shown any benefit. The data on vitamin D in COVID-19 are largely confounded by observational bias, and whether vitamin D supplementation improves outcomes in COVID-19 remains unclear. Vitamin D should not routinely be recommended for the treatment or prevention of COVID-19 at this time, but it likely has low risk of harm.

ZINC

Zinc is a trace mineral that is essential for several body functions. It plays vital role in signaling pathways and is essential for normal immune, cardiovascular, nervous and reproductive systems[85,124]. Zinc deficiency results in immune dysfunction and supplementation of zinc improves T-cell function[125]. A randomized control study involving 231 HIV-infected patients reported zinc supplementation delayed failure of immune system and improved clinical symptoms in patients[126]. Moreover, supplementation of zinc has been reported effective as prophylaxis for respiratory tract infections, pneumonia and diarrhea in children[127,128].

Adjunctive therapy with zinc has shown improved dermatitis and mucositis in cancer patients treated by radiotherapy[129], reduced cardiovascular risk in patients with acute renal failure[130], improved clinical symptoms in asthmatic children[131], improved sleep quality[132], and reduced insulin resistance and blood glucose, and improved pancreatic beta cell function along with improved lipid profile in prediabetic patients[133]. It also has been shown in some studies to reduce symptoms of viral respiratory infections in adults[134].

Zinc has been shown, *in vitro*, to have a potent antiviral effect[135], specifically against coronaviruses. For example, SARS-CoV-infected Vero-E6 cells treated with a

combination of zinc and pyrithione showed inhibition of RNA-dependent RNA polymerase elongation and reduced template binding[136]. Another study showed that zinc reduces angiotensin converting enzyme (ACE)-2, the primary entry site of SARS-CoV-2 into cells, in rats[137]. Interesting is the notion that another proposed treatment, HCQ, serves as a zinc ionophore, aiding its entry into cells where zinc can then exert its antiviral effects. One limitation to many of these animal model coadministration studies is the use of ultra-supra-physiological concentrations of zinc[138].

Zinc deficiency in COVID-19 patients has been associated with severe infection, increased complications and mortality[139,140]. In a case report series of four patients with COVID-19, high dose oral zinc (up to 200 mg) was associated with improved respiratory symptoms after 1 d[141]. A prospective study with 242 patients did not find a significant correlation between zinc supplementation and mortality[142]. There are no standalone randomized trials of zinc in patients with COVID-19, although there is one randomized study where it was coadministered with HCQ, and zinc was not shown to increase the effects of HCQ[143]. There are also several observational studies of zinc with other therapies, like HCQ, with mixed results[144-146]. There is one ongoing randomized study of high-dose intravenous zinc as adjunctive therapy in COVID-19 critically ill patients, a pilot randomized controlled trial, and several other ongoing studies with coadministration of zinc with other therapies[147-150].

The recommended daily allowance of zinc is 11 mg/d for men and 8 mg/d for women[151]. Zinc supplementation can inhibit copper absorption and lead to copper deficiency[152,153]. Paradoxically, one study showed that 150 mg zinc supplementation caused immune dysfunction and dyslipidemia in healthy volunteers[154,155]. Zinc is found in high concentrations in the prostate, and zinc supplementation has been associated with hospitalizations for genitourinary issues[156], and even prostate cancer at doses > 100 mg/d[157]. High doses of zinc are also associated with gastrointestinal side effects, like nausea, vomiting, diarrhea and cramping.

There are several known adverse effects of zinc, some of which can be serious. Therefore, despite the possible role of zinc in prophylaxis/treatment of COVID-19, well conducted, randomized studies need to be conducted before it should be used in clinical practice.

AZITHROMYCIN

The macrolide antibiotic azithromycin is used in bacterial respiratory infections. In addition to antibacterial effects, it has immunomodulatory properties within the respiratory tract[158-160]. It also has antiviral activities[161]. *In vitro* studies have shown antiviral activity of azithromycin against Ebola, Zika, dengue and rhinoviruses [162-169]. In mice infected with H1N1 influenza virus, azithromycin pretreatment led to reduced fever and viral load[169]. Studies on mice have also shown azithromycin to be effective against enterovirus and coxsackievirus[170].

Azithromycin accumulates in high concentrations in epithelial cells, like those found in the lungs. *In vitro* studies with SARS-CoV-2-infected cells have shown antiviral activity of azithromycin[171]. There are several proposed mechanisms, but one is that macrolides like azithromycin interfere with binding of SARS-CoV-2 spike proteins to ACE2 receptor on host cells[172,173]. Macrolides also may alter the pH of the lysosomes, and therefore inhibit viral replication[174]. In other studies, lower concentrations of azithromycin were shown to have antiviral activity only when combined with HCQ[171].

Clinical studies using azithromycin in combination with other drugs have reported its potential antiviral activity, although results are mixed and inconclusive. In studies on infants with respiratory syncytial virus, azithromycin showed mixed results and no clear benefit on symptoms or inflammatory markers[175-177]. In a retrospective study of 329 patients infected with H1N1 influenza virus, combination treatment with oseltamivir and azithromycin was associated with decreased symptom severity compared to oseltamivir alone[178]. Another small randomized trial, however, showed that the combination of oseltamivir and azithromycin had a small effect on maximum fever (likely not clinically relevant) but had no effect on inflammatory cytokines compared to placebo. In observational data of 349 MERS patients, azithromycin treatment was not associated with clinical improvement, reduction in viral load, or mortality[179]. However, in a retrospective study on critically ill patients with SARS-CoV, azithromycin use was associated with decreased mortality and decreased ventilator-days[180].

Most studies with azithromycin in COVID-19 have been used with combination therapy, often with HCQ. In an uncontrolled evaluation of COVID-19 infected patients treated with azithromycin and HCQ, 97.5% of patients had no detectable virus by day 5[66]. These authors also showed an association with combination therapy increasing viral clearance over HCQ alone[66]. Other observational studies have shown no significant difference for azithromycin and HCQ in reducing viral load or clinical improvement[181]. In Iran, 56 COVID-19 patients were administered with combination of HCQ, LPV/RTV with or without azithromycin. The patients who received azithromycin had overall better condition at discharge, with shorter duration of hospital stay; however, mortality rate was the same as the control group that did not receive azithromycin[182]. A randomized trial showed no clinically significant difference among patients receiving azithromycin with HCQ compared to HCQ alone [183].

The use of azithromycin has been associated with a wide range of mild to moderate adverse effects. Most antibiotics are known to cause gastrointestinal side effects like nausea, vomiting, diarrhea and cramping, and azithromycin is no exception. *Clostridium difficile* infections are also side effects of many antibiotics, with macrolides having a moderate risk[184,185]. The inappropriate use of antibiotics can also increase resistance patterns, rendering them useless for bacterial infections in the future. Azithromycin is known to prolong QTc, with some case reports of fatal Torsades de pointes[186], and association with cardiac death in large analyses[187]. All drugs carry the risk of anaphylaxis, but this has been rarely documented with azithromycin[188]. The concerning feature is the delayed biphasic reaction, despite cessation, of which the US FDA warns[189]. Cholestatic hepatitis and transaminitis have also been reported in several patients taking azithromycin[190-193]. As noted above, azithromycin is often coadministered with other drugs, like HCQ, that may also prolong the QTc and increase the risk for cardiac adverse events and fatal dysrhythmias[194,195].

Azithromycin has known deleterious side effects and no clinical evidence for benefit of monotherapy in COVID-19. Therefore, it should not be used for treatment of COVID-19 unless sufficient evidence of clinically significant efficacy is clearly demonstrated.

INTERFERON

Interferons (IFNs) are immune system mediators with varying biological functions such as antiviral activity, pathogenic antiproliferative activity and immunomodulatory functions. Clinical studies have reported efficacy of IFN treatment for chronic viral cardiomyopathy[196] and multiple sclerosis[197], and it was previously the treatment of choice for viral hepatitis[198,199]. There are several subtypes of IFNs, the most common being alpha and beta. While there are some differences, the alpha and beta subtypes share a common multicomponent, cell surface receptor and elicit a similar range of biological responses, including antiviral, antiproliferative and immunomodulatory activities[200]. In an *in vitro* study on SARS-CoV- and MERS-CoV-infected cells, IFN-β treatment showed significant antiviral activity[201-203].

A clinical human study using combination of IFN-β1b (0.025 mg intravenously on alternate days) and LPN/RTV (400/100 mg over 12 h) for treatment of MERS patients (*n* = 95) reported lower mortality in treated patients, with greater effect in patients receiving treatment within 7 d of infection[204]. In another observational study, IFN-β along with mycophenolic acid treatment reduced mortality of MERS; however, the treatment was effective in patients with less severe disease compared to patients with severe symptoms[205].

In a clinical trial involving 80 COVID-19 patients treated with 250 g IFN-β1b on alternate days for 2 wk, the patients showed earlier clinical improvement with reduced rate of mechanical ventilation and reduced mortality with no adverse effects[206]. IFN-β1b (8 million IU on alternate days) in combination with LPN/RTN (400/100 mg BID) and ribavirin (400 mg BID) administered to 144 COVID-19 patients showed clinical improvement in symptoms, reduced viral load, and shorter recovery time of mild to moderately ill patients[207]. A randomized trial on 81 COVID-19 patients conducted in Iran reported administration of IFN-β1a (12 million IU three times/wk), HCQ (d 1: 400 mg BID; d 2–14: 200 mg BID), and LPN/RTV (400/100 mg BID) (or atazanavir/ritonavir) for 14 d showed no change in clinical recovery time, mildly shortened discharge time of patients, and significantly reduced 90-d mortality compared to the control group[208]. Another randomized trial of 60 severely ill patients randomized to IFNβ1a (subcutaneous injections of 12 000 IU on d 1, 3 and 6), IFNβ1b (subcutaneous

injections of 8 000 000 IU on d 1, 3 and 6), or placebo showed a mild difference in time to clinical improvement in the IFN groups, driven mostly by the IFNβ1a, but there was no significant difference in mortality[209].

The most common acute adverse events with IFN administration are flu-like: nausea/vomiting, fever/chills, myalgias and headache[205,206]. Adverse effects appear to be dose related, with 66% of patients treated with high-dose IFN having at least one Grade 3 adverse event and 14% a Grade 4 event. The rates of adverse events were lower in lower-dose groups, with only one patient (0.05%) having a Grade 4 adverse event in one study[210] and Grade 3 events in about 10%–15% of patients[211-213]. In the randomized study by Hung *et al*[207] on COVID-19 patients treated with IFN-β1b, ribavirin and LPV/RTV, adverse events such as nausea, diarrhea, increase in liver enzymes, and fever were observed in patients, but no significant difference was seen between the treatment and control groups. Similar findings, with the addition of some electrolyte and hematological laboratory changes, were found in a randomized trial of IFN-β1b, HCQ, and LPV/RTV or atazanvir/ritonavir[208]. Again, there were no significant differences between the groups, with more of the adverse events occurring with a higher frequency in the control group. In another study with similar therapy, there were eight (19%) infusion-related reactions, one (2%) hypersensitivity reaction, and a clinically significant increase in neuropsychiatric events (*n* = 4, 10% *vs* 0%). There are well-recognized longer-term side effects of IFN therapy, although these are mostly with longer therapy for cancer or viral hepatitis. The most common is chronic fatigue[214]. There have also been a wide range of other reported effects: gastrointestinal, hepatic, psychiatric, endocrine and rarer neurological, autoimmune, pulmonary, and cardiac complications[214].

The evidence gathered by clinical studies so far suggests the potential of IFN-based therapies, particularly IFN-β1b and IFN-β1a, as a therapeutic option for COVID-19; however, more clinical trials with larger populations should be conducted to confirm this. Furthermore, there is a significant potential of adverse effects with this therapy.

INTERLEUKIN ANTAGONIST THERAPIES (TOCILIZUMAB, SARILUMAB AND ANAKINRA)

SARS-CoV-2 is associated with elevated levels of IL-6 and cytokine storm in patients with severe infection[215,216]. Tocilizumab (TCZ), and sarilumab are monoclonal antibody blocking agents for IL-6 receptor, and siltuximab is a monoclonal antibody directed at IL-6. Historically, the FDA approved TCZ (intravenous) for rheumatoid and juvenile arthritis[217], sarilumab (subcutaneous) for rheumatoid arthritis[218], and siltixumab (intravenous) for Castleman's disease[219]; however, the US FDA more recently added an indication to TCZ for patients with cytokine storm receiving CAR-T (chimeric antigen receptor T) immunotherapy in 2017[220]. They have been used successfully in other inflammatory conditions. Some examples include Takayasu arteritis[221] and systemic sclerosis[222].

IL-1, particularly IL-1α and IL-1β, is also elevated in patients with severe COVID-19 [223], and the inflammatory overactivation (cytokine storm) in these patients has been compared to that found in hemophagocytic lymphohistiocytosis (HLH) or macrophage activation syndrome (MAS). Therefore, the IL-1 receptor antagonist anakinra (subcutaneous) has also been proposed to be helpful in critically ill patients with COVID-19[224,225]. Anakinra was initially approved by the US FDA for the treatment of rheumatoid arthritis and then the rare congenital deficiency of IL-1 receptor antagonist and neonatal onset multisystem inflammatory disease[226]. It has also been used successfully in several other inflammatory conditions; most notably HLH/MAS [227-229].

Canakinumab is a monoclonal antibody against IL-1β, specifically. It also, has been suggested for use in COVID-19, but is only currently approved for use in periodic fever syndromes (*e.g.*, familial Mediterranean fever) and juvenile idiopathic arthritis [230].

Preclinical evidence of effectiveness of TCZ was suggested by an *in vitro* study with lipopolysaccharide-induced THP-1 cell line as a sepsis model. In this study, TCZ treatment for 24 h reduced phagocytosis, cytokine production and immune activation, implying potential of TCZ as a therapeutic option for cytokine storm[231]. In a study in mice with severe H1N1 influenza virus infection, IL-6 was associated with activation of the immune system that in turn induced muscular dysfunction during respiratory distress and TCZ treatment attenuated severe muscular dysfunction[232]. In another rat sepsis model, TCZ treatment reduced mortality in rats with sepsis and

inhibited the inflammatory process inducing renal and lung injury[233]. Analysis of single cells of critically ill COVID-19 patients receiving TCZ showed inhibition of inflammation and associated cytokines. The immune cells (CD8+ T cells and B cells) were stable, thereby suggesting cytokines and their receptors as potential targets for future therapies[234].

The first case report on effectiveness of TCZ administration (a single IV dose at 8 mg/kg) to a 60-year-old patient with multiple myeloma and severe COVID-19 showed that he recovered from infection within 10 d of drug administration[235]. An uncontrolled case series of critically ill COVID-19 patients suggested TCZ was associated with rapid clinical improvement[236,237]. In an observational study on 1351 patients (40% critically ill), TCZ treatment was associated with reduced mortality and mechanical ventilation[238]. Another observational study on COVID-19 patients (*n* = 196) suggested effectiveness of TCZ + steroid treatment in clinical improvement of intubated patients[239]. Given that steroids have known benefit and the observational nature of the data, it is unclear how much of this benefit can be attributed to TCZ *per se.*

There have been several equivocal randomized trials on the use of TCZ in patients with COVID-19. In one study, TCZ within 24 h of admission did not improve outcomes in 123 patients with PaO_2/FiO_2 between 200 and 300 and inflammatory phenotype (*i.e.*, fever or elevated C-reactive protein)[240]. Another randomized trial of 377 patients with COVID-19 who were hospitalized but not intubated showed that TCZ reduced the composite mortality of mechanical ventilation or mortality, but not mortality alone[241]. The other randomized trial on the topic showed no difference between TCZ and placebo in terms of death or need for mechanical ventilation[242]. Preliminary results from the industry-sponsored study COVACTA also showed disappointing results in composite outcome or mortality for patients with severe COVID-19[243]. The other industry-sponsored study on TCZ in patients hospitalized with COVID-19 (EMPACTA) showed preliminary results with a relative 44% reduction (19% *vs* 12%) in the composite outcome of mechanical ventilation or death, but, again, no difference in 28-d mortality[244]. The preprint of a large (*n* = 755), randomized trial of patients (the REMAP-CAP study) showed critically ill COVID-19 patients receiving 8 mg/kg of TCZ within 24 h of ICU admission had a 7.8% absolute reduction in mortality[245]. This study also had a smaller group who received 400 mg sarilumab, which had a 13.6% reduction in mortality, but a much wider confidence interval, although still statistically significant. TCZ and sarilumab were effective across all secondary outcomes, including 90-d survival, time to ICU and hospital discharge, and improvement in the World Health Organization ordinal scale at day 14. Secondary analyses in this study suggested that steroids in combination with IL-6 antagonism had an additive protective effect[245]. The industry-sponsored study on sarilumab (and the only other large, *n* = 420, randomized trial to date in COVID-19) showed no difference in clinical improvement[246].

Anakinra was shown to be associated with improved clinical outcomes in two small retrospective case–control studies[247,248], and two small prospective observational studies[249,250]. No randomized study have been performed to date, but several are ongoing[251,252].

Of course, interleukin inhibitors raise concern for serious infections. Indeed, in the long-term randomized trials of these agents, there is an increase in risk of infections, mostly pneumonia, sinusitis, pharyngitis, and urinary infections[217-219,226,230]. There were reports of serious infections requiring hospitalization and opportunistic infections, but they were less common. This will be important to consider when selecting patients who are critically ill with COVID-19 for these medications, and may have concomitant bacterial infections. The three subcutaneous formulations (sarilumab, canakinumab and anakinra) are associated with local injection site reactions, at rates of 5%–10% for sarilumab[218], 7%–9% for canakinumab[226], and about 15% for anakinra[230]. Laboratory abnormalities appear to be associated with this class of medications and include neutropenia, thrombocytopenia, liver function abnormalities, and elevated triglycerides (Table 2). Reports of mild symptoms like nausea, headache, nausea, and abdominal pain exist, but appear no higher than for placebo. There have been rare reports of gastrointestinal perforation, mostly associated with coadministration of steroids and nonsteroidal anti-inflammatory drugs. Anaphylaxis is a known rare complication (< 1%).

In the five of six randomized trials of TCZ for COVID-19, concomitant infections were shown to be higher in the placebo/standard care groups. Mild reactions were more common than serious ones. Laboratory abnormalities seem to contribute the most to any increased signal of adverse effects, mostly neutropenia and sometimes elevated liver function tests. Differences in triglyceride levels were not reported.

Drug	Class	Adverse effects
Anakinra	Interleukin 1 inhibitor	Abdominal pain; anaphylaxis; elevated liver enzymes; flu-like symptoms; headache; local reactions; nausea/vomiting/diarrhea; neutropenia; sinusitis
Canakinumab	Anti-interleukin 1β monoclonal antibody	Abdominal pain; elevated liver enzymes; flu-like symptoms; hematologic cytopenias; hypersensitivity reactions; local reactions; nausea/vomiting/diarrhea; sinusitis
Dexamethasone	Corticosteroid	Bone loss; edema/weight gain; hyperglycemia; hypernatremia; hypertension; myopathy; neuropsychiatric disturbance; peptic ulcer disease; reactivation of latent infections (*i.e.*, TB or strongyloidosis); secondary infections; venous thromboembolism
Interferon-α	Interferon	Elevated liver functions; flu-like symptoms; hematological cytopeniaInfusion reaction; local reaction; nausea/vomiting; neuropsychiatric disease
Interferon-β	Interferon	Elevated liver functions; flu-like symptoms; hematological cytopeniaInfusion reaction; local reaction; nausea/vomiting; neuropsychiatric disease
Siltuximab	Anti-interleukin 6 monoclonal antibody	Elevated liver enzymes; gastrointestinal perforation; headache/dizziness; hyperuricemia; hypersensitivity reaction; neutropenia; pruritis/rash; reactivation of latent infection (*i.e.*, HBV); secondary infections
Sirulimab	Anti-interleukin 6 Receptor monoclonal antibody	Elevated liver enzymes; gastrointestinal perforation; hypersensitivity reaction; neutropenia; reactivation of latent infection (*i.e.*, HBV); secondary infections
Tocilizumab	Anti-interleukin 6 Receptor monoclonal antibody	Elevated liver enzymes; gastrointestinal perforation; changes in platelets and lipids; hypersensitivity reaction; neutropenia; reactivation of latent infection (*i.e.*, HBV); secondary infections

Table 2 Common adverse reaction of immunomodulators used in treatment of COVID-19

TB: Tuberculosis; HBV: Hepatitis B virus.

Gastrointestinal perforation did not appear to be increased, even when steroids were coadministered.

Therefore, there appears to be some emerging evidence of the benefit of interleukin blockade in critically ill patients with COVID-19, with the most promising agent being TCZ. There are theoretical risks of serious adverse events, most notably serious infections, but they do not appear to be increased in randomized trials. There are some mild events, with neutropenia being the most common. In carefully selected critically ill patients, early administration of TCZ (within the first 24 h) may be considered. Other agents require further study, which is ongoing.

IVERMECTIN

Recently, the antiparasitic agent ivermectin has gained interest as an outpatient treatment for COVID-19, mostly by the I-MASK group[253]. Despite that it is primarily known as an antiparasitic agent, ivermectin is known to have *in vitro* activity against many viruses, including West Nile encephalitis virus[254], HIV[255,256], and dengue [255-257], Chikungunya[258], adenovirus[259] and influenza[256,260] viruses. Ivermectin also has several anti-inflammatory properties *in vitro* and in animal models [261-263]. Most notably, ivermectin has been shown to have antiviral properties against SARS-CoV-2 *in vitro* and in animal models[264-266].

Ivermectin has been proposed not only for treatment, but also prophylaxis of patients at high risk for COVID-19[267]. Preliminary data from a large randomized trial show that ivermectin (2 doses, 72 h apart) may reduce development of symptoms of close household contacts of patients with COVID-19 (7.4% *vs* 58.4%). Another preprint study randomized 200 household contacts to ivermectin and personal protective equipment (PPE) or PPE alone and showed progression to symptomatic disease improved with ivermectin (10% *vs* 2%)[268].

In one observational study, ivermectin with doxycycline was associated with improved viral clearance[269]. There are several retrospective/observational trials that suggest an association between ivermectin and improved clinical outcomes[270,271], including mild to moderate COVID-19[272], and patients hospitalized with COVID-19 [273]. One randomized study on 70 patients hospitalized with COVID-19 in Iraq randomized them to receive both ivermectin (2–3 d) and doxycycline *versus* standard therapy. They showed a reduction in progression, and an improvement in mortality in severe patients, but worsened mortality in critically ill patients; all limited by the small sample size[274]. A small, three-arm study in Bangladesh randomized 72 patients

hospitalized with COVID-19 to either ivermectin (5-d course), ivermectin and doxycycline, or placebo. They showed that clinical symptoms of fever, cough and sore throat were comparable among the three groups. Virological clearance was earlier in the ivermectin treatment arm when compared to the placebo group (9.7 *vs* 12.7 d), but this was not the case for the ivermectin and doxycycline arm (11.5 d)[275]. One large study randomized 100 patients each to HCQ plus standard care or ivermectin plus standard care in severe and mild/moderate groups (4 relevant groups), and showed that ivermectin improved progression of disease and mortality compared to HCQ and improved multiple laboratory parameters (this study has subsequently been retracted due to concerns of plagiarism and falsified data)[268]. Larger randomized trials are ongoing, with one study of 400 patients with mild disease and less than 7 d of symptoms recently published showing no benefit of 300 g/kg ivermectin daily for 5 d [276].

For parasitic infections, symptoms associated with Mazotti reactions (life-threatening allergic response to proteins released by dying parasites) are noted, but they would be unlikely to occur in viral infections like COVID-19. Based on US FDA data, less than 2% of patients had each of the following minor symptomatic adverse effects: rash, fatigue, gastrointestinal symptoms, somnolence, headache, myalgia and tremor. Slightly more patients reported dizziness/vertigo[277]. There were minor laboratory abnormalities in a small proportion of patients (1%–3%): leukopenia, eosinophilia and elevated liver functions[277]. Rare neurological manifestations, as severe as coma, have been noted and are thought to be due to congenital absence of ATP-binding cassette subfamily B member 1 transporter[278]. Two randomized trials of treatment of patients with COVID-19 with ivermectin reported no adverse events in either group, but these studies were small (142 patients combined) [274,275]. In a larger, more recent study, 154 patients (77%) in the ivermectin group and 161 (81.3%) in the placebo group reported adverse events[276]. Fifteen patients (7.5%) in the ivermectin group *versus* five (2.5%) in the placebo group discontinued treatment due to an adverse event. Headache was the most common, occurring in 52% of patients in the ivermectin group and 56% on patients in the placebo group[276].

Ivermectin has promise and a relatively reassuring safety profile in other indications, but there is not enough clinical evidence at this time to support its use for treatment of COVID-19. Further research should be directed at this intervention.

CONVALESCENT PLASMA THERAPY

Passive immunization or plasma transfusion has been used for treatment and prevention of infectious diseases since the 19th century. Pathogen-specific immuno-globulins isolated from plasma or whole blood of surviving patients can serve as a lifesaving therapy for those suffering from an infectious disease. This technique was used to treat diphtheria and bacterial infections in the 19th century[279] and the Spanish influenza outbreak[279,280]. Moreover, plasma transfusion therapy has been used in H5N1 (Asian avian) influenza virus infection[280,281], H1N1 (swine flu) influenza virus infection[282,283], and Ebola virus infection[284-287]. Passive immunotherapy has also been favorable for treatment of SARS[288,289] and MERS [290,291]. It is not considered first line for any of these indications.

The US FDA offered convalescent plasma therapy for clinically serious patients on EUA based on reported efficacy of the treatment during historic outbreaks[292]. Several small uncontrolled case series involving COVID-19 patients reported complete recovery with no adverse effects after patients received plasma transfusion[293-296]. In another observational study with 5000 critically ill participants, plasma transfusion was associated with decreased mortality when received earlier or if the transfused plasma had higher IgG levels. A large observational Mayo Clinic study on 20 000 patients showed similar results to earlier transfusion[297].

On top of the aforementioned case series, observational studies of plasma transfusion for treatment of COVID-19 infection suggested beneficial effects[298,299]. However, subsequently, three randomized trials (2 of which were stopped early) showed no benefit[300-302].

The risks of convalescent plasma mostly mirror those of any transfusion: infections (*e.g.*, HIV, hepatitis, *etc.*), immune reactions, anaphylaxis, hemolysis, and transfusion-associated circulatory overload, and transfusion-associated lung injury. These risks are generally thought to be less in plasma than red blood cell transfusions, but cases of the development of ARDS after convalescent plasma transfusion have been reported[285, 290]. In the large Mayo Clinic study with 20 000 patients, the incidence of serious

adverse events was low; these included transfusion reactions (< 1%), thromboembolic or thrombotic events (< 1%), and cardiac events (3%). Most thromboembolic or thrombotic events (*n* = 55) and cardiac events (*n* = 562) were judged to be unrelated to the transfusion[297]. In one randomized trial, minor adverse events of pain at the local infusion site, chills, nausea, bradycardia, and dizziness were reported in one patient (0.4%) each. Fever and tachycardia were reported in three patients (1.3%) each. Dyspnea and intravenous catheter blockage were noted in two participants each (0.8%). Mortality was assessed as possibly related to convalescent plasma transfusion in three patients (1.3%)[300]. In another study in Wuhan on 86 patients (43 assigned to receive convalescent plasma), no serious adverse events were reported[301]. Another large randomized trial on 101 patients (51 randomized to receive convalescent plasma) reported two serious adverse events related to convalescent plasma administration: one patient with chills and rash 2 h after administration, deemed a nonsevere allergic reaction and a probable non-severe febrile hemolytic transfusion reaction; and another patient with life-threatening COVID-19 who developed severe dyspnea and cyanosis within 6 h of administration, which was deemed possibly transfusion-related dyspnea [302].

Given there was no proven efficacy in several randomized trials and a risk of serious reactions and adverse events, convalescent plasma should not be used for the treatment of COVID-19 at this time.

DISCUSSION

The on-going COVID-19 pandemic highlights the limitation and the need for exploring therapeutic options for coronavirus infections. Though previous SARS (2003) and MERS (2012) outbreaks initiated *in vitro*, *in vivo*, and clinical research, so far there is no specific drug to treat coronavirus infections. These outbreaks and the current coronavirus pandemic indicate the possibility of future coronavirus outbreaks and the threat these viruses pose to public health globally. Even mutations of the current SARS-CoV-2 have already been reported[303,304]. Since drug development is a time-consuming process, repurposing the existing drugs offer the fastest option for treatment of infectious diseases. However, this does not negate the need for well-done randomized trials to evaluate efficacy. Safety can be extrapolated from prior randomized studies, but also needs to be examined in studies in patients with this novel disease process. Recently published *in vitro* and *in vivo* studies on the efficacy of different therapeutic options for prophylaxis and treatment of SARS-CoV-2 infection were analyzed for this review.

Dexamethasone and other steroids are a widely accepted intervention for COVID-19 patients requiring oxygen, which have shown in several studies to reduce mortality and disease progression. They do have well-known side effects, many of which can be monitored (hyperglycemia) or reduced (gastrointestinal bleeding, myopathy). They have the strongest evidence for efficacy, but must be used in appropriate patients (*i.e.*, those requiring supplemental oxygen).

An analysis of the data presented in this review suggests remdesivir and TCZ (an IL-6 receptor antibody) are promising therapeutic options for select patients with COVID-19, but they, too, have risks of adverse events. Remdesivir should be considered for patients hospitalized with COVID-19 and TCZ considered for early administration in a select group of critically ill patients with COVID-19. In large trials, the rates of serious adverse events using these drugs seem to be low. Nevertheless, randomized, placebo and controlled clinical trials with larger and geographically diverse population size must be conducted to test the efficacy of these treatment options.

Although available data on different treatments such as azithromycin, IFNs, anakinra, and ivermectin have provided some evidence on their efficacy against COVID-19, this review demonstrates clearly that additional data are needed to establish the efficacy of these treatments at a clinical level. Available data are only preliminary and lack larger population and comparative data; moreover, incidences of adverse events should be analyzed to establish the safety of these drugs for clinical administration.

Vitamin C has not shown to be reliably effective in septic shock, but there are no major studies in COVID-19. Zinc also has plausible mechanistic antiviral properties and a signal of benefit in prior studies on respiratory infection but no large studies as monotherapy in COVID-19. Vitamin D also has no benefit in randomized studies in general critically ill patients, but it has shown some mixed evidence in the few

randomized trials in COVID-19. These supplements are all likely safe interventions that need further research.

The previously widely used therapies HCQ, LPV/RTV, and convalescent plasma have robust randomized evidence of no beneficial effect. They, like all therapies, have the potential for adverse effects. They should be abandoned for COVID-19 therapy unless convincing new evidence emerges. These therapies highlight the problems with basing treatment decisions on mechanistic studies, case reports, or observational data. Clinicians would be wise to bear this recent history in mind when evaluating potential new therapies.

Additionally, more therapeutic options including use of alternative medicine, supplements, drug combinations, and nonpharmacological therapies must be considered and tested for effective management of COVID-19 infection.

LIMITATIONS

This review is limited by the limitations of the studies included: limited available data, lack of comparative data, lack of randomization, and number of participants. While we did search several databases and use several methods, this review is not a systematic review and is therefore subject to bias and missing potentially germane articles. Research is rapidly ongoing on the topic of COVID-19 diagnosis and treatment, so the conclusions in this article are based on available evidence. Also, this review was done on drugs used in isolation. It is possible that combination therapy may yield different results or safety risks.

CONCLUSION

Dexamethasone appears to be the most efficacious drug for patients with COVID-19, but it should only be used in patients requiring supplemental oxygenation. Remdesivir may reduce length of hospitalization with mild side effects. While they do not have enough evidence to be recommended at this time, ivermectin, and zinc should be studied further for early illness and IFN and interleukin blockade should be studied for critical illness. HCQ/CQ, vitamins C/D, and azithromycin have no convincing evidence of benefit at this time.

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