Current Approaches to COVID-19: Therapy and Prevention

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ABSTRACT

The coronavirus disease-2019 (COVID-19) pandemic has affected millions of people worldwide. As our understanding of the disease is evolving, our approach to the patient management is also changing swiftly. Available new evidence is helping us take radical decisions in COVID-19 management. We searched for inclusion of the published literature on treatment of COVID-19 from around the globe. All relevant evidences available till the time of submission of this article were briefly discussed. Once advised as blanket therapy for all patients, recent reports of hydroxychloroquine with or without azithromycin indicated no potential benefit and use of such combination may increase the risk of arrhythmias. Clinical evidence with newer antivirals such as remdesivir and favipiravir is promising that can hasten the patient recovery and reduce the mortality. With steroids, evidence is much clear in that it should be used in low dose and for short period not extending beyond 7 days in moderate to severe hospitalized patients. Low-molecular-weight heparin should be initiated in all hospitalized COVID-19 patients and dose should be based on the coagulation profile and risk of thromboembolism. Immunomodulatory drugs such tocilizumab may be considered for severe and critically ill patients to improve the outcomes. Though ulinastatin can be a potential alternative immunomodulator, there is lack of clinical evidence on its usage in COVID-19. Convalescent plasma therapy can be potentially lifesaving in critically ill patients. However, there is need to generate further evidence with various such therapies. Though availability of a potent vaccine is awaited, current treatment of COVID-19 is based on available therapies, which is guided by the evidence. In this review, we discuss the potential treatments available around the globe with current evidence on each of such treatments.

Keywords: Coronavirus, Coronavirus disease-2019, Heparin, Hydroxychloroquine, Remdesvir, SARS-CoV-2, Tocilizumab.

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INTRODUCTION

The coronavirus disease-2019 (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has affected 7,410,510 people globally and caused 418,294 deaths, so far. The majority of patients of COVID-19 develop only mild or moderate illness; however, 5% require organ support in the intensive care unit (ICU).[1,2] The case fatality rate (CFR) varies in different countries. The estimated CFR from some of the majorly affected countries differs substantially from 14.27 in Italy, 14.25 in the United Kingdom (UK), 11.18 in Spain to 5.6 in the United States, 5.48 in China, 4.71 in Germany, and 2.85 in India.[1] The SARS-CoV-2 virus appears to cause immune dysregulation leading to cytokine storm and progressively worsening organ damage in patients who are severely affected.[3] So far, there is no effective therapy, and most healthcare systems have been left to rely on social distancing, hand hygiene, and personal protection for the general population and barrier precautions for healthcare workers (HCWs). Therefore, there is an urgent need to identify therapeutic and preventive options for COVID-19. Considering the complexity of the disease, researchers have tried to approach the management of COVID-19, targeting multiple plausible mechanisms of this highly contagious disease. These involve trialing out antiviral, anti-inflammatory, and immunomodulatory therapies. In this review, we discuss the current status of investigational drugs and vaccines being developed for COVID-19. We believe this will enable clinicians to make an informed decision and optimize the patient outcomes.

CURRENT OPTIONS BEING TRIED FOR COVID-19 TREATMENT

Therapeutic options management of COVID-19 can be broadly categorized into antiviral agents, drugs repurposed as antiviral drugs, immunomodulators, and adjunctive treatments (Table 1).

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Table 1: Currently drugs under investigation for treatment of COVID-19

Drug class	Molecules
Antiviral drugs	Remdesivir
	Lopinavir-ritonavir
	Favipiravir
	Others (umifenovir, ribavarin, oseltamivir)
Repurposed as antiviral drugs	Chloroquine/hydroxychloroquine ± azithromycin
	Nitazoxanide
	Ivermectin
	Doxycycline
	Nafamostat, camostat
Immunomodulatory drugs	Steroids
	Tocilizumab, sarilumab
	Interferon-1
	Bevacizumab
	Fingolimod
	Eculizumab
	Ulinastatin
	Itolizumab
Adjunctive therapies	Anticoagulant (LMWH/UFH)
	High-dose IV vitamin C
	Convalescent plasma
	CytoSorb
Vaccines	

Antiviral Drugs

As the majority of patients with COVID-19 have a mild infection, there may not be a need for any specific antiviral therapy in most patients. However, our experience with influenza and severe acute respiratory syndrome (SARS) infections indicates that early institution of the antiviral therapy may shorten the course of disease. Though there is a pressing need to find an antiviral drug from randomized clinical trials (RCTs), most of these agents are used based on *in vitro* and extrapolated data.[4]

Remdesivir

Remdesivir is a nucleoside analog prodrug. *In vitro* studies have demonstrated its inhibitory effect on pathogenic animal and human coronaviruses including SARS-CoV-2.[5]

A study from Grein et al. tried using remedesivir in 61 patients with severe COVID-19, for a 10-day period, and found an improvement in oxygen-support class in 68% of patients. In median 18 days of follow-up, 57% patients were extubated, 47% were discharged, whereas 13% of them died.[6]

Antinori et al. conducted a prospective open-label study in 35 severe COVID-19 patients. Overall, 63% completed the 10-day course of remdesivir and 22.8% discontinued treatment due to adverse events (AEs). At day 28, 82.3 and 33.3% of patients from the ward ($n = 17$) and the ICU ($n = 18$) were discharged whereas 5.9 and 44.8% died. Hypertransaminasemia (42.8%) and acute kidney injury (22.8%) were the frequently encountered severe AEs.[7]

A double-blind, multicenter, placebo-controlled RCT was performed by Wang et al. in adults with severe COVID-19 infection. Compared to placebo, remdesivir was not associated with significant improvement in time to clinical improvement.

In patients with symptom duration of ≤10 days, time to clinical improvement was numerically faster but statistically nonsignificant with remdesivir. The author concluded that there was a need for further studies to confirm whether early initiation of remdesivir results in clinical improvements.[8]

A recent trial showed a shortened time to recovery in patients admitted with evidence of lower respiratory tract involvement with COVID-19, with the use of remdesivir as compared to placebo [11 vs 15 days [(rate ratio for recovery, 1.32; 95% CI, 1.12–1.55; $p < 0.001$)]. There were no significant adverse effects as well with remdesivir. However, it remains to be seen if this effect persists in patients with severe COVID-19.[9]

On June 1, 2020, the Indian regulatory authority—Drug Controller General of India (DCGI)—has granted "restricted emergency use" of remdesivir in hospitalized COVID-19 patients.[10]

Lopinavir/ritonavir

Lopinavir is an antiretroviral drug used in combination with ritonavir, which is a booster agent. In an *in vitro* study, lopinavir showed an antiviral effect against the SARS-CoV-2 virus in Vero E6 cells.[11]

In a study from Ye et al. involving 47 patients, compared to the standard of care, the addition of lopinavir/ritonavir to the standard of care resulted in a shorter time for temperature reduction as well as a less number of days (7.8 ± 3.09 days vs control: 12.0 ± 0.82 days, $p = 0.0219$) necessary for the negative report on SARS-CoV-2. The authors suggested use of this combination along with other pneumonia adjuvant drugs in COVID-19 treatment.[12]

Another study from Li et al. assessed the efficacy and safety of lopinavir/ritonavir ($n = 34$) or arbidol (Umifenovir) monotherapy ($n = 35$) in mild to moderate cases. Compared to the control population ($n = 17$), there was no significant benefit with either therapy in the primary endpoint of the rate of positive-to-negative conversion of SARS-CoV-2 nucleic acid. Additionally, there were no differences in groups with regards to rates of antipyresis, cough alleviation, or improvement of chest CT at days 7 or day 14.[13]

In an open-label RCT involving 199 hospitalized patients with severe COVID-19, Cao et al. found no difference in control (standard care) and lopinavir/ritonavir treatments, for time to clinical improvement or mortality at day 28. The frequency of gastrointestinal side effects (13.8%) was more with combination treatment, leading to discontinuation of therapy.[14]

Umifenovir

Umifenovir is a hemagglutinin inhibitor that blocks the influenza virus entry in the host cell. It also stimulates the endogenous production of interferon against virus replication, enhances the phagocytic function of macrophages, and activates natural killer cells.[15,16]

In 81 patients with COVID-19, Lian et al. performed a retrospective study comparing umifenovir ($n = 45$) to the no treatment ($n = 36$) group. There was no difference to time to negativity of COVID-19, RT-PCR in either group at 7 days or overall; however, hospital length of stay (LOS) was significantly longer with umifenovir.[17]

Favipiravir

Favipiravir (FPV), a pyrazine carboxamide derivative, is a novel broad-spectrum antiviral, which is used for the treatment of influenza.[18] In an open-label study, Cai et al. compared the effects of FPV to lopinavir/ritonavir for the treatment of COVID-19. The FPV ($n = 35$) dose was 1600 mg twice daily on day 1 and 600 mg twice daily from day 2 to 14. The lopinavir/ritonavir ($n = 45$) dose was 400 mg/100 mg twice daily for 14 days. Interferon-α was coadministered by aerosol inhalation (5 million U twice daily) in both arms. The viral clearance time was significantly shorter in the FPV arm (4 days vs 11 days, $p < 0.001$), which was also seen in the multivariate analysis. The chest imaging improvement rate was significantly greater in the FPV arm (91.43% vs 62.22%, $p = 0.004$), which persisted even after adjustment for potential confounders. Fewer AEs were seen with the favipiravir arm as compared to control.[19]

In India, FPV is under evaluation in phase III, open-label, randomized study (CTRI/2020/05/02511) compared to the standard of care in adult patients with mild to moderate COVID-19.[20]

Ribavirin

Ribavirin, a guanosine analog, interferes with the replication of RNA and DNA viruses. Favorable clinical outcomes with the use of ribavirin have been indicated in SARS-CoV and MERS-CoV outbreaks.[21] In a multicenter, prospective, open-label, randomized, phase 2 trial from China, Hung et al. compared the combination of therapy with lopinavir/ritonavir, ribavirin, and interferon β-1b ($n = 86$) with lopinavir/ritonavir (control, $n = 41$). The median duration from symptom onset to starting therapy was 5 days. The primary endpoint, i.e., median time to nasopharyngeal swab negativity, was significantly shorter in combination treatment (7 days vs 12 days, $p = 0.0010$). Adverse events were limited to nausea and diarrhea. There were no deaths reported in any group. They concluded that early combination therapy can achieve faster defervescence.[22]

Oseltamivir

Oseltamivir in its active form inside the body binds to and inhibits the active site of the neuraminidase enzymes that are present on all influenza viruses.[23] Considering the highly selective action of oseltamivir in influenza viruses, it is expected to be less likely effective in COVID-19. In a Chinese observational study, where 89.9% (out of 138) patients were given oseltamivir, there was no effect on clinical outcomes.[24]

OTHER DRUGS REPURPOSED AS ANTIVIRAL DRUGS

Antimalarial Drugs

Chloroquine/hydroxychloroquine

Chloroquine (CQ) or hydroxychloroquine (HCQ) may act by multiple mechanisms. It inhibits the pre-entry step by inhibiting viral particle binding to cellular receptors, impairing the early stage of viral replication by changing the pH in endosomes, and interfering with posttranslational modification of viral proteins. In addition, immunomodulatory effects by virtue of inhibition of interleukins (ILs) such as IL-1beta and IL-6 also contribute to reducing the inflammatory response to SARS-CoV-2.[25]

An *in vitro* study demonstrated that half maximal effective concentration (EC50) for SARS-CoV-2 with CQ was lower than HCQ, indicating both were capable of *in vitro* inhibition.[26]

A large observational study from New York, which included 1,376 patients, of whom 811 (58.9%) received HCQ within 48 hours of hospitalization, found that there was no association of treatment with HCQ and the primary endpoint, i.e., death or need for intubation, over a median follow-up period of 22.5 days.[27]

Horby and Landray, the principle investigators of the Recovery Trial, reported the results of the interim analysis. To date, 1,542 patients were randomized to HCQ and 3,132 to usual care. There was no effect on 28-day mortality [25.7% HCQ vs 23.5% usual care; HR 1.11 (95% CI 0.98–1.26, $p = 0.10$)] or on hospital LOS. Therefore, the recruitment to HCQ was stopped.[28] Whether HCQ given early in asymptomatic COVID-19 or patients with mild illness remains to be seen.

Hydroxychloroquine Plus Azithromycin

Some investigators have used azithromycin (AZT) in addition to HCQ in suspected bacterial superinfection.

A very small study from Molina (11 hospitalized patients) looked at outcomes of patients treated with HCQ and AZT. In these patients, nasopharyngeal swabs remained positive for SARS-CoV-2 RNA even after 5–6 days of beginning the treatment.[29]

In an early study from France, which was an open-label study in 36 COVID-19 patients, the authors found a significant 100% viral clearance with HCQ-AZT on day 6, as compared to lower clearance rates with HCQ alone (57.1%) or the control group (12.5%). This study has been widely criticized in the literature since its publications ($p < 0.001$).[30] In fact, the International Society of Antimicrobial Chemotherapy (ISAC) published a statement on the IACC paper on its website, which stated, "ISAC shares the concerns regarding the above article published recently in the International Journal of Antimicrobial Agents (IJAA). The ISAC Board believes the article does not meet the Society's expected standard, especially relating to the lack of better explanations of the inclusion criteria and the triage of patients to ensure patient safety."[31]

A recent retrospective multicenter trial from Rosenberg et al. compared the in-hospital mortality rate in 1,438 hospitalized patients, with HCQ plus AZT (735 patients) compared to HCQ (271 patients) or AZT (211 patients) alone or no therapy (221 patients). The mortality rates in these four groups were 25.7, 19.9, 10, and 12.7%, respectively. Compared to the control arm, the risk of cardiac arrest was significantly higher with the combination therapy, but not with either drugs used alone.[32]

Because of the increased risk of QT prolongation and cardiac death with concomitant use of HCQ and AZT, the American College of Cardiology, the American Heart Association, and the Heart Rhythm Society suggested QT assessment and monitoring protocol for studies conducted with two drugs together.[33,34] DeJong and Watcher in their editorial raise a concern that *amidst the rising toll of COVID-19, healthcare settings are under enormous and understandable pressure to do something for it. We must understand the potential use of any therapy should be based on medicine and the notion should first do no harm. Best way to protect the patients is to stay grounded in evidence and to fight misinformation.*[35]

Antiprotozoal Drugs: Nitazoxanide

It is a broad-spectrum antiparasitic agent, which is being suggested for treatment of influenza and other viral respiratory infections.[36] Some investigators have suggested the use of nitazoxanide in COVID-19 in combination with AZT and HCQ,[37,38] but no clinical studies have yet been performed. Though potential evidence from

in vitro studies is suggestive, lack of clinical studies makes it difficult to determine its recommendation in COVID-19.

Antiparasitic Drugs: Ivermectin

An *in vitro* study from Caly et al. demonstrated that ivermectin inhibits the SARS-CoV-2.[39]

However, there are concerns about the therapeutic levels of drug being achieved in the usual doses.[40] Currently, there is one comparative ongoing trial (NCT04391127) of this drug (comparison with HCQ, placebo, three arms) for treatment of COVID-19.[41]

Antibiotics: Doxycycline

Coronavirus is known to bind to metalloproteases (MMPs) of the host to ensure viral survival. Commonly used antibiotics like doxycycline (tetracycline) is known to chelate zinc from MMPs. This chelating property of doxycycline may help inhibit COVID-19 infection. In France, a phase III randomized, double-blind placebo-controlled clinical study is currently recruiting nonhospitalized patients with COVID-19 to confirm the safety and efficacy of doxycycline (ClinicalTrials.gov Identifier: NCT04371952).[42]

Serine Protease Inhibitors: Camostat, Nafamostat

The host cell protease TMPRSS2 is necessary for SARS-CoV$_2$ spike protein receptor priming for its effective attachment to the ACE2 receptor.[43] Given these observation, inhibition of TMPRSS2 with serine protease inhibitors like camostat and nafamostat can be a potential option to prevent SARS-CoV-2 viral entry in host cells. These drugs are undergoing clinical trials in various countries for their effectiveness against COVID-19.[44] In India, a clinical study of nafamostat in patients with Covid19 is recently been approved by DCGI.[45]

Immunomodulatory Drugs

Besides viral factors, the host immune response plays an essential role in disease progression. Li et al. suggested that immunopathogenesis in response to the dysregulated immune response leads to disease progression. In the incubation period and early stage of the disease, a specific adaptive immune response may preclude the disease progression. In some situations, the cytokine release syndrome (CRS) in the later stages of the infection leads to more severe disease.[46] Multiple factors such as age, underlying comorbidities, secondary infections, and elevated inflammatory indicators can predict the mortality in COVID-19. Virus-activated "cytokine storm syndrome" or fulminant myocarditis are considered to be the cause of death in COVID-19.[47] Therefore, modulating the immune response is a potential therapeutic target in COVID-19 patients.

Corticosteroids

Guidelines from the Society of Critical Care Medicine and the European Society of Intensive Care Medicine (SCCM-ESICM) indicated use of low-dose systemic corticosteroids for a short period only in mechanically ventilated COVID-19 patients with acute respiratory distress syndrome (ARDS).[48] The WHO advised against the use of steroids in patients with COVID-19.[2] This WHO recommendation is probably because of the lack of clinical evidence pertaining to corticosteroids in COVID-19.

A single-center, retrospective study from China by Wang et al. showed that among 138 cases of confirmed COVID-19 pneumonia, 44.9% received corticosteroids and were administered in a significantly higher proportion of patients admitted to ICU than non-ICU setting (72.2% vs 35.3%, $p < 0.001$).[24]

A study from Zha et al. from China, 11 of 31 severe patients with COVID-19 who received corticosteroid treatment, demonstrated no association between steroid treatment and virus clearance time, length of hospital stay, or duration of symptoms.[49]

A retrospective study by Wu et al. involving COVID-19 patients with pneumonia identified that in patients with ARDS, treatment with methylprednisolone was associated with a 62% relative risk reduction of mortality.[50]

These data indicate that more severe the disease, there is a greater likelihood of steroid use. Villar et al. consider that in patients of COVID-19 with ARDS, corticosteroids can be lifesaving in severe life-threatening cytokine storm.[51]

In a recent study involving moderate to severe COVID patients ($n = 213$), Fadel et al. demonstrated that compared to the standard of care, the early corticosteroid treatment (methylprednisolone 0.5–1 mg/kg/day divided in two doses for 3 days) significantly lowered the rate of the composite endpoint, i.e., escalation of care from ward to ICU, a new requirement for mechanical ventilation, and mortality (34.9% vs 54.3%, $p = 0.005$). The benefits were also reported with individual outcomes.[52] This clearly indicates that a short course of low-dose steroids is effective in reducing the mortality and other outcomes in COVID-19.

News released by the principle investigators of the Recovery Trial said that dexamethasone is the first drug, which has shown reduction in the mortality in patients with COVID-19. They compared mortality in 2,104 patients randomized to dexamethasone 6 mg once a day (either by oral or intravenous route) for 10 days and 4,321 patients randomized to usual care alone. It was found that dexamethasone reduced the risk of 28-day mortality by 17% with a highly significant trend showing greatest benefit among those on ventilators. No evidence of benefit was found for patients who did not receive oxygen. The baseline 28-day mortality for patients on usual care was 41% in ventilated patients, 25% on oxygen therapy, and 13% on those who were not receiving any respiratory intervention. Dexamethasone has several advantages over methylprednisolone, pure glucocorticoid as against methylprednisolone, which has additional mineralocorticoid activity, which can be bad for ARDS patients due to fluid retention and it is five times more potent than methylprednisolone with profound anti-inflammatory properties. Results of this study would be published soon.[53]

Interleukin-6 Inhibitors: Tocilizumab

Tocilizumab (TCZ) targets the IL-6 receptors and blocks their action. It has proved its safety and effectiveness in the treatment of rheumatoid arthritis.[54]

In a retrospective study on 15 patients (two moderately ill, six seriously ill, and seven critically ill) from China, Luo et al. observed that of the four critically ill patients treated with only a single dose, three died and one patient did not show a decline in C-reactive protein levels. Clinical stabilization was achieved in 10 patients, whereas disease progression was reported in 2 cases.[55]

Xu et al. reported outcomes in 21 severe COVID-19 patients who were treated with TCZ; 75% had decreased FiO$_2$ requirement and lung opacities were resolved in most (90.5%) patients within 5 days. The elevated CRP levels reduced significantly in 84.2% of patients. After a mean of 15.1 days after tocilizumab administration, all patients were discharged and there were no obvious adverse

reactions.[56] This data indicate the potential benefits of tocilizumab in lowering mortality in severe COVID-19 patients.

A prospective single-arm multicenter study in 63 adult patients with severe COVID-19 demonstrated that TCZ administration within 6 days from admission increased the likelihood of survival.[57]

In an Italian study, 100 consecutively patients with confirmed COVID-19 pneumonia were given two IV infusions of tocilizumab 12 hours apart. Of the 57 patients treated in ward, 35 patients improved and NIV could be stopped, 7 continued on to be stable on NIV, while 13 patients worsened. Overall, after 10 days of follow-up, 77 patients had improved or stabilized respiratory condition. Among 61 of these 77, significant clearing of diffuse bilateral opacities was reported. Remaining 23% patients worsened and 20 of them died. The study concluded that the response to tocilizumab was rapid, sustained, and resulted in significant clinical improvement.[58]

Clinical trials for another IL-6 inhibitor, Sarilumab (ClinicalTrials. gov Identifier: NCT04327388, ClinicalTrials.gov Identifier: NCT04315298), in severe COVID-19 patients are underway.[59,60]

Interferon-1

Type 1 interferons (IFN-I) are a group of cytokines comprising of the various subtypes such as α, β, ε, ω, and κ.[61] Antiviral effects of it are majorly mediated by inducing the production of antiviral effector proteins, which inhibit viral replication and activate cellular immunity by promoting proliferation and activation of cytotoxic T lymphocytes (CTL) and activating natural killer (NK) cells and macrophages to clear the virus.[62]

SARS-CoV-2 displays a substantial sensitivity to IFN-α and especially IFNα2b nasal drop/sprays can reduce the infection rate. It indicates IFN-I can be used as a prophylaxis against SARS-CoV-2.[61]

Experts from China recommend administering 5 million U of IFNα by vapor inhalation twice a day to the patients, especially in combination with ribavirin.[63] As discussed above, a trial from Hung et al. demonstrated better defervescence with a combination of lopinavir/ritonavir (400/100 mg every 12 hours), ribavirin (400 mg every 12 hours), and interferon beta 1b (three doses of 8 million international units on alternate days).[22]

Bevacizumab

Recent reports indicated that the levels of the vascular endothelial growth factor (VEGF) are increased in COVID-19. As one of the most potent vascular permeability inducer, VEGF can contribute to pulmonary edema and progressive lung disease. With this rationale, Bevacizumab, an anti-VEGF drug, is now under investigation for use in COVID-19. BEST-CP is an ongoing open-label clinical trial (ClinicalTrials.gov Identifier: NCT04275414) in COVID-19 patients, with inflammatory exudation or pleural effusion.[64]

Fingolimod

Fingolimod is a sphingosine-1-phosphate receptor regulator, which is widely used in multiple sclerosis. As COVID-19 patients develop pulmonary edema and hyaline membrane from within lungs, immune modulator use along with ventilator support may be considered in managing such patients. A phase 2 clinical trial is underway in patients with COVID-19 pneumonia (ClinicalTrials. gov Identifier: NCT04280588) using fingolimod (0.5 mg orally once daily, for 3 consecutive days) to assess the lesion change on X-ray images from day 5 to baseline.[65]

Eculizumab

Eculizumab is a long-acting humanized monoclonal antibody that inhibits cleavage of C5 into C5a and C5b. Thus, deployment of the terminal complement system is inhibited including the formation of the membrane attack complex.[66]

In a case series of four patients with SARS-CoV-2 infection and severe pneumonia or ARDS, Diurno et al. showed that four infusions of eculizumab in addition to enoxaparin, lopinavir/ritonavir, HCQ, ceftriaxone, and vitamin C for 4 days resulted in a successful outcome in all patients. Mean C reactive protein levels dropped from 14.6 mg/dL to 3.5 mg/dL and the mean duration of the disease was 12.8 days.[67]

A clinical study (ClinicalTrials.gov Identifier: NCT04288713) is underway for evaluating the safety and efficacy of Eculizumab in COVID-19 patients.[68]

Ulinastatin

Ulinastatin is a broad-spectrum serine protease inhibitor that is currently available for the treatment of severe sepsis and mild to severe acute pancreatitis. The 2019 Shanghai Expert consensus recommends ulinastatin for the prevention and treatment of cytokine storm in COVID-19.[69] Besides its effect on reduction in levels of TNF-α, IL-1β, IL-6, and IL-8, ulinastatin has confirmed significant efficacy in removing oxygen free radicals, improving microcirculation and tissue perfusion, and alleviating endothelial injuries.[70,71] A phase II placebo-controlled study with ulinastatin infusion has been proposed in the United States by Stanford University (ClinicalTrials.gov Identifier: NCT04393311).[72] In India, DCGI recently approved a protocol for conduct of a phase III clinical study of ulinastatin in COVID-19 patients with mild to moderate ARDS.[73]

Itolizumab

Itolizumab is a humanized recombinant anti-CD6 monoclonal antibody that is indicated in psoriasis management. Itolizumab has a potent anti-inflammatory effect reducing the production of pro-inflammatory cytokines IL-6, TNF, IFNγ, and IL. It could be an attractive therapeutic option to control the cytokine storm in patients with COVID19.[74] Itolizumab is under phase II clinical study in India for the management of moderate to severe ARDS in patients with COVID-19 disease (CTRI Identifier: CTRI/2020/05/024959).[75]

Adjuvant Therapies

Vitamin C

The expert consensus from the Shanghai medical association recommends that 100–200 mg/kg intravenous (IV) vitamin C daily can lead to an improvement in the oxygenation index.[69] By virtue of its actions on oxidative stress and inflammation and immunological function, vitamin C has shown efficacy in patients of sepsis with ARDS. In the CITRIS-ALI trial involving patients of sepsis and ARDS ($n = 167$), IV infusion of vitamin C (50 mg/kg in dextrose 5% in water over 96 hours) resulted in significantly lower 28-day mortality (29.8% vs 46.3%, $p = 0.03$).[76]

Heparin/low-molecular-weight Heparin

In COVID-19, there is no typical disseminated intravascular coagulation, but there is formation of local microthrombi in lung and other organs. Disruption of the endothelium in viral infection, along with a virus-induced increase in von Willebrand factor

levels, activation of the toll-like receptor, and the tissue factor pathway lead to the formation of fibrin clots. In addition, the long duration of bed rest in COVID-19 may increase chances of venous thromboembolism.[77]

Heparin with its anticoagulant and anti-inflammatory (bind to inflammatory cytokines, inhibition of neutrophil chemotaxis, and leukocyte migration) properties can reduce the inflammatory response in COVID-19.[78] Tang et al. demonstrated that in patients with SARS-CoV-2, heparin was beneficial in reducing mortality in patients who met the criteria for sepsis-induced coagulopathy. The majority of the patients received low-molecular-weight heparin (LMWH).[79] Atallah et al. proposed a patient-tailored algorithm for coagulopathy. In patients at high risk of thromboembolism, continuous heparin infusion or enoxaparin BD was advised.[77]

The International Society on Thrombosis and Haemostasis (ISTH) recommends thromboprophylaxis with LMWH in hospitalized COVID-19 patients.[80] Revised guidelines from the Ministry of Health and Family Welfare India recommended pharmacological prophylaxis LMWH or heparin (5,000 units subcutaneously twice daily) in adults and adolescents.[81]

Convalescent Plasma

In five critically ill COVID-19 patients, transfusion with convalescent plasma with a SARS-CoV-2-specific antibody (IgG) binding titer greater than 1:1,000 and a neutralization titer greater than 40 resulted in negative viral load within 12 days. ARDS resolved in four out of five patients on day 12 of transfusion. This indicates convalescent plasma may be useful in clinical recovery of critically ill patients.[82]

The United States Food and Drugs Administration issued guidelines for the use of investigational COVID-19 convalescent plasma. Criteria laid down for eligibility for the use of convalescent plasma are laboratory-confirmed, severe COVID-19 (dyspnea, O_2 saturation $\leq 93\%$, respiratory rate ≥ 30 per minute, the partial pressure of arterial oxygen to fraction of inspired oxygen ratio <300 and lung infiltrates >50% within 24–48 hours) or a life-threatening COVID-19 (respiratory failure, septic shock, multi-organ dysfunction) disease along with an informed consent provided by the patient or healthcare proxy.[83] The Indian Council of Medical Research (ICMR) has initiated PLACID Trial (CTRI/2020/04/024775), which is a phase II study to assess the safety and efficacy of convalescent plasma to limit COVID-19-associated complications. As of May 22, 2020, the ICMR has approved 46 sites. Total of 452 patients will be recruited into the study.[84]

CytoSorb

Cytosorb is an extracorporeal cytokine adsorber. Either stand-alone or with renal replacement therapy, it has been used in COVID-19 patients in China, Germany, the United States, Italy, and other countries. It has been approved by the FDA (United States) and DCGI (India) for use in COVID-19 and is recommended in Panama and Italian Nephrology guidelines for COVID-19.[85]

Vaccines

In a race to develop the effective vaccine to control the further spread of COVID-19, there are nearly 118 candidate vaccines identified globally, out of which 8 are already in phase I/II of clinical evaluation and remaining in the preclinical phase. Two vaccine candidates have successfully completed phase I of clinical development. The first is Ad5-nCoV from CanSino Biologicals in China and the second one is mRNA-1273 from Moderna in the United States.[86] In India, nearly 14 private and academic institutes are in hunt for developing the vaccine for COVID-19.[87] Apart from these, the BCG (Bacillus Calmette-Guerin) vaccine is under clinical study for COVID-19 in countries like Australia, Germany, and India. It is based on reports of some epidemiological studies suggesting countries with mandatory BCG inoculation for tuberculosis may be experiencing fewer cases and mortality due to COVID-19.[88]

CONCLUSION

The COVID-19 pandemic is affecting an increasing number of people. A number of antivirals, immunomodulators, and adjuvant therapies are being proposed for use in the management of COVID-19. Based on available evidence, we consider few of the discussed treatments have potential to be considered in majority of the patients with COVID-19. Table 2 enlists such therapies with disease stage and our remarks about their use. It is possible that the early use of antiviral agents may be useful in improving clinical conditions. Among different antiviral agents, remdesivir shows promise in COVID-19. Though HCQ has been widely used and recommended in treatment of COVID-19, recent observations from RCTs indicate no benefit in terms of mortality outcomes. However, the ICMR advises HCQ use for prophylaxis of COVID-19 in high-risk individuals such as HCWs.[89] Immunomodulatory therapies such as tocilizumab may be tried in moderate to severe and critically ill patients to control cytokine storm and possibly reduce disease progression. The use of LMWH is advised in both prophylactic and therapeutic doses in select patients. Trials of multiple vaccines are currently underway, but will take at least few more months before they are introduced for clinical use. Adhering to basic principles of critical care, till evidence-based treatment for COVID-19 becomes available, should be the way to go. Adjuvant therapies may be tried in selected patients, with full disclosure to the patient and family, since these therapies may be expensive. With currently available therapies with other indications such as vitamin C, ulinastatin, etc., there is need to generate further evidence for their use in COVID-19.

Table 2: Potential current treatments tailored to disease severity

Therapy	Disease stage	Authors remarks
Remdesivir	Moderate and severe	Initiate early in disease course
Hydroxychloroquine (HCQ)	Mild, moderate, and severe	Current evidence contradictory to opine for or against the use of HCQ
Corticosteroids	Moderate, severe, and critically ill	Low dose (e.g., methylprednisolone 0.5–1 mg/kg/day divided in two doses for 3 days or dexamethasone 6 mg OD by either oral or IV route for 10 days)
Tocilizumab	Moderate, severe, and critically ill	Consider two infusions 12 hours apart
Heparin/low-molecular-weight heparin	Mild, moderate, severe, and critically ill	Use dosage tailored on the risk of thromboembolism
Convalescent plasma	Severe and critically ill	Consider it whenever available

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