doi.org/10.36721/PJPS.2021.34.4.REG.1469-1484.1

REVIEW

Insights into Off-Label therapeutic strategies against mild and severe COVID-19 infection

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Abstract: Currently, prevention and control of the coronavirus disease pneumonia epidemic situation are grim globally. To cope with total sheer carriers and patients of COVID-19 requires intensive medical support and adjunctive therapies to overcome the disease. The epidemic can be controlled with the help of both, disease suppression via community health measures and adjunctive therapies for patients suffering from infection. Till date, we do not have any proper anti-COVID-19 therapy. In order to achieve the overall realization of this pandemic, there is a need to identify treatments depending upon their direct or indirect targets; like inhibition of polyprotein synthesis, transmembrane serine protease, inhibition of viral entry and endocytosis. This could be possible by turning the focus in the direction towards the development of numerous tentative drugs, particularly in the severe to badly ill. Though, majority of these off-label adjunctive medicines are being inspected in a lot of clinical trials at different stages, scientific organizations have endeavored to elucidate the situation where these adjunctive drugs might be practiced as off-label, open- label or compassionate. Our review compiles the adjunctive therapies adopted in COVID-19 infected patients according to clinical severity in conjugation with practicing recommendations from existing guidance rules issued by global professional bodies in healthcare.

Keywords: COVID-19, epidemic, polyprotein synthesis, therapies, healthcare.

INTRODUCTION

In December 2019, pneumonia related with the novel COVID-19 or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) appeared in a person from Seafood Whole Sale Market hospitalized in Wuhan, China (Siordia Jr, 2020). However, on March 14, 2020, the World Health Organization (WHO) confirmed coronavirus manifested a pandemic and created health emergency worldwide. This extraordinary unparalleled global load on healthcare organizations has been particularly devastating for standard care (ICUs + medical personnel treating mechanically ventilated patients) and subsequent treatment (Fauci *et al*., 2020, Wang *et al*., 2020c). Unfortunately, with no proper anticovid-19 therapy (Zaman *et al*., 2020, Khan *et al.*, 2020) available, World health organization (WHO) suffered a serious setback. This global outbreak of COVID-19 called for immediate development of vaccines and potent therapeutic agents. However realistically, there is a long way to provide effective vaccine to the public.

Some potentially capable pharmaceutics accelerated human clinical trials. Many investigations were carried out for adjunctive therapies auxiliary to standard care procedures to sustain life (Xu *et al*., 2020). It is therefore recommended that investigations must be carried out for the treatment of covid-19 in approved, controlled, and randomized trials. Although larger experiments are in progress, but the clinical outcomes of small trials may help to devise treatment guidelines of COVID-19 based on literature evidence/consent of expert and clinical trials (Micallef *et al*., 2020). Along with extensive public health measures promoting social distancing and reducing the massive strain on the healthcare infrastructure, global efforts are currently directed to the development of a vaccine and therapeutic agents while optimizing marketed medications, mainly employed in severe respiratory viral infections. Nevertheless, no effective prophylactic or post-exposure therapies are currently available.

Here, we briefly review the latest, recommended, and most promising pharmacological treatments with clinical guidelines for usage as medicine against COVID-19 currently under investigation. Further, we discuss their

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potential use by virtue of either documented efficacy and important key approaches for handling in similar viral infections, or their activity against the so-called "cytokine storm" or the newly defined sepsis-induced coagulopathy (Barlow *et al*., 2020). It will facilitate health care providers with the basic information on clear therapeutic options that have been recommended as antagonists of COVID-19 for severely ill patients. Fig. 1 illustrates the main pharmacological strategies proposed so far.

Epidemiology

SARS-CoV-2 or COVID-19 is a beta coronavirus belonging from the family of severe acute respiratory syndrome-coronavirus (SARS-CoV), which triggered the SARS epidemic in 2003 and the Middle East respiratory syndrome coronavirus (MERS-CoV) that generated the MERS flare up in 2012. As of September 3, 2020, a total of 25,327,098 cases of COVID-19 in at least 216 countries and territories were confirmed, with roughly about 3.3 % of fatality rate (848,255/25,327,098). In China, 90,402 confirmed cases were reported, suspected, and asymptomatic patients exposed numerous significant epidemiological features of COVID-19. Commonly, the majority of the reported cases are of age 30–79 (86.6%) (Coronavirus, 2019). Among the 1,023 deaths, the majority of patients aged above 80 have highest fatality rate (20.3%) (Chan *et al*., 2020). Relatively fewer cases were reported among young children below the age of 10 years (Chan *et al*., 2020) although males were more prone to be affected by the disease, as compared to females. Fortunately, majority of the affected COVID-19 persons exhibit mild pneumonia. Moreover, COVID-19 is extraordinarily contagious, patients with mild or moderate COVID-19 remained positive for less days as compare to severe cases (Martinez, 2020). While, 50% of patients could be categorized as critical cases (Zhang *et al*., 2020). In this sense, a basic curative coherent approach to spot COVID-19 epidemic would be the already prescribed drugs of SARS and MERS outbreak. Novel drugs (potent open label) and off-label existing medications are considered as agnostic remedial strategies of COVID-19 (Yang *et al*., 2020).

General Clinical Features of COVID-19

The clinical symptoms of COVID-19 are extremely wild ranging from nonspecific disease indication like fever (83–98%), dry cough (59–82%), sometimes combined with mild pneumonia (19–55%), and dyspnea and very often associated with olfactory and gustative disorders, to severe pneumonia and altered gas exchange, resulting in approximately 5% of infected patients with severe lung dysfunction, or multiple (extra pulmonary) organ failure (Marietta *et al*., 2020)and fatigue (11–44%), same as in SARS and MERS manifestations(Yang *et al*., 2020). Infected person might suffer from pharyngitis, runny nose, migraine in initiation phase earlier than fever, indicating increased body temperature to be a vital sign, and not the very initial manifestation of the disease (Yang *et al*., 2020). Hemostatic abnormalities, together with disseminated intravascular coagulation (DIC), have been observed in individuals affected by COVID-19. Moreover, the rigorous inflammatory reaction, serious illness, and underlying traditional risk factors may all lead to blood clotting (Stenvinkel and Alvestrand, 2002).

Consequently, it is very difficult to predict the development of coagulopathy in COVID-19 patients. It is worth paying attention that, platelet activation may also likely contributeto hypercoagulability, but its mechanism of action and signaling routes need discussion(Wang *et al*., 2020a). In addition, few cases of COVID-19 are observed to be asymptomatic (Chan *et al*., 2020). In the above mentioned clinical scenario, heparins have been investigated due to their anticoagulant activity, currently authorized worldwide (902 as of April 26th) (Warkentin *et al*., 2020).

COVID-19 disease and ongoing curative strategies

According to current understanding, SARS-CoV-2 targets cells, but mainly the lungs and also damages heart, liver, kidney and the lower gastrointestinal tract (Wadman *et al*., 2020, Sanders *et al*., 2020). In the light of this evidence, it is suggested that COVID-19 may require a multi-target approach thus relating viral access and lifecycle, patient response or even both. SARS-CoV-2 accesses human cells at the advent of its viral spike (S) protein to target (human cell) receptor angiotensin-converting enzyme 2 (ACE2) in addition to class 2 transmembrane serine protease (TMPRSS2). Off-label drugs have been formerly prepared for some other specific pathogens and were directly adopted for COVID-19 trials (table 1).

On the whole, the access of coronavirus into vulnerable cells is stimulated by the rigorous action among binding receptor and proteolytic S protein to promote virus-cell fusion (Walls *et al*., 2020). Hence, this access route becomes 1000 times better than the endosomal route and the key factor of tropism in the extracellular milieu is the proteases accessibility (Belouzard *et al*., 2012). Currently, there is not sufficient evidence of any existing anti-COVID-19 medication which can competently cure COVID-19. However, several clinical trials have been done and some are in progress on off-label and open-label potential therapeutics.

The therapies can be handled depending on their targets. By acting on the COVID-19 directly, either by inhibiting crucial viral enzyme responsible for genome replication (polyprotein synthesis (i.e. lopinavir, remdesivir, darunavie, ebselen, etc), along with drugs, preventing viral entry into human cells by inhibiting TMPRSS2 (i.e. camostatmesylate), targeting S protein/ACE2 interaction (i.e. umifenovir), and inhibiting viral entry and

endocytosis (i.e. cloroquine/hydroxychloroquine, colchicines, baricitinib), all qualifying as potential adjunctive therapies. To date, such approaches seem extremely potent in early phases of infection, however their efficacy in progressive phases is still quite uncertain (Wang *et al*., 2020a, Cao *et al*., 2020) (fig.1). In addition to the above mentioned drugs, immunomodulators are also used to boost innate and adaptive immunity against SARS-CoV-2, which has a particularly important therapeutic avenue with inhibition of IL-6 signaling playing a protective role against viruses, if given at the time of overly elevated immune response to the virus.

In this context, it has been speculated that drugs targeting immune regulation pathway (i.e. tocilizumab, sarilumab) may control the extreme cytokine reaction (termed "cytokine storm") that is accompanied by infiltration of inflammatory monocytes/macrophages into the lung without deleterious effects on virus replication (Buonaguro *et al*., 2020). A stage classification system has been recently proposed to improve curative strategies for COVID-19 patients so far by distinguishing each stage, with viral pathogenicity dominating in comparison to patient inflammatory response (Siddiqi and Mehra, 2020). Such approach may be helpful to better correlate the stage of illness severity with response to therapy and clinical outcomes, and to weigh the benefit/risk ratio for the currently investigated pharmacological treatments. In the meantime, numerous trials have originated to generate precise vaccines and antibodies particularly to spot COVID-19. In this article, we tried to sum up the ongoing off-label therapeutic options which may be promising to cope with Covid-19 epidemic (fig. 2). This review reports the proposed adjunctive off-label global treatment protocols for COVID-19 with the detail of completed and ongoing clinical trials.

Clinical classification of COVID-19

In this article, we have described the details on COVID-19 treatment according to the clinical severity of the disease, which is basis of COVID-19 treatment protocol (fig. 1). Globally, clinical categories of COVID-19 are incoherent, therefore we are using here the information to develop clinical classification which includes "mild", "moderate", "severe" and "critical" groups. We tried to combine treatment targets with respect to clinical classification of COVID-19.

Mild COVID-19

Mild COVID-19 is an uncomplicated upper respiratory tract infection with mild clinical signs. It does not show any cough, dyspnoea and radiologic symptoms of pneumonia. In addition to the stated manifestations, the patient also suffers from fever (> 37.5°C). There is no requirement of oxygen supplementation, hemodynamic compromise, or chest x-ray findings.

Moderate COVID-19

Patient of moderate COVID-19 suffer from high body temperature or sore throat, cough, in addition to any of the conditions mentioned below: Severe respiratory distress or respiratory rate greater than 30/min, or Hypoxia (peripheral capillary oxygen saturation≤94% but>90%) on room air or Dyspnoea, > 30/ min or presence of infiltrates in more than half of the lung area but without any serious manifestation.

Severe COVID-19

Severe COVID-19 sufferer presents with pneumonia (fever/cough) along with respiration rate being greater than 30 or severe respiration distress; SpO2 ≤ 90%. Supplementation of oxygen is required. In this condition, chest X-ray shows lung infiltrates raised more than 50% of the lung field within one or 2 days.

Critical COVID-19

Any of the three manifestations is an indication of Critical COVID-19; 1) Acute respiratory distress syndrome (ARDS); 2) grim infectious condition that creates the foundation for Sepsis when the immune system starts attacking your own body; 3) severe organ failure or severe sepsis. The patient strictly requires ventilator for respiration and monitoring in intensive care unit. The patient suffers from severe shock and hemodynamic failure due to multi-organ dysfunctions.

Therapeutics against Mild and Moderate COVID-19

Most of the guidelines generally recommend a curative protocol against different signs and symptoms of mild COVID-19 (table 2), that have been defined as a simple respiratory tract inflammation and the sufferer can easily be recovered at home with prescribed medication(Bhimraj *et al*., 2020, Van Ierssel *et al*., 2020). So, according to the recommendations, the off-label medicines include the use of anti-malarial drugs (chloroquine/HCQ) and/or viral protease inhibitors (lopinavir/ ritonavir), considered to treat moderate COVID-19 (Van Ierssel *et al*., 2020). Protocols for the treatment of COVID-19 eagerly suggest chloroquine and HCQ in emergency situation for which few clinical trials have been done and some are ongoing (United States Center for Diseases (https://www.cdc.gov/)). One health regulatory authority (NHC) also considered umifenovir in therapeutic protocols of mild and moderate COVID-19. So, antimalarial drugs, viral protease inhibitors and umifenovir are going to be discussed in this section.

Lopinavir/Ritonavir (viral protease inhibitors)

Lopinavir is anti-HIV type-1 and 2 drug that can inhibit aspartate protease by inhibiting the separation of the gag-pol polyprotein, and generate an immature virus, which is not infectious. Consequently, the antiviral effect mediated by lopinavir is chiefly attributable to its ability to avoid the illness of susceptible cells (Talasaz *et al*., 2020).

Ritonavir inhibits CYP3A4 isoenzyme of cytochorme to increase the bioavailability of lopinavir by protecting it from metabolism by first-pass effect. Therefore, boosting the pharmacokinetic activity and serum concentration of the Lopinavir for long duration with ritonavir brings about better activity in the susceptible cell and is often given in co- formulation (Cvetkovic and Goa, 2003). Lopinavir/ritonavir commercially named as Kaletra is an orally administered, fixed dose combination with a dosage of 400/100 mg or (200/100 mg) approved by EMA and FDA (biting or grinding is highly restricted). An oral suspension (with 42.4% ethanol) is also accessible for all those patients who have difficulty in swallowing or are intubated(Savarino *et al*., 2003). Currently, in HIV-1 infection, the lopinavir/ritonavir co-formulation mostly in conjugation with some other antiviral drugs is considered for patients above the age of 18 years, adolescents and children (aged from 14 days and older) (Veugelers and Zachmann, 2020). The use of the same combination has already been practiced in SARS and MERS outbreak. However, SARS-CoV-2 protease is a member of the cysteine protease group but has a different morphology due to the absence of C2 catalytic site.

Several scientific evidences argued for the off-label anti-COVID-19 prescription of lopinavir/ritonavir. Specifically, *in vitro* and *in vivo* experiments have revealed that lopinavir may inactivate 3-chymotrypsin-like protease (3CLpro, also known as Main protease, Mpro), which represents a crucial target for human coronavirus replication (i.e. COVID-19 and MERS-CoV) (Barrila *et al*., 2006). A recent *in vitro* experiment exhibited that lopinavir inhibits also coronavirus replication with EC50of 26.63 μM (Choy *et al*., 2020).

A clinical trial evaluating lopinavir/ritonavir potential in SARS showed some benefits, such as reduced intubation rates and mortality, particularly if treatment was started at early stage, i.e. within the first 7-10 days of exposure (Chan *et al*., 2003). However, the observational retrospective nature of the study prevents conclusive recommendations. From the results of systematic review of the literature, short guidelines issued by the hospital of Wuhan University in February 2020, for the diagnosis and treatment of SARS-COV-2 pneumonia were published, which suggested the use of lopinavir/ritonavir in the initial stages of disease to reduce mortality and glucocorticoid consumption (Mao *et al*., 2020a). More recently, an open-label randomized controlled trial (LOTUS China-Lopinavir Trial for Suppression of SARS-CoV-2 in China) evaluated efficacy and safety of lopinavir/ritonavir versus standard care on 199 hospitalized adult subjects with COVID-19.

Although delayed treatment may partially account for the ineffectiveness of treatment. Moreover, therapy should be discontinued because of gastrointestinal adverse events (Cho *et al*., 2012). Although, several RCTs are ongoing, current evidence suggests poor benefit from lopinavir/ritonavir therapy. Detail of lopinavir/ritonavir clinical trials is presented in Table 1. Therapy with LPV/r may create the following adverse effects. The patient can suffer from gastrointestinal disturbances and nausea, however drug administration after proper meal could lower down these types of intolerance. One fourth of the suffering population may experience dysentery, a condition which is generally recovered without any medication in fourteen days (Zouboulis *et al*., 2019). Most prominent side effects of this medication on patients in intensive care unit included severe pancreatitis, hepatitis, hepatic deterioration in liver patients with elevated PR intervals. Literature data described that prescription of this medication might raise the blood amylase and liver enzyme. To avoid the above mentioned side effect, the patient requires strict regular functional monitoring of the liver, with care of compassionate antiemetic and anti-motility agents should (Chu *et al*., 2004). However, thee patients are not at risk of heart and metabolic irregularities while using lopinavir/ritonavir for COVID-19.

In addition, darunavir/cobicistat combination (i.e., protease inhibitor/CYP3A4 inhibitor) is being used as an alternative to lopinavir/ritonavir because of its greater intestinal tolerability (Navarro and Curran, 2016). An *in vitro* study also showed thee activity of darunavir against SARS-CoV-2 (Touret *et al*., 2020).

Chloroquine and hydroxychloroquine

From the last century, Chloroquine analogs (chloroquine and hydroxychloroquine), are usually prescribed as curative agents of both malaria and some autoimmune conditions, like systemic lupus erythematosus and rheumatoid arthritis (Schrezenmeier and Dörner, 2020, Savarino *et al*., 2003, Micallef *et al*., 2020). The diversified characteristics of chloroquine and hydoxychloroquine with minor toxicity reports have made it a competent agent for its examination as an anti-viral agent to overcome the pathologic features of viral attack mainly motivated by an inflammatory response by immune system, as in HIV-coupled immune reconstitution inflammatory syndrome (Savarino *et al*., 2001, Gérard *et al*., 2020). The basic nature of chloroquine analogs makes them capable of entering and concentrating inside the organelles with low pH (endosomes and lysosomes). Moreover, very minute quantity of left in intracellular moiety, as in protonated form, which is the reason to raise the pH of vesicles, leading to hindrance of intravehicular transport, destabilization of enzymes, and defective viral replication within the cell (Savarino *et al*., 2003).

Chloroquine analogs inside cell interference with pro-inflammatory cytokines interleukin 1 beta release superoxide by neutrophils (Schrezenmeier and Dörner,

2020). The above said mechanism raised the need of chloroquine analogs as a part of COVID-19 therapeutics and plays a potent role to impede translational steps of ACE2 receptor (terminal glycosylation) which hold back the binding of covid-19 receptor and subsequent extend of contagion(Vincent *et al*., 2005). In *in vitro* models, chloroquine analogs showed antiviral effects against SARS-CoV-2 infection. These agents appear to block viral entry into the cells through endosomal acidification, which mediates the virus-host cell fusion, proteolytic processing and inhibition of host receptor glycosylation (Ak-Bari, 2017).

A phosphate salt of chloroquine is available as a tablet (for oral use). In COVID-19 therapeutic protocols, health care professionals advised dosage of chloroquine phosphate (tablet500 mg) twice a day for 1/3month (Zhonghua *et al*., 2020). This drug needs the time duration of 30 min for maximal bioavailability (~60–100%) after intake. Hydroxychloroquine is a (hydroxy) derivative of chloroquine due to enhanced safety profile, hence it has been more eagerly evaluated *in vitro* against COVID-19 with 3-times more cytotoxic aptitude for virus in contrast to chloroquine (Yao *et al*., 2020). Due to the above mentioned characteristics (antiviral and anti-inflammatory effects), chloroquine was suggested for its use as a COVID-19 therapeutic. Based on ongoing clinical trials for hydroxychloroquine listed it as anti-COVID-19 drug after detailed studies against corona virus (Barlow *et al*., 2020).

Chloroquine has bioavailability and prolonged retention time in each organ of the body. Chloroquine is converted into desethylchloroquine (active form) by multiple hepatic enzymes (cytochrome P450 (CYP) 2C8 and CYP3A4), responsible for little pharmacologic activity. Chloroquine is a chief substrate of hepatic enzyme (CYP2D6), reported for ~30% of its inactivation. Prominent elimination route of chloroquine is urine with half of the dose eliminated as unchanged. Patients receiving continuous renal replacement therapy (CRRT) should obtain proper dosage of this drug (Barlow *et al*., 2020).Hydroxychloroquine (sulfate) is accessible for oral usage in (film-coated) tablets. Still, there is no proper dose suggestion for COVID-19 treatment. Multiple clinical *in vitro* studies are going on for optimization. A recent *in vitro* pharmacokinetic study design recommends the first day dose of hydroxychloroquine 400 mg 2 times a day, pursued by 200 mg twice in a day for next 4 days. A study reported that 400 mg of hydroxychloroquine provides same efficacy (cytotoxic effects) against COVID-19 as chloroquine 500 mg (twice/day) however, *in vivo*, there is still not clarification regarding high cytotoxic effects of hydroxychloroquine (Yao *et al*., 2020). However, the terminal half-life within blood is more than one and a half month of hydroxychloroquine, and traces could be found in the body till 3 months. It is highly suggested to take chloroquine and hydroxychloroquine with meal to save patient from nausea and vomiting. Bitter taste of powdered chloroquine could be masked with different flavors of suspensions and/or gelatin coating capsules (Barlow *et al*., 2020). On the other hand, crushed or grinded tablet of hydroxychloroquine is not recommended to make the solution for intake via enteral tubes. A hypothetical drug-drug interaction between PPIs drugs and chloroquine analogs could suppress immune dilatory effect of chloroquine. The presence of proton pump inhibitors drugs creates basic environment in lysosome representing the blocked H+, K+ ATPase, elevating the pH and diminishing chloroquine accumulation (Tripathy *et al*., 2020). However, there is no proof of this interaction *in vivo*.

Generally, both drugs are safe for use, however hydroxychloroquine shows less toxicity profile as compared to Chloroquine. The most frequent adverse effects are gastrointestinal disturbances like nausea, vomiting, abdominal cramps, and a metallic taste. Moreover, retinopathy cardiomyopathy, neuropathy, or myopathy and hearing loss (signs of acute toxicity) are linked with high dosing. During the use of this medication, hypoglycemia is also observed in diabetic patients. So, insulin dose must be reduced up to 30% while using hydroxychloroquine (Pareek *et al*., 2014). More clinical trials should be conducted to establish the non-hazardous and potent protocol of chloroquine/HCQ, chiefly for severe to critically ill COVID-19 patients.

Umifenovir

Umifenovir, a small indole-derivative molecule (also known by its trade name Arbidol), is a more promising antiviral agent approved as a therapeutic agent of prophylaxis of influenza A and B in Russia and China. This drug is not approved by US FDA. Umifenivor is recommended at a dose of 200 mg orally every three time a day. In addition, umifenovir showed *in vitro* activity against SARS-CoV (Khamitov *et al*., 2008). Its mechanism of action is mainly by blocking the entry of virus within the host cell. The drug seems to block the interaction between S-protein and ACE2 receptor, thus preventing the fusion of viral envelope with cell membrane (Kadam and Wilson, 2017). Currently 8 clinical trials are studying umifenovir in COVID-19 patients (https://clinicaltrials.gov/ct2/who_table), in combination with other therapeutics or in monotherapy. At the moment, clinical evidence in COVID-19 is limited to observational data, though suggesting lower mortality and higher discharge rate in umifenovir-treated patients (Wang *et al*., 2020a). The most common adverse side effect seen in children is umifenovir sensitization. However, allergic body response is restricted to hypersensitive persons.

Table 1: Summary of clinical studies on investigational therapies of COVID-19 patients in various countries (Food and Drug Administration) (Xu *et al.*, 2020)

Drug and Mechanism of action	Dosage and formulation	Results	Conclusion	Side effects	Countries
Chloroquine/ Hydroxychloroquine Intracellularly, chloroquine analogs become protonated and increase intravesicular pH, resulting in the prevention of endosomal trafficking, dysfunctional cellular enzymes, and impaired protein synthesis, resulting in early inhibition of viral replication through interference with endosome-mediated viral entry or late transport of the enveloped virus	1. HCQ (200 mg three times a day for 10 days) + azithromycin (500 mg on day 1, followed by 250 mg one time a day for 4 days) 2. HCQ (200 mg three times a day for 10 days) 2. Controls oral tablets or solutions	1. Virological clearance at day 6 post-inclusion. 2. Virological clearance over time. 3. Clinical follow-up. 4. Side effects	HCQ improved rate of viral clearance. Its effect appeared enhanced by azithromycin.	Not reported	France
	1. HCQ (200 mg bid for 5 days) ($n = 31$) 2. No HCQ	1. Time to clinical recovery 2. Clinical characteristics and radiologic results 5 days after treatment 3. Severe adverse reactions	HCQ shortened time to clinical recovery and hastened improvement in pneumonia	Mild: rash, headache	China
	1. HCQ (400 mg/d for 5 days) ($n = 15$) 2. Controls ($n = 15$)	Negative conversion rate of viral nuclei acid in pharyngeal swab on day 7 of treatment	No clear benefit in common COVID-19	Diarrhoea, elevated aspartate aminotransferase, disease progression	China
	1. HCQ ($n = 97$) 2. HCQ + azithromycin ($n = 113$) 3. No HCQ ($n = 158$) (doses and duration unknown)	1. Result of hospitalisation (discharge or death) 2. Need for ventilation 3. Result of hospitalisation among patients requiring ventilation	Risk of death from any cause higher in the HCQ group. HCQ with or without azithromycin did not reduce risk of ventilation	Not reported	United States of America (USA)
	1. High dose chloroquine (600 mg bid for 10 days) + ceftriaxone (1 g bid for 7 days) + azithromycin (500 mg od for 5 days) ($n = 41$) 2. Low dose chloroquine (450 mg bid on day 1, then od on days 2–5) + ceftriaxone (above dose) + azithromycin (above dose) ($n = 40$)	Safety and efficacy of chloroquine at high and low doses	High dose chloroquine should not be recommended due to safety concerns. Recruitment of patients to high dose arm prematurely halted.	Severe rhabdomyolysis (1 patient), prolonged QTc especially in high dose group at days 2 & 3, ventricular tachycardia followed by death (2 patients)	Brazil
	HCQ (600 mg/day for 10 days) + azithromycin (500 mg on day 1, followed by 250 mg od for 4 days)	Nil	No clear evidence of antiviral or clinical benefit of HCQ + azithromycin in severe COVID-19	Prolonged QT interval resulting in discontinuation of HCQ (1 patient)	France
	1. HCQ (600 mg/d) ($n = 84$) 2. No HCQ ($n = 97$)	1. Transfer to ICU within 7 days from study inclusion 2. Death from any cause 3. Occurrence of ARDS	No benefit of HCQ in severe COVID-19	9.5% in the HCQ group had ECG changes requiring discontinuation of HCQ	France

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Lopinavir-ritonavir protease inhibitors which prevent viral replication, thus limiting spread into host cells. The therapeutic rationale for LPV/r arises from in vitro studies demonstrating inhibition of the 3-chymotrypsinlike protease found in novel coronaviruses.	1. Lopinavir-ritonavir (400 mg/100 mg) PO bid for 14 days (n = 99) 2. Standard care alone (n = 100)	Time to clinical improvement or discharge from hospital			China
	Lopinavir-ritonavir (dose unknown) (n = 41)	Nil			China
	Lopinavir-ritonavir (400 mg/100 mg bid for up to 14 days)	Nil			Singapore
	Lopinavir-ritonavir (400 mg/100 mg, dose per day and duration unknown.	Nil			Korea
	Lopinavir-ritonavir (400 mg/100 mg bid; duration unknown	Nil			Korea
Umifenovir (Arbidol®) Umifenovir is small indole-derivative molecule that has broad-spectrum antiviral properties, including Influenza A and B. It blocks viral fusion with the target membrane, thus providing viral entry into target cells.	1. Arbidol (0.2 g tid) and lopinavirritonavir (400 mg/ 100 mg bid) until RTPCR negative for virus 3 times (n = 16) 2. Lopinavir-ritonavir only (n = 17)	RT-PCR negative for SARS-CoV-2 at days 7 and 14 from date of diagnosis, chest CT findings	Arbidol with lopinavirritonavir might decrease the viral load of COVID-19 and delay progression of lung lesions	Elevated bilirubin, mild gastrointestinal	China
	Arbidol (0.4 g tid), median duration 9 days (n = 36)	Nil	Arbidol might improve rate of discharge from hospital and mortality rate	None reported	China
Remdesivir is a novel nucleotide analogue prodrug which is incorporated into nascent viral RNA chains, causing premature termination of RNA transcription. In-vitro studies had shown that remdesivir effectively inhibited the replication of SARS-CoV and MERS-CoV, and appeared to have effect on SARS-CoV-2 replication as well in non-human cells.	Remdesivir (200 mg on day 1, then 100 mg od for 9 days)	Incidence of key clinical events, hospital discharge, adverse event, proportion of patients with clinical improvement.	Clinical improvement observed in 68% of patients with severe COVID-19	Common: Elevated hepatic enzymes, diarrhoea, rash, renal impairment, hypotension. Serious adverse events: multiple organ dysfunction syndrome, septic shock, cute kidney injury, hypotension.	Canada, Austria, Japan
	1. Remdesivir (200 mg once on day 1, then 100 mg od for 4–10 days until clinical improvement (n= 3) 2. No remdesivir (n =9)	Nil	No conclusions can be drawn about efficacy or safety	Transient gastrointestinal symptoms (nausea, vomiting, gastroparesis), elevated aminotransferase	United States of America (USA)
	Remdesivir (200 mg loading dose, then 100 mg od for 10 days) (n=3)	Nil	No conclusions can be drawn from efficacy or safety	Remdesivir discontinued in 1 patient due to combined elevated alanine aminotransferase and rash (uncertain drug adverse reaction)	France
	Remdesivir (dose and duration unknown)	Nil	No conclusions could be drawn from efficacy or safety	None reported	United States of America (USA)
Corticosteroids	Systemic corticosteroids	1. Risk of mortality 2. Duration of pneumonia 3. Duration of hospitalization 4. Duration of fever	Reduced duration of fever, but no mortality risk, Long duration of pneumonia. Associated with longer hospital stay.	None reported	China
	Median hydrocortisone equivalent dose of 400 mg per day after ICU admission in severe cases	Nil	No survival advantage in ICU patients with severe COVID-19, especially when complicated by ARDS and shock or multi-organ injury	None reported	China
	IV methylprednisolone (30–80 mg/d for 3–5 days) (n = 40)	Nil	No observable benefit of corticosteroids	None reported	China

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Heparin	1. LMWH (enoxaparin 40–60 mg/d, at least 7 days) (n = 94) 2. Unfractionated heparin (10,000–15, 000 U/d, at least 7 days) (n = 5) 3. No heparin (n =350)	Nil	Heparin may improve 28-day mortality in severe COVID-19 patients meeting sepsis-induced coagulopathy criteria	None reported	China
	1. LMWH (n = 21) 2. Controls (n = 21)	Nil	Heparin can increase the proportion of lymphocytes and decrease IL-6 levels in severe COVID-19	None reported	China
Tocilizumab	Tocilizumab (400 mg, once dose) + LPV + methylprednisolone	Nil	Improved clinical status in severe to critical COVID-19	None reported	China
	1. Tocilizumab (8 mg/ kg, once, renewable once) (n = 30) 2. No tocilizumab	Nil	Reduced ICU admission and requirement of mechanical ventilation in severe to critical COVID-19	Hepatic cytolysis	France
Convalescent plasma	1 transfusion of 200 ml of convalescent plasma from donors with neutralizing antibody titres> 1:640 (n = 10)	1. Safety of convalescent plasma transfusion 2. Improvement in clinical symptoms & laboratory parameters within 3 days of transfusion	Convalescent plasma was well-tolerated and could potentially improve clinical outcomes in severe COVID-19	None reported	China
	2 consecutive transfusions of 200–250 ml of convalescent plasma with neutralizing antibody titre> 40	Nil	Improved clinical status in critically ill patients with ARDS	None reported	China
	2 transfusions of 250 ml of convalescent plasma at 12-h interval (optical density ratio for IgG: 0.532 & 0.586) (n = 2)	Nil	Favorable clinical outcome in critically ill patients with ARDS (combined with systemic corticosteroids)	None reported	South Korea
Mesenchymal stem cell (MSC) treatment	1. MSC transplant (n = 7). 2. Placebo (n = 3)	1. Adverse events. 2. Cytokine variation, C-reactive protein, oxygen saturation. 3. Total lymphocyte count and subpopulations, chest CT, respiratory rate, patient symptoms	Symptoms, pulmonary function and biochemistry apparently improved after MSC transplantation	None reported	China
	MSC transplant 3 times, 3 days apart	Nil	No conclusion could be drawn	None reported	China

Poor data are available on the adverse effects of umifenovir. However, mixed reviews of its toxicity (hyperbilirubinemia and mild manifestations of digestive system such as diarrhea and vomiting) and nontoxicity have been obtained during COVID-19 trials (Xu *et al*., 2020). As there is little literature on adverse effects, so there is no clear evidence of its toxicity profile.

Severe and critical COVID-19 adjunctive treatments

According to international guidelines, remdesivir is recommended as a compassionate drug for severe and critical cases of COVID-19 (Xu *et al*., 2020, Van Ierssel *et al*., 2020). Anticoagulant (Heparin) is used to overcome the issue of venous thromboembolism at this stage of disease (Van Ierssel *et al*., 2020). In addition to the above-mentioned drugs the corticosteroids are also included in the treatment protocol of this stage (Lombardy, 2020). Sarilumab or Siltuximab and convalescent plasma are also added in the treatment of severe and critical COVID-19 cases (Lombardy, 2020). So, in this group, the above mentioned supportive label and open label therapeutics will be discussed.

Remdesivir

Remdesivir is a novel monophosphoramidate prodrug of the nucleoside analogue of adenine (GS-441524). It pharmacologically becomes active by the addition of two pyrophosphates from the internal medium of cell and is integrated in growing nascent viral Riboxy nucleic acid chain. Hence, in turn, nucleotide analogue drug is capable to cause premature termination of RNA transcription by inhibiting viral RNA-dependent RNA polymerase (RdRp). In addition, active remdesivir is capable of lethal mutagenesis by inhibiting the proof reading capability of

Table 2: Summary of International guidelines for the use of investigational adjunctive treatments of COVID-19 (Food and Drug Administration) (Xu *et al.,* 2020)

Severity of COVID-19 (WHO classification)	NHC (China)	SIMIT Lombardy section (Italy)	SWAB (Netherlands)	Sciensano (Belgium)
Mild Pneumonia	Symptomatic treatment Other general treatments: • Interferon-alpha (5 million units or equivalent dose added to 2 ml sterile water, delivered via nebulizer bid) • Lopinavir-ritonavir (400 mg/100 mg bid; not > 10 days) • Ribavirin (500 mg bid/tid, not > 10 days)(recommended in combination with interferon or lopinavir-ritonavir) • Chloroquine phosphate (500 mg bid for 7 days in adults 18–65 years and body weight > 50 kg; 500 mg bid for days 1–2, followed by 500 mg od for days 3–7 in adults < 50 kg) • Umifenovir (200 mg tid, not > 10 days)	Symptomatic treatment In age > 70 years old and/or co-morbidities • Consider lopinavir-ritonavir (400 mg/ 100 mg bid) + Chloroquine (500 mg bid) or HCQ (200 mg bid) for 5–20 days) Alternatives to lopinavir- ritonavir: • Darunavir + ritonavir (800 mg/ 100 mg od), or • Darunavir + cobicistat (800 mg/ 150 mg od) • Lopinavir-ritonavir (400 mg/ 100 mg bid) + Chloroquine (500 mg bid) or HCQ (200 mg bid) for 5–20 days) BCRSS* score ≥ 2, consider adding: - Dexamethasone 20 mg/day for 5 days, then 10 mg/d for 10 days (discuss with intensivist) and/or - Tocolizumab	Nil	Symptomatic treatment • Consider starting HCQ (400 mg at diagnosis, then 400 mg 12 h later, followed by 200 mg bid up to day 5) or • chloroquine base (10 mg/kg at diagnosis, 5 mg/kg 12 h later, followed by 5 mg/kg bid up to day 5) or • chloroquine phosphate (1000 mg at diagnosis, then 500 mg bid, followed by 300 mg bid up to day 5) (including age > 65 years and/or underlying end-organ dysfunction)
Severe	• Convalescent plasma • Tocolizumab (extensive lung disease, increased IL-6; prohibited in active tuberculosis)(IV, 4–8 mg/ kg, maximum 2 cumulative doses) • Glucocorticoids (not exceeding equivalent of methylprednisolone 1–2 mg/(kg·d), for 3–5 days) • Xuebijing (TCM)(100 ml bid) • Probiotics	Nil mentioned	• Chloroquine (600 mg loading dose, 300 mg 12 h later, followed by 300 mg bid on days 2–5 or • HCQ (400 mg bid loading dose, then 200 mg bid on days 2–5) Consider switching or adding remdesivir if insufficient response or clinical deterioration	• Prophylactic LMWH • Start HCQ or chloroquine (above dose) • Consider lopinavir-ritonavir (400 mg/100 mg bd for 14 days) only if HCQ/ chloroquine is contraindicated and if it can be administrated with 12 days of symptom onset
Critical		• Remdesivir (IV 200 mg loading dose on day 1, maintenance dose 200 mg/d from day 2– 10) + chloroquine/HCQ (above dose) or • Lopinavir-ritonavir + chloroquine/HCQ (above dose) ARDS: • Dexamethasone 20 mg/d for 5 days, then 10 mg/d for 5 days; to initiate within 24 h of ARDS diagnosis (discuss with intensivist) and/or • Tocilizumab	• Chloroquine/ HCQ + remdesivir (200 mg loading dose on day 1, then 100 mg daily for days 2–9) or • Remdesivir alone	• Remdesivir (200 mg loading dose within 30 min, followed by 100 mg daily for 2–10 days) • Consider HCQ/ chloroquine if remdesivir is unavailable • IL-6 inhibitors should only be used in clinical trials

Table 3: **C**ommonly used antiviral drugs used for COVID-19 mild and severe infection in various countries

Sr. No	Drug name	Combination	Mechanism of action	Side effects	Clinical trial against Covid-19	Reference
1.	Ribavirin	Interferon beta-1b, lopinavir–ritonavir, and ribavirin	Guanosine analog that interferes with the replication of RNA and DNA viruses. Ribavirin is a pro drug activated by the liver through metabolism of analog purine nucleoside, exhibiting its antiviral activity by incorporating itself into the growing chain of RNA and halting subsequent addition during viral RNA synthesis	Hemolytic anemia with deficiency of calcimine and magnesium, not much safe to use in the heart and kidney patients, hepatic impairment Child-Pugh because its metabolism requires CYP enzyme. This drug also has teratogenic and carcinogenic effects in animal model	ClinicalTrials.gov, NCT04276688.	(Khalili *et al.*, 2020)
2.	Favipiravir	Alone or in combination	Selectively inhibits RNA-dependent RNA polymerase (RdRp) of RNA viruses, by phosphoribodylation and phosphorylation, interrupting the nucleoside incorporation process, halting the viral replication. The catalytic domain of RdRp is preserved in various types of RNA viruses, which supports the wider antiviral spectrum of favipiravir. In addition, the drug has shown to inducee a high rate of destructive RNA mutations, (intra shifting of purines and pyrimidines) thus generating a non-viable viral phenotype	Hyperuricemia, diarrhea, elevated transaminases and neutropenia, occurring in a dose-dependent manner	In more than 5 clinical trials	(Du and Chen, 2020)
3.	Oseltamivir	Combination with chloroquine and favipiravir	Attacks the enzyme that performs glycoside bond catalysis of neuraminic acid spread on the viral membrane surface	nausea and vomiting, abdominal pain		(Wu *et al.*, 2020[a])
4.	Nitazoxanide	In combination with other drugs	Interferes with electron transfer (enzyme-dependent pyruvate ferredoxin oxidoreductase), thus impairing anaerobic energy production of protozoa	Intolerance of digestive system. In addition to it, the sufferer might experience yellowing of eyes and urine, dysentery and redness of skin		(Khalili *et al.*, 2020)
5.	Nelfinavir	Alone or in combination with other antiviral and immune suppressants	protease blocker drug, developing linkage with HIV-1 protease active site, cleaving the viral Gag-Pol polyprotein precursors into functional proteins (conformational changes) basically designed to work with other HIV drugs to attack the virus by halting/modifying multiple vital process	Digestive problems like dysentery, vomiting, and occasionally skin rashes		(Barlow *et al.*, 2020)
6.	Sirolimus	Corticosteroids and Sirolimus and oseltamivir plus sirolimus	mTOR, is a former protein complex of mTORC1, playing a vital function in viral replication. In an in vitro trial, sirolimus exhibited its antiviral activity against COVID-19 by disturbing PI3K/AKT/mTOR	More research is required to find out, side effects of this drug in COVID- 19 patients	https://ClinicalTrials.gov/show/NCT04341675	(Kadam *et al.*, 2017)
7	Interferon α	Ribavirin, LPV/r)	Interferon-a has the potential to evoke host-mediated immune cell reaction which is the main part in therapy in viral infections	Due to insufficient research, side effects of interferon alpha are not clear in COVID- 19 patients	Multiple Clinical trials are ongoing	(Barlow *et al.*, 2020)
8	Systemic corticosteroids	Ribavirin, LPV and corticosteroids	Immunosuppressive and anti-fibrotic drug capable to resolve inflammation of respiratory tract to avoid a huge cytokine response. Particularly, methylprednisolonecan recover sepsis induced immune system dysregulation of COVID-19 with potential to boost up blood pressure	There is a chance of having serious ARDS after using corticosteroids in COVID-19 clinical trials. The use of corticosteroids is controversial and raised the negative risk of SARS, MERS, or COVID-19	Multiple clinical trials are ongoing	(Khalili *et al.*, 2020)

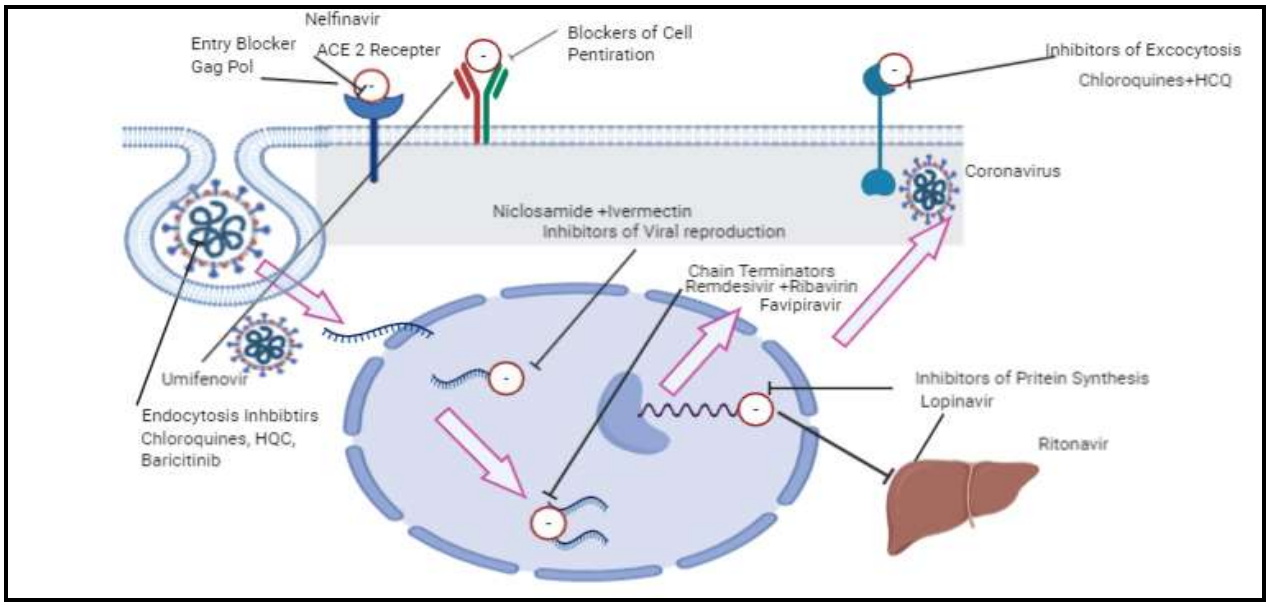

Fig. 1: Therapeutic targets of antiviral agents against entry and spread of covid-19 in human cells

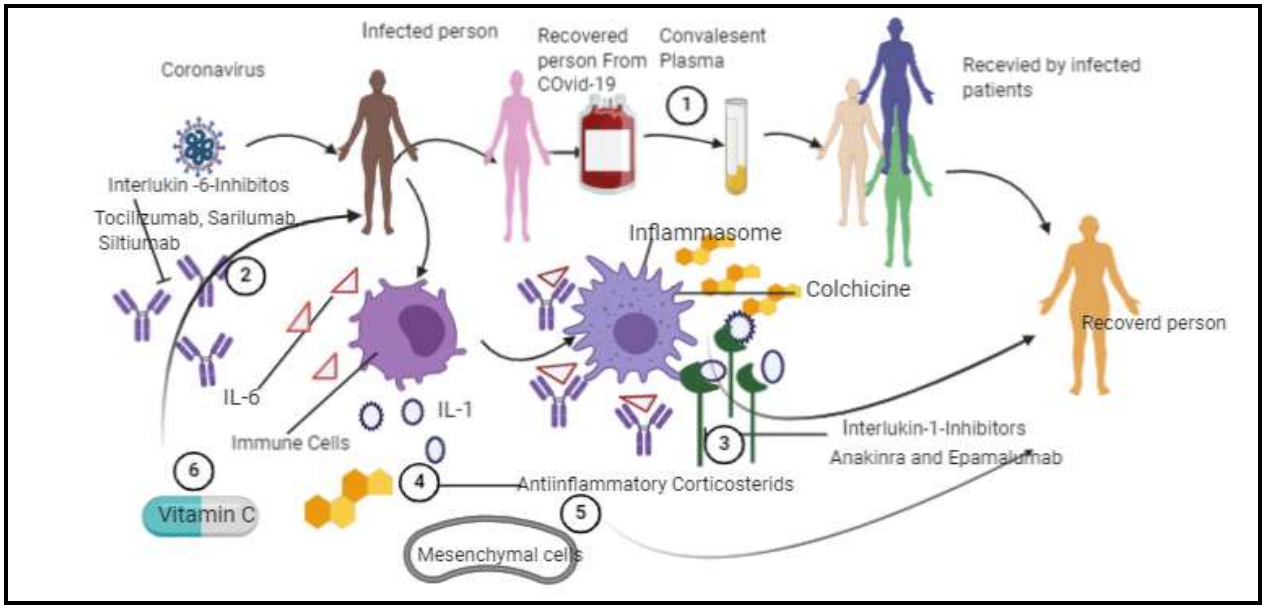

Fig. 2: Immunological and another possible target against COVID-19.

nascent viral chain via exo-ribonuclease. This characteristic of remdesivir makes it a potent antiviral therapeutic agent for respiratory disease COVID-19 in *in vitro* clinical trials. For improved results, remdesivir is used in combination with chloroquine (Sheahan *et al*., 2017, Gordon *et al*., 2020).

Remdesivir was basically developed and is still in clinical trials as an antiviral agent against Ebola infections (hemorrhagic fever) to inhibit RdRp with a low 0.77 μM EC50 and with high selectivity towards the viral enzyme (Wang *et al*., 2020b). Remdesivir has proved promising broad-spectrum antiviral agent with good *in vitro* and *in vivo* efficacy in animal models against various RNA viruses, such as SARS-CoV, paramyxoviridae, filoviridae, MERSCoV, including COVID-19(Gordon *et al*., 2020). Rationales of this drug are presented in Table 1. Remdesivir still has not been approved internationally for public use in any country for any medical issue and must be obtained via compassionate use or enrollment in a clinical trial. The recommendation of compassionate use depends on patient's clinical status. Although, the use of remdesivir was banned after RCT evaluation of safety, pharmacokinetics, and efficacy with monoclonal antibodies terminating random assignment to remdesivir because of high mortality rate.

The most reported undesirable effects of remdesivir are gastrointestinal manifestations (from digestion to excretion) with raised level of aminotransferase within few days of drug intake (Saez *et al*., 2020). However, in phase 1 analysis of this drug for Ebola virus, one death was reported due to cardiac arrest (patient suffered from hypotension) (Mulangu *et al*., 2019). Based on the existing facts, no proper data can be drawn regarding therapeutic effectiveness or safety report for anti-COVID-19 therapies.

Low molecular weight heparin

Heparin is used for the prevention and treatment of thrombosis and embolism in heart patients since nineteenth century. However, the pharmacokinetic profile, biotransformation, and biological properties of unfractionated heparin (UFH) show few restrictions, which raised the development need of low-molecular-weight heparins (LMWHs). LMWHs, are actually derivatives of heparin (chemically or enzymatic depolymerization) with better anticoagulative characteristics easy to administer and monitoring (Mukherjee and Topol, 2002, Yan and Goodman, 2004).

Severity of disease in critically ill COVID-19 patients showed manifestations like disseminated intravascular coagulation due to sepsis due to long duration of bedrest. So, the use of anticoagulants proved effective for above-mentioned complications and laboratory indication of hypercoagulability, however, the use of an anticoagulant at earlier stages could inhibit micro and macro thrombosis and protect the endothelium, thus decreasing the risk of major organ failure. Anticoagulants such as heparin for critically ill COVID-19 patients were initially suggested by an expert consensus in Wuhan China(Li *et al*., 2020). Patients on anticoagulant treatment showed decreased mortality rate (Tang *et al*., 2020). Lastly, another interesting rational to use heparin is the anionic nature that would make it an anti-inflammatory substance and hinder coronavirus binding with the susceptible cell by changing the structure of receptor membrane (Spike) S1(Mycroft-West *et al*., 2020) (136-138). Anticoagulant (heparin) in critical cases of COVID-19 was also observed to be linked with another therapeutic benefit of decreasing the serum IL-6 in addition to the treatment of thrombosis(Shi *et al*., 2020). The international guidelines recommended heparin as an adjunctive treatment of COVID-19 against venous thromboembolism (Wu *et al*., 2020b, Silva *et al*., 2013). It is not recommended in those patients with active bleeding, and platelet count less than 25 × 109/L (Wang *et al*., 2020a). Available research proved the treatment of venous thromboembolism in hospitalized cases with both low molecular weight and unfractionated heparin. The use of anticoagulant can also be done in quickly progressing respiratory deterioration or in diagnosed thrombosis by clinician.

Interleukin-6 inhibitors Tocilizumab (Actemra)

Tocilizumab (Interleukin-6 inhibitors) is available with trade name Actemra, a humanized immunoglobulin (monoclonal antibody) developed by Roche and Chugai Pharmaceuticals. Tocilizumab is an interleukin 6 receptor blocker, which is capable of hindering the downstream inflammatory cascade. It is licensed in the US and Europe by FAD for the treatment of severe rheumatoid arthritis (RA), chimeric antigen receptor T-cell-induced severe (CAR) or life-threatening cytokine release syndrome (CRS), giant cell arteritis, and polyarticular or systemic juvenile idiopathic arthritis (SJIA)(Oved *et al*., 2019) in adults and pediatric patients (aged 2 years or older). Within the body, interleukin 6 (IL-6) is a cytokine relevant to many inflammatory and metabolic processes (Jones *et al*., 2011). Literature data advocate that patients with severe or critically ill COVID-19 experience acute respiratory distress secondary to a surge of inflammatory cytokines may trigger a "cytokine storm" (100). Quick progression in viral duplication induces high secretion of IL-6 (signaling proteins), implicated in the pathogenesis of diverse inflammatory and autoimmune disorders syndrome like raised level of various pro-inflammatory cytokines (e.g. TNF-α, IL-1, IL-6) and chemokines (e.g., IL-8) and, produces long-term damage and fibrosis of the lung tissue, clotting disorders and multi-organ dysfunction (Mehta *et al*., 2020). Tocilizumab binds to IL-6 receptors, thus blunting cell signaling and effectively down regulating the surplus inflammatory response.103 The rationale for its off-label use in COVID-19 is presented in Table 1. Studies conducted in Italy recommend maximum dose of Tocilizumab to be 800 mg, that is 8mg/Kg in a one infusion. However, for COVID-19 patients, its dosing is still not well established (Fu *et al*., 2020). In most of the COVID-19 patients, a single infusion of 400 mg was given (Xu *et al*., 2020). Although the 400 mg dose for obese patients with severe COVID-19 would not be enough. During COVID-19 treatment, tocilizumab should be detained in case of severe deficiency in neutrophil and platelet count and abundance of liver enzymes(Mao *et al*., 2020b). Tocilizumab elimination is not influenced by renal dysfunction. No dose adjustments are required for kidney patients. Tocilizumab got black box warning from FDA regarding its use in serious infectious microbial diseases. It is only recommended in critically ill COVID-19 patients under proper monitoring. Recent verifications are inadequate to defend its use except in clinical trials. Infusion reactions of tocilizumab include hypertension, headache, and skin rashes within a day (Barlow *et al*., 2020).

Convalescent plasma

Passive immunity may be achieved as anti- COVID-19 antibodies from the plasma of recovered COVID-19 patient might be recommended as another novel curative approach to treat coronavirus patients. According to this therapeutic protocol, plasma from the survivors of the

coronavirus after cure of COVID-19 is used with antibodies against COVID-19 (Chen *et al*., 2020). For achieving more effective result from convalescent plasma, management should be done early in the initiation period of infection (within half month) as viremia from SARS has revealed to peak in the first week of therapy followed by a primary immune response of less than 12 days (Soo *et al*., 2004). This technique has been used for decades (Luke *et al*., 2006) and works as a defensive agent for already infected persons to mitigate the severity of disease(Casadevall and Pirofski, 2003). Defensive mechanism starts with the association of the transfused antibodies to the particular antigen (coronavirus), consequently resulting in cellular cytotoxicity, and the plasma membrane engulfs these large complexes of antibodies with coronavirus(Van Erp *et al*., 2019). This mode of treatment has already shown its potency in both SARS-CoV and MERS(Zhang *et al*., 2005). Preliminary studies data regarding the use of convalescent plasma in the COVID-19 pandemic proved effective without or least adverse effects (Liu and Li, 2020). However, reported adverse effects from studies include raised body temperature and respiratory discomfort(Wu *et al*., 2020a). The rationale of convalescent human plasma is presented in table 1.

For clinically improved safe, treatment of COVID-19 selected anti- COVID-19 antibodies is in process (https://reference.medscape.com/features/guidelines).
Internally reputed pharmaceuticals (Takeda) have declared exploration for novel plasma derived treatment, termed TAK-888. Convalescent therapy remains in the experimental phase, but appears it may favorably influence the treatment course, and enrollment of patients into a clinical trial will aid in defining its role in therapy.

Others

Some medicines such as ribavirin, favipiravir, oseltamivir, nitazoxanide, Nelfinavir, Sirolimus, Niclosamide, ivermectin, mesenchymal stem cell treatment, Interferon-alpha and corticosteroids are provided in Table 3 with possible effects and side effects, which are being used in clinical investigated during pandemic of COVID-19 (Table 3), but not yet part of any treatment protocol (Saha *et al*., 2020). Ribavirin and Favipiravir, both are antiviral pro drugs and analog purine nucleosides for activation(Oestereich *et al*., 2014). It showed great absorption when taken with fatty meal and should only be used in patients with stable renal function. More than four clinical trials are going on in China with co-formulations. Recently, favipiravir has also been approved in China for the treatment of COVID-19 and in phase IV clinical trials. Favipiravir showed a higher antiviral activity than lopinavir/ritonavir, in terms of virus elimination and rate of improvement of thoracic CT imaging in a study. Oseltamivir **(**Tamiflu) is an approved anti-influenzal (A+B) drug, catalyzing the glycoside bond of neuraminic acid(Ward *et al*., 2005). Numerous clinical trials are still going on to evaluate the effectiveness of oseltamivir as a therapeutic of COVID-19 infection alone or in combinations with other antivirals. A lot of research is required still to establish the effectiveness of all above mentioned drugs to use in critically ill patients of coronavirus. Concrete evidence of positive and negative effects of all discussed drugs in this section is required to take final approval regarding administration in treatment protocol of COVID-19.

CONCLUSION

The COVID-19 pandemic has created an emergency to develop our interest in finding the treatment of new viral infection that could have the potential to bring out the world from this outbreak. Although, medical professionals are bound to sustain patient's life by using supportive therapeutic measures. All the data presented in this review regarding COVID-19 adjunctive therapies are based on international standard. We know that rigorous large clinical trials are needed to device proper COVID-19 treatments with efficacy, safety and promising results. We tried to summarize fundamental treatment measures for moderate and severe patients, and practice has proved to be effective. We are facing enormous health crisis of COVID-19 globally. This pandemic brought about huge interest of pharmacological industry to develop potent targeted treatment of COVID-19. Presently, time protocols developed by health regulatory bodies are using drugs with different therapeutic targets (antivirals, anti-inflammatory, immunomodulatory) to combat with COVID-19. All the candidate medicines include both open-label or investigational drugs, off-label or repurposed drugs. Hence, from the results of these primary studies, some drugs are promising, and some are with disappointing information. To overcome critical stage of the disease, it is important to gain proper knowledge about efficacy of drugs and their pharmacokinetics for designing important therapeutic protocols.

ACKNOWLEDGMENT

We are thankful to Ministry of Science and Technology Pakistan for providing basic resources to conduct this review.

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