Chapter

Pharmacotherapy for COVID-19: A Ray of Hope

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Abstract

Most viral infections have limited treatment options available and the same holds for COVID-19, its causative agent being the SARS-CoV-2 virus. Drugs used in the past against Severe Acute Respiratory Syndrome (SARS) or Middle East Respiratory Syndrome (MERS) viruses, which belong to the same family of viruses as the novel Coronavirus included ribavirin, interferon (alfa and beta), lopinavir-ritonavir combination, and corticosteroids. There remains controversy regarding their efficacy to date, except for the last one. Hence, large-scale multicentric trials are being conducted involving multiple drugs. Chloroquine and hydroxy-chloroquine were initially taking the race ahead but have now been rejected. Remdesivir was a promising candidate, for which the FDA had issued an emergency use authorization, but now is not recommended by the WHO. Convalescent plasma therapy had promising results in the early severe viremia phase, but the PLACID trial made an obscure end. Only corticosteroids have shown demonstrable benefits in improving mortality rates among severe COVID-19 cases. Many new modalities like monoclonal antibodies and tyrosine kinase inhibitors are discussed. In this chapter, we review the therapeutic drugs under investigation for the COVID-19 treatment, their mode of action, degree of effectiveness, and recommendations by different centers regarding their use in current settings.

Keywords: antiviral, monoclonal antibody, coronavirus disease 2019, dexamethasone, immunomodulator, ivermectin, remdesivir

1. Introduction

Because of the high rate of infectivity of the COVID-19 virus, the global burden associated with the disease, and its impact on the economies of different countries, efforts are being made to find a possible cure for the disease as soon as possible [1]. As with most viral infections, limited options are available for the treatment of COVID-19. Since there is no efficient therapy available for the same, given the public emergency, efforts are ongoing to find drugs helpful in COVID-19 infection. Drugs used in the past against Severe Acute Respiratory Syndrome (SARS) or Middle East Respiratory Syndrome (MERS), which also belong to the group of Beta coronaviruses, included ribavirin, interferon, lopinavir-ritonavir, and corticosteroids [2]. Most randomized controlled trials (RCTs) performed to test the effectiveness of these drugs have not shown any satisfying results, apart from corticosteroids. Many RCTs are still undergoing, the results of which are awaited. Studies about the virus-induced host immune response and viral processing within target cells have led to several potential therapeutic targets.

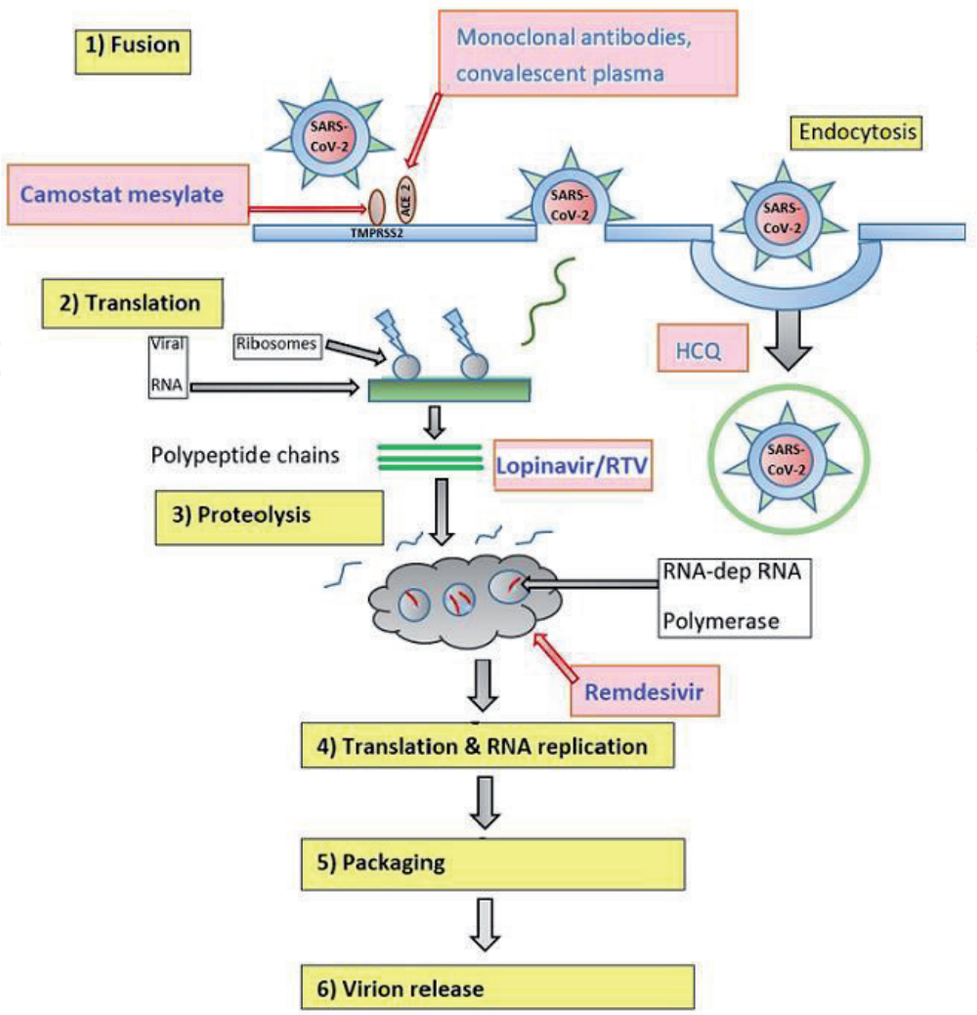

Figure 1.
Site of action of different possible pharmacotherapeutics used in COVID-19 treatment.

Drug	Mode of action	Effectiveness	Recommendation
Corticosteroids	Immunosuppressant	Decreased death rate in ARDS, no effect in non-ARDS	WHO, CDC, and IDSA recommendations
Remdesivir	RdRp inhibitor	Decreases recovery time	FDA approval in October, WHO issued a conditional recommendation against use in November, IDSA suggests the use
Convalescent plasma	Anti-COVID 19 antibodies	No benefit	FDA EUA issued
Monoclonal antibodies	Directed against COVID spike proteins	Benefit in Mild cases, no benefit in hospitalized cases	FDA EUA issued for OPD patients
Azithromycin	Immunomodulation	No benefit	No recommendation, but widely used
Ivermectin	Viral IMPα/β1(Importin) mediated nuclear import inhibition	Benefit in prophylaxis	NIH: Insufficient data for or against the use
Melatonin	Pineal gland hormone, anti-inflammatory	Benefit in critical patients	No recommendation

Drug	Mode of action	Effectiveness	Recommendation
Tocilizumab	IL-6 R inhibitor	Reduces inflammatory markers	Single-dose in addition to dexamethasone in critical patients with rapid progression of respiratory failure may be given: NIH
Favipiravir	Inhibits RNA polymerase	Faster viral clearance, improved imaging findings	No recommendation yet
Ribavirin	Inhibits RNA polymerase	No concrete evidence	No recommendations yet
Chloroquine/ Hydroxy-chloroquine	Increases endosomal pH, interfere with glycosylation of receptor, immunomodulator	Benefit in clinical parameter & virological clearance	Removed from Solidarity trial, no other recommendation
Lopinavir/ Ritonavir	Protease inhibitor: SARS-Cov-2 3CL pro	Not significant	Removed from Solidarity trial, no other recommendation
Interferon	Immunomodulation	No concrete evidence	Removed from Solidarity trial, no other recommendation
Tyrosine Kinase inhibitors	Inhibit STAT phosphorylation, decrease hyperimmune state	No concrete evidence	Use with remdesivir if corticosteroids are contraindicated: NIH/IDSA

RdRp: RNA dependent RNA polymerase; ARDS: Acute respiratory distress syndrome; WHO: World Health Organization; CDC: Centers for Disease Control and Prevention; FDA: Food and Drug Administration; IDSA: Infectious Disease Society of America; EUA: Emergency Use Authorization; NIH: National Institute of Health; Il-6 R: Interleukin-6 receptor; STAT: Signal transducer and activator of transcription.

Table 1.
Summary of various pharmacotherapeutics being considered for COVID-19 treatment.

We hereby discuss the potential therapeutic drugs under investigation for the COVID-19 treatment, their modes of action (**Figure 1**), degree of effectiveness, and recommendations (**Table 1**) by different centers regarding their usage in the current settings.

2. Review of pharmacotherapy

2.1 Chloroquine/hydroxychloroquine

The first studied drugs for COVID-19 were chloroquine and hydroxychloroquine (HCQ). Chloroquine was found to be effective against Avian influenza A H5N1 virus in animal models [3, 4] and also had demonstrable activity resulting in in-vitro inhibition of SARS-CoV [5]. COVID-19 infection showed high pandemicity in countries where malaria is the least prevalent and least pandemicity where malaria is highly prevalent. This observation led to the concept that chloroquine may be beneficial in COVID-19 since it is used as an anti-malarial. The mechanism of chloroquine action depends on the pathogen involved. Chloroquine increases the endosomal pH and interferes with the glycosylation of cellular receptor [Angiotensin Converting Enzyme (ACE) II] of SARS-CoV [6]. It also inhibits quinone reductase-2, which is involved in sialic acid biosynthesis. There is inhibition of MAO-kinase, virion assembly, and processing of M protein [7]. Besides its antiviral activity, it also has immunomodulatory effects that may be synergistic. HCQ was found to be equally

effective as chloroquine, although a study concluded that HCQ was more effective and less toxic than chloroquine [8]. Chloroquine inhibitory actions against SARS-CoV were equal whether the primate cells were treated before or after exposure. This suggested that chloroquine could have both prophylactic and therapeutic applications [9]. One of the first studies performed to study the effect of chloroquine was done in the Chinese population. In this trial, patients in the study group who received chloroquine had reduced symptom duration, radiological improvement, and earlier seroconversion to the virus-negative state compared to controls [10]. Following this study, the National Health Commission of the People's Republic of China included chloroquine in its guideline for the management of pneumonia due to Covid-19. In a study conducted by Gautret et al. in France, chloroquine treatment group had significant clearing of the nasopharyngeal swab viral load compared to the control [11]. The virological clearance day-6 post inclusion (primary outcome) with HCQ vs. controls was 70% vs. 12.5% ($p < 0.001$). The virological clearance at day 6 in HCQ plus azithromycin, HCQ and control arms were 100%, 57.1%, and 12.5% respectively ($p = 0.001$) thus suggesting synergistic action of azithromycin to HCQ. Gradually the side effect profile of HCQ, that is QTc prolongation with concomitant use of Azithromycin, lead the American Heart Association (AHA) to recommend withdrawal/withholding these drugs in patients with QTc ≥ 500 millisecond (either baseline or developing during treatment). On 28 March 2020, Food and Drug Administration (FDA) had issued Emergency Use Authorization (EUA) for Chloroquine/HCQ. However, the Centers for Disease Control and Prevention (CDC) on April 7 issued a statement stating no drugs or other therapeutic measures were approved by the US FDA to prevent or treat COVID-19. In April, the FDA issued a Drug Safety Communication cautioning against the use of HCQ or chloroquine for COVID-19 outside the hospital setting or a clinical trial due to the risk of heart rhythm problems. In June 2020, it was announced by World Health Organization (WHO) that the HCQ arm of the Solidarity Trial (Multi-national trial including remdesivir, HCQ, lopinavir/ritonavir, and lopinavir/ritonavir with interferon beta-1a) would be stopped [12]. This was keeping in view the lack of any mortality benefit of HCQ. Hence in June itself, FDA revoked the EUA of HCQ and chloroquine [13]. The pre-exposure prophylaxis benefit of HCQ needs further research.

2.2 Lopinavir/ritonavir

The combination of lopinavir/ritonavir was considered as an option for the treatment of Covid-19 during initial pandemic days. Lopinavir is an HIV-1 protease inhibitor, which is combined with ritonavir to increase its half-life through cytochrome p-450 inhibition. Both anti-HIV drugs interact with residues at the active site of SARS-CoV 3C-like protease, suggesting the mechanism of action in COVID-19 [14]. Its role was first evaluated in the treatment of SARS where patients treated with lopinavir/ritonavir for 14 days combined with ribavirin for 21 days. They had a milder disease in form of less diarrhea, fever, lymphadenopathy, the incidence of nosocomial infections, viral loads, demonstration of virus in the fecal sample by reverse transcription-polymerase chain reaction (RT-PCR), and 21 days adverse outcomes [15]. The combination was tested for MERS-CoV. It was postulated that the lopinavir/ritonavir combination may inhibit the 3C-like protease of MERS-CoV and may affect apoptosis in human cells. Results revealed that treatment with lopinavir/ritonavir led to clinical, radiological, and pathological improvement. Those animals treated with this combination had the lowest mean viral load detected by RT-PCR in lung and other extrapulmonary tissue [16]. There was only a single case report of a man being treated and recovered with a combination of lopinavir/ritonavir, ribavirin, and interferon-α for the MERS [17]. Based on this data, an

urgent RCT was done to study the efficacy of lopinavir/ritonavir in the Wuhan province of China [18]. The analysis revealed no significant difference in terms of time for clinical improvement and mortality at 28 days. The median time for clinical improvement was just one day shorter in the lopinavir-ritonavir group compared to the standard care group. In July 2020, WHO discontinued the lopinavir/ritonavir arm of the solidarity trial due to a lack of any mortality benefit [19]. It causes QTc prolongation, just like HCQ [20].

2.3 Azithromycin

Azithromycin is a broad-spectrum antibiotic belonging to the macrolide group, having anti-inflammatory properties also. It is commonly used for treating atypical respiratory pathogens. Azithromycin's anti-viral efficacy against some RNA viruses has also been described. Its efficacy has been demonstrated in-vitro against Zika virus and rhinovirus, as well as SARS-CoV-2 [21, 22]. As described, azithromycin also has immunomodulatory effects and can decrease acute exacerbations of chronic airway disease. Owing to its wide availability, excellent safety profile, and easy availability, azithromycin is one of the commonest drugs being used in the COVID-19 pandemic also. The Lancet reported the result of the COALITION II trial, [23] which was an open-label randomized trial evaluating azithromycin in addition to the standard of care (including HCQ), against the standard of care alone in severe COVID-19 patients. Azithromycin demonstrated no benefit in clinical outcome including clinical status or mortality, as compared to the standard of care alone (OR 1·36 [95% CI 0·94–1·97], p = 0·11). There was no increase in adverse events with azithromycin. In a study published in NEJM, HCQ alone or in combination with azithromycin had no demonstrable improvement in clinical status at 15 days compared with standard care in mild to moderate COVID-19 admissions [24].

2.4 Ivermectin

Ivermectin is a commonly used drug for various parasitic infestations including head lice, scabies, strongyloidiasis, ascariasis, and lymphatic filariasis. It is a macrocyclic lactone, which is derived from streptomyces avermitilis [25]. Its mechanism of activity against SARS-CoV-2 is believed to be via viral IMPα/β1 (Importin) mediated nuclear import inhibition. This leads to a decrease in the multiplication of the virus and hence the viral load [26, 27]. Ivermectin and doxycycline combination also inhibit viral entry and increases viral load clearance by the targeting of multiple viral proteins [28]. A recent study from India demonstrated that 2-dose ivermectin prophylaxis (300 micrograms/kg) within a gap of 3 days led to a 73% reduction in the number of COVID-19 infections among healthcare workers [29]. In studies conducted in Bangladesh also, the ivermectin-doxycycline combination was demonstrated to be highly effective in virological clearance in mild to moderate COVID-19 patients [30, 31]. National Institute of Health (NIH) stated in January 2021 that there was insufficient data to recommend either for or against the use of ivermectin for the treatment of COVID-19 [32].

2.5 Melatonin

Melatonin is a hormone, which is synthesized from tryptophan in the pineal gland of the body and also by mostly all the organs of the body, as its production is associated with mitochondria. Higher levels of melatonin have positive roles in

health and aging. Melatonin promises to be a great adjunctive drug for viral infections owing to its anti-inflammatory, anti-apoptotic, immunomodulatory, and antioxidant activities [33]. Sirtuin-1 (SIRT1) is the proposed mediator of melatonin's anti-inflammatory action. This is via inhibition of high mobility group box-echromosomal protein-1 (HMGB-1), leading to down-regulation of the polarization of macrophages towards pro-inflammatory type [34]. It inhibits the over-activity of the innate immune system. Hence, theoretically, the cytokine storm induced by COVID-19 can be suppressed by melatonin. But the use of melatonin in COVID-19 is still very sparse, with only a few studies evaluating the same, hence further research is warranted [35]. Owing to melatonin's anti-inflammatory, anti-oxidant, and anti-viral actions, its role in critical illness caused due to COVID has been studied. Melatonin has easy availability, is not expensive, and has an excellent safety profile [36]. A trial (EudraCT: 2020–001808-42) is ongoing for the identification of the doses of melatonin that may prove effective in this disease. It is a phase II, single-center, double-blind, RCT to address the efficacy and safety of intravenous melatonin in COVID-19 ICU patients [37].

2.6 Remdesivir

Remdesivir is a 1′-cyano-substituted adenosine nucleotide analog prodrug, which was found to be effective against several RNA viruses. It was initially developed in 2017 by Gilead science for the treatment of the Ebola virus [38]. It has demonstrated extensive antiviral activity & effective treatment of lethal Ebola and Nipah virus infections in nonhuman primates [39]. Subsequently, it was investigated for SARS-CoV and MERS-CoV. Studies have shown that Remdesivir inhibits viral replication in human airway epithelial cell culture by affecting the early stages of viral replication through viral RNA synthesis inhibition, as an RNA-dependent RNA polymerase (RdRp) inhibitor [39]. This may be due to the absence of Exon-mediated proofreading in viruses sensitive to Remdesivir [40]. One of the first trials of Remdesivir was performed by the Gilead sciences center in hospitalized patients with confirmed SARS-CoV-2 having oxygen saturation < 94% or a need for oxygen support. Till 28 days of follow-up, the cumulative incidence of clinical improvement was 84% (95% CI 70–99) by Kaplan–Meier analysis and it was less among patients receiving invasive ventilation compared to non-invasive ventilation [41]. In another randomized, double-blind, placebo-controlled, multicentre trial at 10 hospitals in Hubei, China, Remdesivir use was not associated with any difference in time to clinical improvement [42]. In February 2020, WHO cast a vote of confidence for remdesivir, indicating that it has great potential. In April 2020, the US National Institute of Allergy and Infectious Diseases (NIAID), announced that a clinical trial in >1,000 people showed that those taking remdesivir recovered in 11 days on average, compared with 15 days for those on a placebo, even adding that remdesivir may become a standard for COVID treatment [43]. US FDA had issued a EUA for remdesivir for severe COVID-19 disease. On 22nd October 2020, the FDA approved remdesivir for use in adult and pediatric patients (≥12 years, ≥40 kg) requiring hospitalization [44]. In October 2020 itself, an interim analysis of the WHO-led, open-label, randomized SOLIDARITY trial demonstrated that 301 (11·0%) of 2743 patients who received remdesivir and 303 (11·2%) of 2708 patients who received standard care died by day 28 (Kaplan–Meier rate ratio 0·95, 95% CI 0·81–1·11; p = 0·50) [45]. The ACTT-1 study had also reported a 29-day mortality of 11·4% in patients receiving remdesivir as compared to 15·2% in placebo (hazard ratio 0·73, 95% CI 0·52–1·03) [43]. Hence in November 2020, WHO issued a conditional recommendation against remdesivir utilization in hospitalized patients, regardless

of their disease severity. This was because they could not find evidence of remdesivir improving survival and other outcomes in the patients [46]. Infectious Disease Society of America (IDSA) still suggests the use of remdesivir in severe and critical patients, as does NIH [47, 48].

2.7 Tocilizumab

Tocilizumab is an Interleukin-6 (IL-6) Receptor inhibiting monoclonal antibody. Studies have shown that infection with the SARS virus leads to a cytokine storm with the release of inflammatory cytokines like IL-6, Tumor Necrosis Factor- α (TNF –α), and IL-12 [49]. Further research done on MERS-CoV showed IL-6, IL-1β, and IL-8 were elevated in these patients. In patients with confirmed COVID-19 infection who were admitted to ICU, levels of IL-2, IL-6, IL-7, IL-10, granulocyte-colony stimulating factor (G-CSF), interferon-γ-inducible protein (IP10), monocyte chemoattractant protein (MCP1), macrophage inflammatory protein 1 alpha (MIP1A), and TNF-α levels were found to be high, suggesting possible cytokine storm [50]. The first trial involving tocilizumab was performed in China in February 2020. The National Institute for Infectious disease had recommended tocilizumab in moderate to severe infections and IL-6 levels >40 pg/mL (or D-dimer levels >1000 ng/mL). However, it is not recommended by the CDC. In an RCT published in JAMA, in moderate-to-severe pneumonia, tocilizumab did not reduce the WHO Clinical Progression Scale scores. The proportion of patients with non-invasive or invasive ventilation or death at day 14 was 36% with usual care and 24% with tocilizumab. There were no differences in 28 days mortality. This meant tocilizumab could decrease the requirement for mechanical and non-invasive ventilation or death by day 14 but not mortality by day 28 [51, 52]. An RCT published by NEJM in October 2020, which included patients fulfilling at least two of the following: fever, pulmonary infiltrates, or the need for oxygen therapy to maintain oxygen saturation more than 92%, concluded that tocilizumab was not effective in preventing intubation or death in moderately ill hospitalized patients with Covid-19 [53]. Sarilumab, another IL-6 receptor antagonist was being tested in a multicentre trial for hospitalized patients with severe COVID-19 [54]. It was concluded that at 28 days, clinical improvement and mortality in severe COVID-19 were not significantly different between sarilumab and standard of care [55]. Preliminary results from the Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP) were released in a non-peer-reviewed report. REMAP-CAP is the largest trial to date investigating the use of IL-6 inhibitors in COVID-19. In February 2021, after reviewing the evidence from REMAP-CAP and other trials, the NIH Panel revised the recommendations on the use of tocilizumab and sarilumab, stating there was insufficient data to recommend either for or against the use of these drugs. But given the REMAP-CAP trial, some members suggested administering a single dose of tocilizumab (8 mg/kg of actual body weight, max 800 mg) in addition to dexamethasone in the ICU patients having high oxygen requirements/invasive and non-invasive mechanical ventilation and exhibiting rapid progression of respiratory failure [56]. The number of patients receiving sarilumab in the REMAP-CAP trial was too low to assess the efficacy.

2.8 Convalescent plasma

There was a hypothesis that plasma collected from the persons who have recovered from Covid-19 may contain antibodies against SARS-CoV-2, which may

be used as a treatment tool. A case series was done in China where 5 critically ill patients with confirmed Covid-19 and Acute respiratory distress syndrome (ARDS) were selected [57]. They received two consecutive transfusions of 200 mL to 250 mL of convalescent plasma (total dose: 400 mL) with a SARS-CoV-2-specific antibody (IgG) titer more than 1:1,000. After receiving the plasma, the SOFA score of the patients decreased and ventilator parameters of the patients (pO2/FiO2 ratio) of the patient improved, and viral load decreased by day 12. ARDS resolved in four patients by Day 12 and 3 were weaned off the ventilators by 2 weeks. Further trials are needed the study the effectiveness of convalescent plasma. FDA is encouraging people who have fully recovered from COVID-19 for at least two weeks to donate plasma. FDA had issued guidance providing recommendations to health care providers & investigators on administration and study of COVID-19 convalescent plasma during the public health emergency. FDA issued a EUA for convalescent plasma on August 23, 2020, although convalescent plasma did not show any stoppage of progression to severe COVID-19 or all-cause mortality in the PLACID trial [58, 59]. In a trial published in NEJM in November 2020, in 228 patients receiving convalescent plasma and 105 receiving placebo at 30 days, there was not any significant difference among the clinical outcome distribution (odds ratio [OR], 0.83 (95% CI, 0.52–1.35; P = 0.46). Mortality in the plasma group was 10.96% as compared to 11.43% in the placebo group [risk difference 0.46% points (95% CI, −7.8 to 6.8) [60].

2.9 Favipiravir

Favipiravir (FPV) is a purine nucleotide that inhibits viral RNA polymerase. It was initially used against Ebola but later found to have in-vitro activity against other RNA viruses. The EC50 (concentration of a drug that gives half-maximal response) of FPV against SARS-CoV-2 in vitro in Vero E6 cells was found to be 61.88 μM/L [6, 61]. A study investigated the effect of FPV vs. lopinavir/ritonavir on the treatment of COVID-19. FPV was independently associated with faster viral clearance and a higher improvement rate in chest imaging. These findings suggest that FPV has significantly better treatment effects on COVID-19 in terms of disease progression and viral clearance as compared with lopinavir/ritonavir [62]. In an RCT on moderate to severe COVID patients, FPV was compared with umifenovir (Arbidol) by measuring the clinical recovery at 7 days [63]. Results showed no significant differences between the 2 groups. At present, there are no recommendations for the use of FPV in Covid-19 patients. Just like HCQ & lopinavir/ritonavir combination, it also causes QT prolongation [20].

2.10 Ribavirin

Ribavirin, a guanine analog, inhibits viral RNA dependent RNA polymerase (RdRp). It has demonstrable activity against many coronaviruses, but when used against SARS-CoV it was found to have less effectiveness in vitro requiring higher doses with combination therapy. When used with interferon in the treatment of MERS-CoV, no benefits were observed in terms of clinical outcomes or the rate of virus clearance [64]. Ribavirin also causes dose-dependent hematological toxicity & transaminase elevation when used in SARS patients and being a teratogen, is contraindicated in pregnancy [65, 66]. A recent trial showed ribavirin not being associated with better negative conversion times for the SARS-CoV-2 test and not being associated with improved mortality rates [67]. Due to its lack of demonstrable efficacy against other coronaviruses and high toxicity profile, it has got a limited

role in the treatment of Covid-19. However, its combination with other antivirals is being tried in the SEV trial, the result of which is yet to be published [68].

2.11 Interferons

Studies with interferon-β had shown its activity against MERS. Most studies involved combination therapy with lopinavir/ritonavir or ribavirin. However, there was no concrete evidence showing its effect on SARS- CoV-2 in-vitro and the lack of clinical trials precluded the justification for its use in Covid-19 patients and hence there are no recommendations regarding its use [69]. In a study, it was shown that early triple antiviral therapy with lopinavir/ritonavir, ribavirin, and interferon beta-1b was safe and superior to lopinavir-ritonavir combinations alone in alleviating symptoms and shortening the duration of viral shedding and hospital stay in patients with mild to moderate COVID-19 [70]. In a trial utilizing interferon β-1a, clinical response time was not significantly different between interferon and the control groups (9.7 ± 5.8 versus 8.3 ± 4.9 days, respectively, P = 0.95). On day 14, 66.7% versus 43.6% of patients in the interferon group and the control group respectively was discharged (OR, 2.5; 95% CI, 1.05–6.37). The 28-day overall mortality was significantly less in the interferon than the control group (19% versus 43.6%, respectively, P = 0.015). Early administration significantly decreased mortality (OR, 13.5; 95% CI, 1.5–1.18) [71]. Another trial testing interferon β-1b showed its effectiveness in reducing the clinical improvement time without any serious adverse events in severe COVID-19 patients. ICU admission and invasive ventilation need also decreased following administration of interferon β-1b [72]. The Lancet Respiratory Medicine showed the results of an RCT of nebulized interferon beta-1a in 101 adults admitted to the hospital with COVID-19. It demonstrated better odds of clinical improvement than placebo (OR 2·32 [95% CI 1·07–5·04]; p = 0·03). No significant difference was there in the hospital discharge odds by day 28 [73]. Recently, the SOLIDARITY trial also showed no benefit of interferon therapy [74].

2.12 Corticosteroids

ARDS is a leading cause of mortality in Covid-19 pneumonia. Cytokine storm plays a key role in the pathogenesis of ARDS in Covid-19 patients and thus immunosuppression may have a role in the treatment of such patients [75]. Glucocorticoids modify the inflammation-mediated lung injury and hence can alter progression to respiratory failure and death. Studies on SARS and MERS showed that corticosteroids did not show any improvement in overall survival but showed delayed viral clearance from the respiratory tract and other steroid-related complications like Hyperglycaemia & Psychosis [76]. A retrospective study was carried out in Covid-19 patients in China who had developed ARDS. Those who received steroids had decreased death rates compared to those who did not [77]. In another study in non-ARDS patients, corticosteroid treatment did not influence virus clearance time, hospital length of stay, or duration of symptoms in mild COVID-19. Another study reported that early application of low-dose corticosteroid improves the treatment effect, presenting as improvement of hypoxia and fever, shortening disease course, and accelerating focus absorption [78]. Steroids are now the only therapy showing mortality benefit in COVID-19 severe disease. RECOVERY trial has concluded that dexamethasone 6 mg given once daily for up to 10 days decreased 28-day mortality in patients with COVID-19 on respiratory support. But a careful decision has to be made regarding severity as patients not requiring oxygen showed no benefit but had a possibility of harm with corticosteroid therapy. In the dexamethasone group, the

incidence of death was less than the usual care group among patients receiving invasive mechanical ventilation (29.3% vs. 41.4%; rate ratio, 0.64; 95% CI, 0.51–0.81) and those receiving oxygen without invasive mechanical ventilation (23.3% vs. 26.2%; rate ratio, 0.82; 95% CI, 0.72–0.94). No benefit was demonstrated among those who were receiving no respiratory support at randomization (17.8% vs. 14.0%, rate ratio, 1.19; 95% CI, 0.91–1.55) [79]. Subsequent RCTs also confirmed the same. Hence, all guidelines advocated steroids as first-line therapy in severe COVID-19. In due course, specific dose, route, and duration of therapy will be answered.

2.13 Monoclonal antibodies

Various novel monoclonal antibodies are under investigation for COVID-19. In a study published in NEJM, it has been described that LY-CoV555 (bamlanivimab) (also known as LY3819253), is a potent anti-spike neutralizing monoclonal antibody [80]. It binds to the receptor-binding domain of SARS-CoV-2. It was extracted from the convalescent plasma obtained from a COVID-19 patient. The protection of bamlanivimab against SARS-CoV-2 in primates has been reported [81]. In the interim analysis of data, patients receiving LY-CoV555 reported fewer hospitalizations and a lesser symptom burden than placebo receivers. In November 2020, it got the FDA EUA [82]. According to FDA, bamlanivimab reduced COVID-19 related hospital admissions in patients who are at high risk for disease progression [83]. This authorization came even after the company making the drug, Lilly, had announced in October 2020 that it was holding the trial in the hospital admitted patients as it not showing any benefits in them (ACTIV-3 trial). Remaining studies of bamlanivimab remain ongoing, including ACTIV-2 trial which includes the newly diagnosed mild to moderate COVID-19 patients; BLAZE-1, including recently diagnosed COVID-19 patients in the ambulatory (non-hospitalized) setting, studying bamlanivimab as monotherapy and in combination with etesevimab; and BLAZE-2, a phase 3 study for COVID-19 prophylaxis. Based on BLAZE-1 data, Lilly had submitted a request for EUA for bamlanivimab for the treatment of recently diagnosed mild to moderate COVID-19 patients to the FDA [84]. FDA reported 3% hospitalizations and emergency room visits in bamlanivimab treated patients compared to 10% in placebo. The FDA has approved bamlanivimab for patients age ≥ 12, and at high risk for progressing to severe covid-19 or hospital admission. However, it is emphasized that bamlanivimab should not be given to in-hospital COVID-19 patients or those requiring oxygen therapy; as such monoclonal antibodies may worsen outcomes in these patients. Another potential antibody treatment for COVID-19, REGN-COV2, a combination of two monoclonal antibodies casirivimab and imdevimab (REGN10933 and REGN10987), also faced some issues among inpatients with high oxygen requirements. In November 2020, the FDA issued EUA to monoclonal antibodies casirivimab and imdevimab (REGN10933 and REGN10987- against spike proteins of SARS-CoV-2) to be administered together for the treatment of mild to moderate COVID-19 in adults and pediatric patients (≥12 years of age) [85]. Although, in this case also, Regeneron Pharma had to halt its antibody cocktail trial in the admitted patients due to safety concerns, hence it was approved for non-admitted patients only [86]. Interestingly, US President Donald Trump had also received this regime when he tested positive for COVID-19 [87]. Astra Zeneca's COVID-19 Long-Acting AntiBody (LAAB) combination AZD7442 trial has also advanced into Phase III [88]. On February 9, 2021, the FDA has issued a EUA for bamlanivimab plus etesevimab for the management of mild to moderate COVID-19 in outpatients at high risk for disease progression. The data come from a randomized, double-blind, placebo-controlled clinical trial in 1,035 non-hospitalized adults with mild to moderate COVID-19, at high risk for progression to severe disease. Hospitalization or death occurred in 36 (7%) of placebo recipients compared

to 11 (2%) patients treated with bamlanivimab 2,800 milligrams and etesevimab 2,800 milligrams administered together, demonstrating a 70% reduction [89].

2.14 Janus kinase (JAK) inhibitors

The kinase inhibitors are being proposed as a novel modality of COVID-19 treatment. The rationale behind this being the prevention of phosphorylation of key proteins that are involved in the signal transduction that in turn leads to immunological activation and inflammation. This includes the cellular responses to the pro-inflammatory cytokines like IL-6 [90]. JAK inhibitors interfere with the phosphorylation of signal transducer and activator of transcription (STAT) proteins [91, 92]. These proteins are in turn involved in cell signaling, growth, and survival. The immunosuppression may reduce the hyperactive immune state induced by COVID-19. Moreover, JAK inhibitors like baricitinib have a theoretical direct antiviral activity via interference with viral endocytosis. This can prevent viral entry in the cells [93]. NIH has recommended that in the rare circumstances where corticosteroids cannot be used, baricitinib in combination with remdesivir may be used for the treatment of hospitalized, non-intubated patients requiring oxygen supplementation. IDSA guidelines also suggest the use of this combination in hospitalized severe COVID-19 patients [47]. Use of baricitinib without remdesivir is not recommended, except in a clinical trial [94]. As for the use of baricitinib in combination with corticosteroids, there is still insufficient data. Both baricitinib and corticosteroids cause immuno-suppression; hence, there is an additive risk of infection.

2.15 Other miscellaneous drugs with a possible therapeutic effect

In the pathogenesis of Covid-19, ACE 2 receptors play an important role by facilitating the entry of the virus into the cell [1, 95]. Thus it could be a possible therapeutic target with the use of ACE-inhibitors and ARB [1, 96]. However, there is a concern that the use of these drugs to stop virus replication may increase the expression of ACE-2 receptors and paradoxically worsen the infection. However, no in-vitro studies are available which show either definite detrimental or protective effect of these agents. As a result, the current guidelines state to continue these drugs in patients who are already taking them [97].

Umifenovir (also known as Arbidol) is an antiviral agent with a unique mechanism of action targeting the S protein/ACE2 interaction and inhibiting membrane fusion of the viral envelope [98]. It is approved in Russia for prophylaxis and treatment of influenza. Of particular interest is its demonstrable in-vitro activity against Covid-19 [99]. In an observational study in China, patients treated with umifenovir for a median duration of 9 days had a higher discharge rate and lesser mortality [100]. But as with other agents, the lack of RCT limits the justification for its use in Covid-19. However, ACE targeting therapy is a promising one [1].

Camostat mesylate is an agent used in the treatment of pancreatitis. It inhibits host serine protease, TMPRSS2.3, and has been shown to prevent viral cell entry in-vitro and thus could be a target for future studies [101].

Nitazoxanide, an anti-helminthic with a relatively favorable safety profile has shown in-vitro activity against SARS-CoV and MERS [102]. Besides it also has additional immunomodulatory action & thus can be used in trials in Covid-19 patients as a therapeutic option.

Many non-allopathic pharmaceuticals are also in pipeline as promising COVID-19 therapy. In June 2020, yoga guru Baba Ramdev announced that his company Patanjali Ayurved had launched a drug called 'Coronil' that could cure COVID-19 [103]. However, no scientific basis for this claim is produced until now.

3. Conclusion

The Global pandemic with COVID-19 is on. Drug therapy holds the key to the treatment and containment of the disease. Hence, large-scale multicentric trials are ongoing involving multiple drugs. Until now, no therapy is absolutely effective in the treatment of the patient as infection and death rates continue to mount all over the world. Corticosteroids have shown a significant effect on reducing the mortality in severe COVID-19 patients. It is hoped that the results of the ongoing trials will open further opportunities towards understanding the disease process and designing safe and effective treatments.

Conflict of interest

The authors declare no conflict of interest.

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