Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

CHAPTER

5

Currently available drugs for the treatment of Coronavirus-2

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5.1 Introduction

Coronavirus disease 2019 (COVID-19) was caused by a novel Coronavirus which was later named severe acute respiratory syndrome Coronavirus 2 (SARS CoV-2). The first case was first reported in Wuhan City, Hubei Province, China on December 31, 2019. It was declared a global health emergency by World Health Emergency (WHO) on January 30, 2020, later declared as Global Pandemic on March 11, 2020 (WHO declares global emergency as Wuhan Coronavirus spreads, 2021. *The New York Times*; WHO declares public health emergency for novel Coronavirus, 2021).

Previously Spanish flu 1918 was a deadly pandemic, affected more than one-third of the world population, and estimated the death of more than 25 million people (Threats I of M US F on M et al., 2005). Now the Coronavirus disease started its first deadly wave in China and then spread all over the world.

Initial records from China also showed the rapid spread of the infection and thousands of deaths in a day due to COVID-19. The World was in a situation that it needs rapid research and developments to control the disease spread and management of the illness caused by COVID-19. The Emergency Use Authorization (EUA) and Expanded Access (EA) programs by USFDA allowed rapid investigation of potential target therapies.

Hydroxychloroquine was the first drug that showed antiviral effects during in vitro studies. Initially, small trials showed some beneficial effects in the management of COVID-19. The USFDA first approved the use of this drug in COVID-19 under EUA. But later investigations showed enough evidence to avoid its usage and FDA approval revoked.

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Remdesivir was the first antiviral drug approved for the treatment of COVID-19 by the FDA in October 2020 for hospitalized patients >12 years of age and weight more than 40 kg (Commissioner O of the FDA Approves First Treatment for COVID-19, 2020). EUA for Convalescent Plasma was issued on August 23, 2020.

Then EUA for monoclonal antibodies (Sotrovimab, Casirivimab plus imdevimab, Bamlanivimab plus etesevimab) was approved by FDA for outpatients who tested RT-PCR positive and are at high risk of hospitalization and progression to severe disease (Commissioner O of the Coronavirus COVID-19, 2020a).

Baricitinib an immunomodulatory agent which inhibits AAK1, JAK1/2, GAK combined with Remdesivir approved by the FDA on November 19, 2020, for hospitalized patients aged more than 2 years and required supplemental oxygen, mechanical ventilation (Commissioner O of the Coronavirus COVID-19, 2020b). Tocilizumab monoclonal antibody against Interleukin-6 receptor was approved by FDA on June 24, 2021, for hospitalized patients more than 2 years of age who receive supplemental oxygen, steroids, required noninvasive and invasive ventilation.

There were several antivirals, immunotherapies, and other investigational drugs as potential therapies against COVID-19. Till now we could not find any specific therapy and duration for this disease. We have strong evidence only for the use of corticosteroids and anticoagulants in COVID-19.

The World Health Organization (WHO) developed a list of potential target agents for COVID-19 in January 2020. WHO published the mega trial called SOLIDARITY mega trial, which solved a lot of questions regarding many drugs used in the management of COVID-19. Hydroxychloroquine, lopinavir/ritonavir, and interferon beta-1a, plus lopinavir/ritonavir were discontinued in July 2020 due to little or no benefits compared to standard care. In October 2020, some antiviral drugs were found to have little or no effect on mortality.

Many potential therapies were published in numerous studies all over the world. It is necessary to analyze and combine all the evidence for better management of COVID-19. In this chapter, we will discuss the detailed analysis of each end of every drug which was being used in COVID-19 till now.

5.2 Anticoagulants

COVID-19 infectious be associated with a hypercoagulable state causing microangiopathy leading to the formation of thrombus throughout the body and its associated complications [deep venous thrombosis (DVT) in legs, pulmonary embolism (PE) in vessel supplying lungs, brain clots causing stroke and myocardial infarction].

5.2.1 Hypercoagulopathy in Coronavirus disease 2019

Coagulopathy manifests as elevated fibrinogen, elevated D-dimers. Although there is minimal change in PT, aPTT, and platelet count in the early stages of infection. Increasing IL-6 levels are correlated with increasing fibrinogen levels. Coagulopathy appears to be related to the severity of illness and resultant inflammation and not intrinsic viral activity. Elevated D-dimer at admission is associated with increased mortality. Rising D-dimer after

admission precedes multiorgan failure and overt DIC. Longer duration of hospital stays is associated with increasing D-dimer and the development of sepsis physiology. Bleeding manifestations are not common despite coagulopathy (Connors & Levy, 2020).

Autopsy series done in COVID-19 patients demonstrated microvascular thrombosis as well as marked inflammatory changes (Danzi et al., 2020; Stein et al., 2004; Tian et al., 2020). Reports of microvascular thrombosis in early pathology specimens or pulmonary emboli (PE) were frequently seen. Anticoagulants have remained the primary modality of treatment of thromboembolism for decades. However, there is no universal consensus regarding the timing, dose, age, and duration of anticoagulation in COVID-19 as well as the need for postdischarge prophylaxis (Wendelboe & Raskob, 2016).

Historically, heparin was the first true anticoagulant to be invented. Purified heparin, including unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH), act by promoting the formation of an intermediate protease−heparin−antithrombin complex which favors inhibition of thrombin and activated factor-X (Jackson, 1990). It has been used as the drug of choice for the prevention and treatment of microthrombi such as DVT and PE. Bleeding is a major disadvantage of heparin; other side effects are thrombocytopenia (in up to 30% of patients), injection site reaction, and hyperkalemia (Ahmed et al., 2007). To prevent bleeding, dose monitoring needs to be done with UFH (by aPTT) or LMHW (by factor Xa levels).

Newer oral anticoagulants (NOACs) ensured a higher safety profile with greater efficacy requiring minimal dose monitoring (Alquwaizani et al., 2013; Harter et al., 2015). Two classes of drugs available are direct thrombin inhibitors such as dabigatran and direct factor Xa inhibitors like apixaban, edoxaban, and rivaroxaban (Franchini et al., 2016). Nonbleeding adverse effects (severe liver injury and gastrointestinal disorders) of these drugs are rare (Maura et al., 2018). A major disadvantage of new oral anticoagulants lies in the present global unavailability of specific reversal agents. Newer antidotes, idarucizumab and andexanet alfa are now approved for reversal of NOACs (Desai & Cornutt, 2019).

Fondaparinux is an indirect inhibitor of factor Xa, which achieves anticoagulation by binding to and activating antithrombin (LiverTox: Clinical and research information on drug-induced liver injury, 2012). The toxicity of fondaparinux is complicated by its long half-life.

Selection of the ideal anticoagulant for any disease takes into account various patient-specific factors such as the underlying thromboembolic state, for example, ischemic stroke or atrial fibrillation, as well as acceptable bleeding risk and presence of comorbidities such as hepatic or renal disease (Schaefer et al., 2016).

5.3 Role of anticoagulants in Coronavirus disease 2019

According to CHEST society recommendations in the management of COVID-19 patients, the choice of anticoagulant depends upon the phase of VTE (Konstantinides et al., 2020). In the acute phase, administration of rapidly acting parenteral anticoagulants as UFH, LMWH, or fondaparinux is advocated. LMWH and fondaparinux are preferred

over UFH due to a lower risk of bleeding. Apixaban is also approved for the acute treatment of DVT and PE (Koehl et al., 2020).

NOAC (such as dabigatran or rivaroxaban) are preferred for anticoagulation (if indicated) in long term (beyond 10 days) and extended duration of treatment of PE lasting beyond 3 months (Kearon et al., 2012).

Summary of various societies for management and prevention of Thromboembolism is as follows:

1. *CHEST Guideline and Expert Panel Report*: In the absence of contraindications, all acutely hospitalized patients with COVID-19 should receive thromboprophylaxis therapy. LMWH or fondaparinux should be used for thromboprophylaxis over UFH and direct oral anticoagulants. Data are insufficient to justify routine increased-intensity anticoagulant dosing in hospitalized or critically ill patients with COVID-19. Recommend only inpatient thromboprophylaxis for patients with COVID-19. In critically ill patients with COVID-19, suggest against routine ultrasonographic screening for asymptomatic DVT (Moores et al., 2020). In critically ill patients with COVID-19 who have proximal DVT or pulmonary embolism (PE), recommend parenteral anticoagulation therapy with therapeutic weight-adjusted LMWH or fondaparinux over UFH (Moores et al., 2020).
2. *NIH COVID-19 Treatment Guidelines*: Measure hematologic and coagulation parameters (e.g., D-dimers, PT, platelet count, fibrinogen) in hospitalized patients. Hospitalized adults with COVID-19 should receive VTE prophylaxis per the standard of care for other hospitalized adults unless contraindicated. Hospitalized patients with COVID-19 should not routinely be discharged on VTE prophylaxis. In hospitalized patients, the possibility of thromboembolic disease should be evaluated in the event of rapid deterioration of pulmonary, cardiac, or neurological function or of sudden localized loss of peripheral perfusion (Information on COVID-19 treatment, prevention, and research, 2021).

Anticoagulants and antiplatelet therapy should not be initiated for the prevention of VTE or arterial thrombosis unless the patient has other indications for the therapy.

5.4 Antivirals

5.4.1 Remdesivir

Remdesivir is an antiviral drug, which was previously used in the treatment of SARS CoV-1 and Middle East respiratory syndrome Coronavirus (MERS-CoV) (Konstantinides et al., 2020).

So remdesivir was considered as one of the promising agents against COVID-19. Remdesivir was approved by the USFDA for the treatment of COVID-19 as EUA in May 2020, then it was fully approved by FDA in October 2020 (Commissioner O of the FDA Approves First Treatment for COVID-19, 2020).

5.4.1.1 Mechanism of action

Remdesivir inhibits the RNA-dependent, RNA polymerase enzyme and thus it prevents the replication of the virus (Brown et al., 2019). It was one of the promising agents

identified earlier for COVID-19 due to its intrinsic ability to inhibit SARS CoV-2 in vitro (Wang et al., 2020). It is recommended to be given during the viral replicating phase (i.e., first 7–10 days of infection).

Dose: 200 mg IV loading dose on day 1 followed by 100 mg maintenance dose daily for 5 days (Beigel et al., 2020; "Solidarity" clinical trial for COVID-19 treatments, 2021). Ten days course was found equally effective as 5 days course in management (Goldman et al., 2020).

Adverse effects: (1) Derangement in liver enzymes, urea, creatinine, (2) bradyarrythmia and tachyarrhythmias, and (3) rashes.

5.4.1.2 Evidence in Coronavirus disease 2019

Studies about remdesivir showing equivocal results. Initially, ACCT-1 trial favors the use of remdesivir in hospitalized patients: the remdesivir group had a shorter hospital stay, improvement in clinical outcome and it was likely that remdesivir prevents the progression of severe disease (Beigel et al., 2020). Based on the n preliminary results of the ACCT-1 study USFDA authorized the use of remdesivir in COVID by EUA. Since then several countries have approved full or conditional use of this drug in COVID-19. Later WHO solidarity trial showed little or no effect of remdesivir on hospitalized patients in view of mortality and hospital stay ("Solidarity" clinical trial for COVID-19 treatments, 2021). Recent trials are now evaluating the use of remdesivir in combination with other drugs like baricitinib, interferon-beta1a.

5.5 Lopinavir/ritonavir

These antiviral drugs are part of antiretroviral therapy (ART), which were also tried in COVID-19 in the initial wave of the pandemic. Most of the studies recommended against the use of these drugs in COVID-19. The NIH panel of COVID-19 management guidelines recommends not to use lopinavir/ritonavir or any other protease inhibitors. The RECOVERY trial reported no beneficial effect in hospitalized patients, hence the WHO Solidarity trial discontinued the use of lopinavir/ritonavir on July 4, 2020 (Horby et al., 2020; "Solidarity" clinical trial for COVID-19 treatments, 2021).

5.6 Immunomodulators

5.6.1 Steroids

Some patients with COVID-19 can develop a systemic hyperinflammatory response that can lead to lung injury and multisystem organ dysfunction. Timely use of corticosteroids can prevent or mitigate these deleterious effects by their antiinflammatory effects.

Autopsy findings of COVID-19 patients showed diffuse alveolar damage, inflammatory infiltrates, and microvascular thrombosis, which followed an acute pneumonic process with extensive radiologic opacity (Carsana et al., 2020). Inflammatory organ injury may occur in severe COVID-19, with patients having markedly elevated levels of inflammatory

markers, including C-reactive protein, ferritin, IL-1, and IL-6 (Huang et al., 2020; RECOVERY Collaborative Group et al., 2021; Ruan et al., 2020).

Various landmark trials have established the indication for steroid use in COVID-19 pneumonia. They are discussed in Table 5.1 (Angus et al., 2020; Corral-Gudino et al., 2021; Jeronimo et al., 2021; Li et al., 2020; RECOVERY Collaborative Group et al., 2021; The WHO rapid evidence appraisal for COVID-19 therapies REACT Working Group, 2020; Tomazini et al., 2020).

TABLE 5.1 Synopsis of trials showing the effect of corticosteroids in patients in Coronavirus disease 2019.

Study	Methods	Results	Interpretation
Recovery trial (RECOVERY Collaborative Group et al., 2021): multicenter, randomized open-label, $n = 6425$	Primary endpoint: all-cause mortality at 28 days after randomization (2:1 ratio) Dexamethasone 6 mg PO or IV once daily plus Standard of care (SOC) for up to 10 days or until hospital discharge, whichever came first SOC alone	28-day mortality was 22.9% in the dexamethasone arm and 25.7% in the SOC arm. Survival benefit appeared greatest among participants who required IMV at randomization. Among these participants, 28-day mortality was 29.3% in the dexamethasone arm versus 41.4% in the SOC arm.	In hospitalized patients with severe COVID-19 who required oxygen support, using dexamethasone 6 mg daily for up to 10 days reduced mortality at 28 days, with the greatest benefit seen in those who were mechanically ventilated at baseline. There was no observed survival benefit of dexamethasone in patients who did not require oxygen support at baseline.
REACT group (The WHO Rapid Evidence Appraisal for COVID-19 Therapies REACT Working Group, 2020) *Meta*-analysis of 7 RCTs of corticosteroids in critically ill patients with COVID-19 in multiple countries ($n = 1703$)	RCTs evaluating corticosteroids in critically ill patients with COVID-19—Identified from clinicaltrials.gov Primary Endpoint: All-cause mortality up to 30 days after randomization Interventions: corticosteroids (i.e., dexamethasone, hydrocortisone, methylprednisolone) Usual care or placebo	Dexamethasone: OR 0.64 (95% CI, 0.50−0.82; $P < 0.001$) in 3 trials with 1282 patients. Hydrocortisone: OR 0.69 (95% CI, 0.43−1.12; $P = 0.13$) in 3 trials with 374 patients. Methylprednisolone: OR 0.91 (95% CI, 0.29−2.87; $P = 0.87$) in 1 trial with 47 patients. For patients on mechanical ventilation ($n = 1559$): OR 0.69(95% CI, 0.55−0.86), with mortality of 30% for corticosteroids versus 38% for usual care or placebo. For patients not on mechanical ventilation ($n = 144$): OR 0.41 (95% CI, 0.19−0.88) with mortality of 23% for corticosteroids versus 42% for usual care or placebo	Systemic corticosteroids decrease 28-day mortality in critically ill patients with COVID-19 without safety concerns. Most of the participants were from the RECOVERY trial, thus the evidence of benefit in the *meta*-analysis is strongest for dexamethasone, the corticosteroid used in the RECOVERY trial.

(*Continued*)

TABLE 5.1 (Continued)

Study	Methods	Results	Interpretation
METCOVID Trial (Jeronimo et al., 2021): double-blind, Phase 2b, RCT of short-course methylprednisolone ($n = 416$)	Primary endpoint: Mortality by day 28 Interventions: Methylprednisolone IV 0.5 mg/kg twice daily for 5 days Placebo (saline) IV	No difference in 28-day mortality: 37.1% in methylprednisolone arm versus 38.2% in placebo arm (HR 0.92; 95% CI, 0.67−1.28; $P = 0.63$). No difference between groups in early mortality at day. No difference in the need for mechanical ventilation by day 7. 28-day mortality in participants aged >60 years was lower in the methylprednisolone group than in the placebo group.	The use of weight-based methylprednisolone for 5 days did not reduce overall 28-day mortality. In a post hoc subgroup analysis, mortality among those aged >60 years was lower in the methylprednisolone group than in the placebo group.
CoDEX Trial (Tomazini et al., 2020): multicenter RCT in patients with COVID-19 and moderate to severe. $n = 299$	Primary Endpoint: Mean number of days alive and free from mechanical ventilation by day 28 Dexamethasone 20 mg IV daily for 5 days, then 10 mg IV daily for 5 days or until ICU discharge plus SOC SOC alone	The mean number of days alive and free from mechanical ventilation by day 28 was higher in the dexamethasone group than in the SOC group (6.6 vs 4.0 days), estimated difference of 2.3 days. No difference in both groups between all-cause mortality at day 28, ICU free days at day 28, Duration of MV, WHO ordinal score at day 15.	Compared with SOC alone, dexamethasone at a higher dose than used in the RECOVERY trial plus SOC increased the number of days alive and free of mechanical ventilation over 28 days of follow-up in patients with COVID-19 and moderate to severe ARDS. Dexamethasone was not associated with an increased risk of AEs in this population.
REMAP-CAP (The Writing Committee for the REMAP-CAP Investigators, 2020) COVID-19 Corticosteroid Domain Randomized, multifactorial, multicentric trial $n = 403$	Primary endpoint: Days free of respiratory and cardiovascular organ support up to Day 21 Hydrocortisone 50 mg 4 times daily for 7 days Septic shock-based hydrocortisone 50 mg 4 times daily for the duration of shock No hydrocortisone	No difference in organ-support-free days at day 21 (median of 0 days in each group). Compared to the no hydrocortisone group, median adjusted OR for the primary outcome: OR 1.43. 93% Bayesian probability of superiority for the fixed-dose hydrocortisone group. OR 1.22. 80% Bayesian probability of superiority for the shock-based hydrocortisone group.	Corticosteroids did not significantly increase support-free days in either the fixed-dose hydrocortisone or the shock-dependent hydrocortisone group.

(*Continued*)

TABLE 5.1 (Continued)

Study	Methods	Results	Interpretation
Early, low-dose, short-term corticosteroids in adults hospitalized with nonsevere COVID-19 pneumonia $n = 55$ matches case-control pairs (Li et al., 2020)	Primary endpoint: rates of severe disease and death Early, low-dose corticosteroids: methylprednisolone 20 mg/day IV or 40 mg/day IV for 3–5 days Prednisone 20 mg/day PO for 3 days No corticosteroids	7 patients (12.7%) in the corticosteroids group developed severe disease versus 1 (1.8%) in the no corticosteroids group ($P = 0.03$); time to severe disease: HR 2.2 (95% CI, 2.0–2.3; $P < 0.001$). 1 death in the methylprednisolone group versus none in the no corticosteroids group.	In this nonrandomized, case-control study, methylprednisolone therapy in patients with nonsevere COVID-19 pneumonia was associated with worse outcomes. But confounding bias prevents analysis of specific factors which may have caused these outcomes. It is unclear whether the results for methylprednisolone therapy can be generalized to therapy with other corticosteroids.
Glucocovid (Corral-Gudino et al., 2020) $n = 180$ the multicentric open-label trial, patients aged ≥ 18 years, receiving oxygen without mechanical ventilation	The composite endpoint that included in-hospital all-cause mortality, escalation to ICU admission, or progression of respiratory insufficiency that required noninvasive ventilation High: methylprednisolone 40 mg IV q12 × 3 days and then 20 mg q12h × 3 days	In the ITT analysis, 14 of 29 patients (48%) in the SOC group and 14 of 35 (40%) in the MP group suffered the composite endpoint (40% vs 20% in patients under 72 years and 67% vs 48% in those over 72 years; $P = 0.25$).	Patients on MP had a significantly lower risk of experiencing the composite endpoint (age-adjusted risk ratio 0.42; 95% confidence interval, CI 0.20–0.89; $P = 0.043$).

Corticosteroids are a double-edged sword; they can also cause a myriad of adverse events ranging from self-limiting to life-threatening events. Some adverse events and their incidence are Gastrointestinal bleeding [relative risk (RR) 1.06, incidence of 51/1000], secondary infections (RR 1.01, incidence of 188/1000), hyperglycemia (RR 1.16, incidence 332/1000), hypernatremia (RR 1.64, incidence 40–66/1000), neuromuscular weakness (RR 1.09, incidence 75/1000), neuropsychiatric effects (RR 0.81, 28/1000), stroke (RR 2.07, incidence 8/1000) and myocardial infarction (RR 0.91, 27/1000) (Corticosteroids for COVID-19, 2021).

Based on the above trials and evidence, steroids are recommended only in hypoxemic patients with COVID-19; COVID-19 patients without hypoxemia, steroids should not be used.

5.7 Tocilizumab

Tocilizumab is licensed in the United Kingdom for the treatment of cytokine release syndrome in rheumatoid arthritis. COVID-19 induced hypoxic respiratory failure causes

the release of pro-inflammatory cytokines, such as IL-1, IL-6, TNF-alpha, which leads to cytokine release syndrome. High IL-6 levels were found in critical and severe COVID-19 cases, whereas lower levels were detected in mild disease (Aziz et al., 2020; Zhu et al., 2020). High IL-6 levels were found to be predictive of the likelihood of intubation and mechanical ventilation (Herold et al., 2020).

5.7.1 Mechanism of action

Tocilizumab is a human recombinant monoclonal antibody against the IL-6 receptor, which inhibits the binding of IL-6 to the receptors and membrane. Thus it blocks the IL-6 mediated inflammatory pathway.

Dose: 400−800 mg (depending upon weight) in 100 mL NS over 1 hour (RECOVERY Collaborative Group, 2021).

Adverse effects: it can lead to serious infections due to immunosuppression like skin infections, bacterial pneumonia. It can also lead to oral ulcers, abdominal pain, gastrointestinal perforation, headache, and hypercholesterolemia.

5.7.1.1 Evidence in Coronavirus disease 2019

Till now there were only a few randomized controlled trials have been done for tocilizumab. Some studies have reported that tocilizumab use in severe COVID patients was associated with a reduction in 28-day mortality (Hermine et al., 2021; Salama et al., 2020; Salvarani et al., 2021; Soin et al., 2021; Stone et al., 2020; Veiga et al., 2021). In one of the subgroups of the RECOVERY trial, tocilizumab was shown to reduce the mortality and requirement of mechanical ventilation (RECOVERY Collaborative Group, 2021).

5.8 Baricitinib

COVID-19 virus enters the host cell through receptor-mediated endocytosis. ACE-2 receptor is found mainly in the lungs, kidney, heart, blood vessels. In lung alveolar type 2 epithelial cells have these ACE2 receptors, are and more prone to viral infections (Zhao et al., 2020). AP2 associated protein kinase 1 (AAK1) is one of the endocytosis regulators. Disruption of which can interrupt the virus entry and assembly into host cells (Lu et al., 2020). Till now we have 47 approved AAK1 inhibitors for medical use, of these six drugs have a high affinity with AAK1. One of these drugs is baricitinib.

Mechanism of action: It inhibits AAK1, JAK1/2 (Janus kinase—the regulator of inflammation), GAK (cyclin G-associated Kinase—regulator of endocytosis) (Sorrell et al., 2016). Thus it downregulates the cytokine storm in COVID-19.

Dose: The US-FDA approved the drug baricitinib for the treatment of COVID pneumonia at a dose of 4 mg (Research C for DE and Coronavirus COVID-19. Drugs, 2021).

Adverse events: Most common adverse events are upper respiratory tract infections, dry mouth, nausea, raised LFT, thrombocytosis, herpes zoster infection. Rarely acne, neutropenia, herpes simplex infections can also occur (Stebbing et al., 2020).

5.8.1 Evidence in Coronavirus disease 2019

Adaptive COVID-19 Treatment Trial 2 (ACTT-2) found that baricitinib combined with remdesivir gives a significantly faster recovery time compared to placebo (7–9 days vs 6–8 days) and significantly reduces the 28-day mortality rate (7.8% vs 5.1%) (Kalil et al., 2021). Another case-control study compared the baricitinib loading dose of 8 mg followed by 4 mg usual dose results in better clinical outcome compared to baricitinib without loading dose (Hasan, Rabbani, Anam, Huq, et al., 2021). A daily high dose of baricitinib results in early stabilization of respiratory functions reduced rehospitalization, and mortality compared to the usual dose (Hasan, Rabbani, Anam, Huq, Polash, et al., 2021).

5.9 Monoclonal antibodies

5.9.1 Casirivimab plus imdevimab (antibody cocktail)

On November 21, 2020, United States Food and Drug Administration (US FDA) authorized monoclonal antibodies coadministration of Casirivimab and Imdevimab (REGN-COV; Regeneron) for the treatment of mild to moderate COVID-19 in patients aged $\geq$12 years and those who have weight >40 kg, and who have a high risk for disease progression and/or hospitalization (Commissioner O of the Coronavirus COVID-19, 2020a).

5.9.1.1 Mechanism of action

Casirivimab and Imdevimab are Ig-G1 human monoclonal antibodies developed by recombinant DNA technology. Directed against the spike protein of the SARS CoV-2, it prevents the attachment of the virus to the human cells and prevents the entry of the virus. These antibodies bind to the different parts of the spike protein. That made these antibodies effective against various strains.

Dose: dose of Casirivimab 600 mg and Imdevimab 600 mg is given IV infusion over 20–30 minutes or subcutaneous route needs to be administered at 4 different sites on abdomen or thigh with 2.5 mL syringes (2 each for both drugs).

Adverse effects: Common side effects are fever, injection site pain, redness, chills, weakness, and throat irritation.

5.9.1.2 Evidence in Coronavirus disease 2019

These drugs reduce the viral load and lead to improvement in symptoms in nonhospitalized patients (Regeneron's COVID-19 Outpatient Trial Prospectively Demonstrates that REGN-COV2 Antibody Cocktail Significantly Reduced Virus Levels and Need for Further Medical Attention | Regeneron Pharmaceuticals Inc., 2021; Weinreich et al., 2021). Patients had a lower risk of death or progression to mechanical ventilation after administration of Casirivimab and Imdevimab (Regeneron Pharmaceuticals. A master protocol assessing the safety, tolerability, and efficacy of anti-spike (S) SARS-CoV-2 monoclonal antibodies for the treatment of ambulatory patients with COVID-19, 2021; Inc RP. Regeneron announces encouraging initial data from COVID-19 antibody cocktail trial in hospitalized patients on

low-flow oxygen, 2021). In one of the subgroups of the UK RECOVERY trial, reduced 28-day mortality was seen in seronegative hospitalized patients (Group et al., 2021).

5.9.1.3 Prophylaxis in Coronavirus disease 2019

In July 2021, US FDA EUA authorized this antibody cocktail for postexposure prophylaxis for high-risk contacts. Household contacts were administered 1200 mg of Casirivimab and Imdevimab SC route within 96 hours of exposure. The symptomatic infection risk was decreased by 72% in the first week and 92% in subsequent weeks. If they develop symptomatic infection they cleared the virus faster than placebo and had a shorter duration of symptoms (O'Brien et al., 2021).

5.10 Sotrovimab

Sotrovimab is a recombinant IgG1 monoclonal antibody that prevents the entry of the virus into the human cells by binding to the conserved epitope of the spike protein receptor-binding domain of the COVID-19 virus (Tuccori et al., 2020).

Dose: 500 mg IV

5.10.1 Evidence in Coronvirus disease 2019

The US FDA granted EUA for Sotrovimab on May 26, 2021. This was based on the COMET-ICE trial (randomized double-blinded placebo-controlled trial) which showed the high-risk patients who received Sotrovimab demonstrated an 85% reduction in hospitalization or death compared to placebo (Inc VB. GSK and Vir Biotechnology Announce Submission of Emergency Use Authorization Request to FDA for VIR-7831 for the Early Treatment of COVID-19, 2021).

5.11 Bamlanivimab plus etesevimab

The FDA approved EUA for combined use of Bamlanivimab plus etesevimab for the treatment of mild to moderate COVID-19 cases who are at high risk for progression into severe disease or hospitalization. This was based on phase 3 BLAZE-1 trial, an ongoing randomized, double-blind, placebo-controlled trial that showed Bamlanivimab 700 mg and Etesevimab 1400 mg together significantly reduced the COVID related hospitalization and death (Dougan et al., 2021; Gottlieb et al., 2021).

5.12 Investigational therapies

Various therapies were used without strong evidence as desperate measures during the COVID-19 pandemic. Most of these are now obsolete since now studies have shown the futility of these drugs.

5.13 Convalescent plasma

Convalescent plasma is a source of neutralizing antiviral antibodies. It is a form of passive antibody immunotherapy, which was used in the treatment of SARS, H1N1 influenza, avian influenza, Ebola, and other viral infections. That resulted in reduced mortality in those diseases (Casadevall & Pirofski, 2020; Mair-Jenkins et al., 2015).

5.13.1 Mechanism of action

Plasma collected from the COVID-19 survivor contains specific antibodies for the receptor-binding of the virus (Robbiani et al., 2020). Other possible mechanisms that plasma could exert its therapeutic effects are antibody-mediated cytotoxicity, activation of complements, phagocytosis (Rojas et al., 2020).

Dose used the Indian PLACID study used the dose of 200 mL of plasma 24 hours apart (Agarwal et al., 2020), and the Indonesian study used 3 mL/kg of body weight plasma was administered 10−20 mL in the first 15 minutes then slowly increased and completed in 4 hours (Rejeki et al., 2021). A donor should be previously positive for COVID by the RTPCR method and fully recovered from the symptoms for at least 14 days (Rejeki et al., 2021).

5.13.2 Evidence in Coronavirus 2019

There is not enough evidence for the use of convalescent plasma for COVID treatment. Most of the studies were focused on reporting convalescent plasma on severe disease, they reported the improvement in clinical outcome and reducing the viral load (Duan et al., 2020; Shen et al., 2020) but only a few studies reported the outcome in moderate disease. The PLACID trial shows symptomatic improvement in moderate disease compared to placebo and higher negative conversion but no difference in the disease progression and 28 days mortality (Agarwal et al., 2020).

The Indonesian trial shows that patients having moderate disease have clinical improvement by plasma therapy (Rejeki et al., 2021). But these studies could not conclude that this improvement is only due to convalescent plasma. Also, they could not define the timing of the plasma therapy. So future studies require to define the patient selection, donor selection, and time of administration of this therapy.

5.14 Hydroxychloroquine and chloroquine

These antimalarial drugs also have immunomodulatory effects and so they are also used in autoimmune diseases. Based on the in vitro studies from China it has been tried in the management of COVID-19 (Wang et al., 2020; Yao et al., 2020). On June 15, 2020, US FDA approved hydroxychloroquine and chloroquine for the management of COVID-19 by EUA (Commissioner O of the Coronavirus COVID-19, 2020c).

Mechanism of action: they have antiviral activity due to the alkalinization of the phagolysosome, which alters the pH and alters the replication steps of a virus. Hydroxychloroquine is found to be more potent than Chloroquine in in vitro studies

Dose: 400 mg PO BD followed by 200 mg BD for 4 days (Yao et al., 2020).

Adverse effects: QT prolongation, irreversible retinal damage are the most serious adverse events. Thus not recommended for cardiac patients and patients with retinal damage.

Headache, diarrhea, abdominal cramps, dizziness, vomiting, tinnitus, hearing loss, hypersensitivity reaction were the other side effects reported by this drug.

We should avoid combining drugs causing prolonged QTc with hydroxychloroquine.

5.14.1 Evidence in Coronavirus disease 2019

It was the first drug, which claimed to have effectiveness (although never confirmed) at least in vitro during the initial periods of the pandemic. So it became popular worldwide and almost all countries started using this. In early 2020, some studies favor the use of hydroxychloroquine (Arshad et al., 2020; Lammers et al., 2020; Lee et al., 2020). Then UK RECOVERY trial results showed that the use of hydroxychloroquine has no significant difference in the 28-day mortality (25% usual care vs 27% hydroxychloroquine) and it was associated with longer hospital stay than usual group (median 16 days vs 13 days) (RECOVERY Collaborative Group et al., 2020). Many other trials also showed no effect with the use of hydroxychloroquine (Ip et al., 2020; Lopez et al., 2020; Magagnoli et al., 2020; Self et al., 2020). Based on interim results, the WHO Solidarity Trial halted the hydroxychloroquine rm and removed its use on July 4, 2020 ("Solidarity" clinical trial for COVID-19 treatments, 2021). Later on, EUA for HCQS was revoked by USFDA.

5.15 2-Deoxy D-glucose (2-DG)

It was developed by the Institute of Nuclear Medicine and Allied Sciences (INMAS), a lab of Defense Research and Development Organization (DRDO), India in collaboration with Dr. Reddy's Laboratories, Hyderabad. This drug was studied for the management of cancer but its effectiveness is still unproven. It was also tried in COVID-19. The phase 3 clinical trial results showed a significantly higher proportion of patients became free from supplemental oxygen and improved symptomatically by day 3 compared to standard of care (42% vs 31%). Hence DCGI granted permission for Emergency use of this drug in moderate to severe cases as an adjunct therapy in COVID-19. Because the evidence of this drug is very minimal and not strong, this drug was not used widely (DCGI approves anti-COVID drug developed by DRDO for emergency use, 2021).

1. *Ivermectin*: Retrospective cohort studies supported the use of ivermectin in COVID-19, but later they were found to have incomplete information and has significant methodological limitations. Ivermectin was shown to inhibit the virus growth in cell cultures but the inhibitory concentration cannot be attained in humans (Momekov & Momekova, 2020). RCT of Ivermectin (300 mcg/kg/day) versus placebo for 5 days did not show any significant difference in outcomes (López-Medina et al., 2021).

2. *Doxycycline*: During the initial periods of the pandemic, small case series and a few case reports supported the use of doxycycline in COVID. The antiinflammatory effects of doxycycline were proposed to alter the cytokine storm in COVID. But due to a lack of strong evidence, this drug is not recommended for the management of COVID-19.

5.16 Future perspectives

Many new drugs and repurposed drugs are being investigated for the possible treatment option for COVID-19. The WHO and the USFDA Coronavirus Treatment Acceleration Program (CTAP) enlisted the potential target therapies which can be tested in COVID-19 management. The WHO Solidarity PLUS Trial will evaluate three treatment arms—artesunate, infliximab, and imatinib and results are expected in 2022 (WHO's Solidarity clinical trial enters a new phase with three new candidates drugs, 2021). The RECOVERY trial now investigating Baricitinib, dimethyl fumarate (an immunomodulatory drug used in psoriasis and multiple sclerosis), high-dose versus standard corticosteroids, empagliflozin (a drug for diabetes and heart and kidney disease) (Welcome—RECOVERY Trial). Molnupiravir, Nitazoxanide, Niclosamide are drugs whose antiviral viral properties are under investigation for COVID-19 management. Remdesivir inhaled route is also under evaluation.

5.17 Conclusion

Many drugs were tried on a compassionate basis in patients with COVID-19 a as desperate measure. Currently only steroids, anticoagulation, and immunomodulators have enough evidence to support their role in the management of COVID-19 patients. Rest all drugs should not be given outside a clinical trial.

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