

Review Article

Medical management of COVID-19: treatment options under consideration

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ABSTRACT

An outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first reported in Wuhan, China in December 2019. Despite the worsening trends of COVID-19, currently, no drugs are validated to have significant efficacy in the clinical treatment of COVID-19. The drugs currently being explored are hydroxychloroquine, antivirals like remdesivir, favipiravir alone or in combination, antibiotics like azithromycin and doxycycline. Low dose corticosteroids, either oral or intravenous, have also shown promising results in reducing mortality. On the other hand, Immunomodulators and biologics are found to be very effective in some cases. Autopsy finding of patients with COVID-19 shows the evidence of endothelial damage and formation of microthrombi with multiorgan involvement and, ultimately, multiorgan failure; hence anticoagulants also seem to have a definite role in preventing microvasculature clogging and multiorgan dysfunction. Pulmonary vasodilators acting via the cGMP/cAMP pathway may also prove to be beneficial in reducing airway hyper inflammation. In this review, authors have attempted to summate the potential drugs therapies with emphasis on convalescent plasma, and at last, the most awaited thing of this pandemic, COVID-19 vaccine.

Keywords: COVID-19, Hydroxychloroquine, Remdesivir, SARS-CoV-2

INTRODUCTION

Most patients with COVID-19 predominantly have a respiratory tract inflammation. However, in a small proportion of cases, they can progress to a more severe and systemic disease characterized by Acute Respiratory Distress Syndrome (ARDS), sepsis and septic shock, multiorgan failure, cytokine storm syndrome including acute kidney injury and cardiac injury. Autopsy findings have shown endothelial damage of pulmonary vasculature, microvascular thrombosis and haemorrhage linked to extensive alveolar and interstitial inflammation that ultimately results in hypercoagulability. Currently, there are no specific drugs or vaccine for COVID-19.

Symptomatic and supportive treatment based on the clinical condition of the patient is the mainstay management. Immunomodulators and biologics are being investigated. Convalescent plasma therapy is also being tried in particular cases. The entire world is waiting for an effective and safe vaccine. In this review article, an attempt is made to summarize the current data to guide potential COVID-19 treatment options.

ANTI-MICROBIAL AGENTS

A variety of anti-microbial agents have been investigated for their therapeutic potential in the management of COVID-19. Hydroxychloroquine and Chloroquine,

Favipiravir, Remdesivir, Lopinavir/ ritonavir, Ribavirin, and Arbidol have all been tried for prevention and treatment. A few of these drugs are discussed here.

HYDROXYCHLOROQUINE AND CHLOROQUINE (HCQ/CQ)

These drugs are best known as anti-malarial agents. While there isn't enough scientific and clinical data to support their use, several countries have already included HCQ/CQ in COVID-19 treatment protocols, not only as a treatment option for severely ill patients but also as a prophylactic measure. Promising results from in-vitro studies lead to their widespread use.^{1,2}

Both the drugs can interfere with the glycosylation of ACE2 and reduce the binding efficiency between ACE2 on the host cells and the spike protein on the surface of the coronavirus. They can also increase the pH of endosomes and lysosomes, through which the fusion process of the virus with host cells and subsequent replication is prevented.³

The additional possible beneficial effects may be due to their anti-inflammatory and anti-thrombotic properties. However, to date, there is no convincing report of in-vivo antiviral effects of HCQ/CQ. Several randomized control trials (RCTs) brought comforting news that CQ and HCQ can reduce respiratory symptoms and pulmonary inflammation as evaluated by high resolution computed tomography (HRCT). Given this report, on 30 March 2020, the US FDA gave Emergency Use Authorization (EUA) to HCQ/CQ for treatment of COVID-19, in the absence of any other approved therapy.⁴

In a retrospective multicenter cohort study in 25 different hospitals on 1438 patients with distinct medications and pre-existing conditions, there were no significant differences in mortality for patients receiving HCQ + azithromycin, HCQ alone, or azithromycin alone. On 24 April 2020, FDA cautioned against the use of CQ/HCQ outside the hospital settings or a clinical trial. Extreme care is required for the HCQ treatment in pregnant women, paediatric patients, and patients with comorbidities. Considering pharmacovigilance and public health concern, no self-medication of HCQ is advisable under any circumstances, which may, at times, be lethal. It is recommended that HCQ should only be taken under medical supervision and a baseline ECG before initiation of therapy is warranted.

In conclusion, HCQ has garnered unprecedented attention as a potential "game-changer" against COVID-19 following several small clinical trials, uncontrolled case series, and public figure endorsements. While there is a growing body of scientific data, there is also a concern for adverse drug reactions, particularly QTc prolongation, myocarditis, and cardiac arrhythmias. However, more clinical trials/ evidences are still awaited to prove its in-vivo efficacy.

Indication and dosage

It may be considered under strict medical supervision in moderate cases, mild cases, and in those having high-risk for severe disease (such as age > 60; Hypertension, diabetes, chronic lung/kidney/ liver disease, cerebrovascular disease, and obesity).

Tablet hydroxychloroquine (400 mg) BD on 1st day, followed by 200 mg 1 BD for 4 days (after ECG assessment).

It has been suggested that HCQ with azithromycin or HCQ with doxycycline, preferably with zinc, may be used in outpatient treatment.⁵

Favipiravir

Favipiravir is an antiviral drug that was approved in 2014 in Japan to treat non-complicated influenza infections and is thought to be an effective drug for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It is a prodrug and, after being converted into an active phosphoribosylated form inhibits RNA dependent RNA polymerase (RdRp).⁶ Its reported side effects are mild to moderate diarrhoea, an asymptomatic increase of transaminases, and decreased neutrophil counts. It is contraindicated in pregnant and lactating women because of its teratogenic effects in animal studies. An important feature is the lack of development of resistance to Favipiravir among influenza viruses.

In an open-label, non-randomized controlled study, oral favipiravir plus interferon-alpha was found superior to lopinavir/ritonavir. The median time of viral clearance in patients treated with favipiravir was significantly shorter.⁷ Favipiravir has demonstrated efficacy against SARS-Cov-2 in in-vitro studies.⁸

Dosage

The approved Favipiravir dose for influenza in Japan is 1600 mg twice daily on day 1 and 600 mg twice daily for four more days. Often it seems challenging to administrate 16 tablets in a day. Considering the emergency situation of the COVID-19 outbreak in some countries, marketing approval has been granted by an accelerated approval process.

REMDESIVIR

Remdesivir is a prodrug; it selectively inhibits viral RNA polymerase. It has broad-spectrum antiviral activity against several viruses such as respiratory syncytial virus, Nipah virus, Ebola virus and SARS-CoV-2. In a randomized, double-blinded, placebo-controlled, multicenter trial, it was found that intravenous Remdesivir did not significantly improve the time to clinical improvement, mortality, or time to clearance of virus in patients with serious COVID-19 compared with

placebo.⁹ Early administration of remdesivir showed a significant reduction in viral load in bronchoalveolar lavage and decreased the pulmonary infiltrates in rhesus macaque model. Moreover, it was found to be a potent inhibitor of SARS-CoV-2 replication in human nasal and bronchial airway epithelial cells. While the first double-blind, randomized-controlled trial (DBRCT) found no significant benefit with Remdesivir compared to placebo, preliminary reports from another DBRCT showed a significant faster recovery, without any difference in mortality.

Interestingly, a short 5-day course of remdesivir was found to have similar efficacy to a long 10-day course with lesser side effects.¹⁰ A preliminary report (29 April 2020) from an interim analysis of an ongoing double-blind (RCT) suggested that Remdesivir has a 31% faster time to recovery, compared to placebo. Remdesivir has been given an Emergency Use Authorization (EUA) for inpatient use in severe patients, both in adults and children by the US FDA. The compassionate use of Remdesivir in patients with severe COVID-19 requiring mechanical ventilation got approval by the European Medical Agency on 3 April 2020.

Safety of Remdesivir in COVID-19 studies

The common adverse event noted during compassionate use of Remdesivir in patients with COVID-19 by Grein et al included rash, diarrhoea, hypotension, abnormal liver function and renal impairment.¹¹ No dose modification is currently recommended in patients with mild and moderate renal impairment, or liver dysfunction. However, it is contraindicated in patients with severe renal impairment (eGFR <30 ml/min) and in patients with severe hepatic dysfunction [alanine transferase (ALT) > 5-times upper limit of normal].

Dosage

Current recommendations are to give a bolus dose of 200 mg IV on Day 1, followed by 100 mg IV, to be given for the next 4 days.

LOPINA VIR-RITONAVIR (LPV/R)

Lopinavir is an HIV protease inhibitor that is usually combined with Ritonavir to increase its half-life via CYP450 inhibition. Antiviral activity of LPV/r against SARS-COV-2 was reported in cell culture. In a marmoset infected with MERS-CoV mouse model, the prophylactic use of LPV/r in combination with interferon- β only slightly reduced the viral loads in the lungs without impacting other disease parameters. Treatment of LPV/r with interferon- β improved the pulmonary function but did not reduce viral replication or severe lung pathology. In SARS-CoV-1, the results of treatment with LPV/r were inconclusive. In a randomized, open-label trial for LPV/r in hospitalized patients with severe COVID-19, no benefit of LPV/r was

found in reducing the time to clinical improvement beyond the standard of care. However, LPV/r was found to have benefit for some secondary endpoints, safety of the treatment was confirmed.¹² The investigators concluded that LPV/r treatment did not significantly accelerate clinical improvement, reduce mortality or diminish throat viral RNA detectability.

Vicky et al screened 143 papers from PubMed and 264 papers from Embase for LPV/r, and seven articles were included in final benefit-risk assessment. Time to clinical improvement was not significantly different for LPV/r in comparison to standard of care. There also appeared to be fewer serious adverse events with LPV/r to other treatments. Based on currently available data, there was no clear benefit for the use of LPV/r compared to standard of care.¹³

Hence the pre-clinical and clinical evidence for the use of Lopinavir/Ritonavir in severe COVID-19 cannot be considered positive until further efficacy and effectiveness data become available.

OSELTAMIVIR

It is an antiviral, neuraminidase inhibitor widely used against influenza and sold under the brand name Tamiflu. The WHO initially recommended it as a preventive measure during the influenza pandemic. Guan et al reported the use of oseltamivir in 35.8% of their 1099 patients with COVID-19, and Huang et al reported the use of oseltamivir in 93% of their cohort of 41 patients. However, no conclusive data is available regarding its effectiveness.¹⁴⁻¹⁵

ARBIDOL HYDROCHLORIDE (UMIFENOVIR)

It is a broad-spectrum antiviral used in the treatment of influenza, parainfluenza, hepatitis C, etc. In a retrospective analysis of 111 patients with COVID-19 pneumonia, Xu et al found that patients who received Arbidol along with empirical treatment had higher virological conversion (59.2% vs. 40.3%) and needed oxygen therapy less frequently. They concluded that patients with mild symptoms benefitted the most from the use of Arbidol.¹⁶ In a trial by Li et al that was discussed earlier under the lopinavir/ritonavir section, there was no significant benefit noted from Arbidol. Thus, the efficacy of Arbidol hydrochloride has not yet been established in COVID-19.¹⁷

IVERMECTIN

It is an anti-helminthic drug and has shown antiviral activity against broad range of viruses including SARS-Cov-2 in-vitro.¹⁸⁻²⁰ In a recent in vitro study, the results showed that treatment with Ivermectin effectively kills almost all viral particles within 48 h. The study was the first to assess the antiviral effect of Ivermectin on COVID-19. Based on the review mentioned above, on 10

April 2020, FDA issued a statement concerning self-administration of Ivermectin against COVID-19.²¹ However, further trials are needed to confirm its safety and efficacy. The approved dose of Ivermectin is (200 µg/kg) as a single oral dose.

IMMUNOMODULATORS AND BIOLOGICALS

A cytokine-storm syndrome-like condition where plasma levels of inflammatory mediators like IL-1, IL-6, IL-12, IL-18, TNF α , etc., are elevated, occurs in some patients. In patients admitted to intensive care units, the syndrome severity is proportional to cytokine increments. Considering the proven role of cytokine dysregulation in causing this hyper inflammation, with IL-6 being a key driver, it is crucial to explore the potential role of selective cytokine blockade. Drugs like tocilizumab, sarilumab, and siltuximab are targeted monoclonal antibodies against IL-6. They can dampen the downstream IL-6 signalling pathways, thus leading to decreased cellular proliferation, differentiation and oxidative stress, all of which improves clinical outcome. However, the use of selective cytokine inhibitors during acute respiratory distress syndrome sepsis might also involve risks, such as reactivation of viral infections and increased sensitivity for bacterial infections.

INTERLEUKIN-6 (IL-6) INHIBITORS

Tocilizumab and Sarilumab are antagonists of the IL-6 receptors, with FDA approval to treat moderate-to-severe rheumatoid arthritis, not responding to DMARDs. In a single-arm Chinese trial, critically ill patients received tocilizumab.²² SARS-Cov-2 patients received only one dose of tocilizumab 400 mg along with standard of care. On the first day, after receiving tocilizumab, the body temperature of all patients returned to normal and they remained stable. Besides, the need for supplemental oxygen decreased by 75% of these patients. Better clinical outcomes were observed in 91% of patients in terms of improvement in lung function and successful discharge with a mean of 15.5 days. Further, a retrospective observational study reported a good response in patients treated with tocilizumab and recommend repeated doses of tocilizumab in critically ill COVID-19 patients. However, the number of cases reported was small and the duration of treatment might not have been sufficient. The use of tocilizumab is currently limited. Clinical trials are required to explore whether tocilizumab can be used effectively in patients with respiratory failure due to COVID-19 and to investigate at what stage of the disease this treatment could be most appropriate.²³

Adverse effects (Tocilizumab)

The primary laboratory abnormalities reported with tocilizumab treatment are dose-dependent elevation in liver enzymes. Additional adverse include risk of serious

infections (e.g., TB, other bacterial infections), have been reported only with continuous dosing of tocilizumab.²⁴

OTHER ANTI-IL-6 DRUGS

Other monoclonal antibodies against IL-6 are sirukumab, olokizumab, elsilimomab, sarilumab and clazakizumab, which are in different phases of clinical trials to establish their efficacy and safety. Another drug that showed potential inhibition of IL-6 related JAK/STAT pathway is Glatiramer acetate which showed potential to downregulate both IL-17 and IL-6 in the central nervous system in autoimmune encephalitis.²⁵

JAK/STAT SIGNALING INHIBITOR (BARICITINIB)

Its inhibitory effect on cytokine release is being explored. It may also reduce the endocytosis of SARS-CoV-2. It can be administered orally and has acceptable side effect profile, besides having little interaction with CYP enzymes and drug transporters. This makes baricitinib a valid option, in the early stages to reduce viral entry in the cells, and in the later stages for its anti-inflammatory properties.²⁶

CORTICOSTEROIDS

According to preliminary results from the Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial, low dose dexamethasone reduced mortality in patients hospitalized with Covid-19. The number of patients was 2104 for the dexamethasone arm (6 mg once daily, taken orally or by injection for 10 days) and 4321 patients receiving standard of care. The preliminary results reported that “overall dexamethasone reduced the 28-day mortality rate by 17% with most significant benefit among patients needing ventilation.²⁷ In a post hoc subset analysis, dexamethasone did not benefit the older age groups, so the benefits and risks of dexamethasone for older adults remains unclear. Longer follow-up of the original cohort will be critical to identify harms associated with corticosteroid use.²⁸

Dose

Oral/Injection Dexamethasone 6mg once daily for 10days. In pregnant and breastfeeding women, Tab prednisolone 40mg or Injection hydrocortisone 80 mg BD is to be given. (Based on RECOVERY trial in moderate to severe cases).

GRANULOCYTE MACROPHAGE COLONY-STIMULATING FACTOR (GM-CSF)

GM-CSF plays a critical role in the defence against viruses and in maintaining a proper function of the immune system. GM-CSF might thus be one of the key cytokines involved in the overreacted inflammatory response observed in COVID-19 pneumonia. The

efficacy of GM-CSF analogues for the treatment of COVID-19 patients with respiratory failure is being evaluated in clinical studies. These agents will be administered in a nebulized form for direct inhalation or through intravenous administration for patients who are already on a respirator.

INTRAVENOUS GAMMA GLOBULINS (IVIGS)

IVIGs are perhaps the safest immunomodulators for prolonged use across all age groups. IVIG, when administered as an adjuvant treatment in severely ill patients with COVID-19, can reduce the need for mechanical ventilation, improve recovery, reduce mortality, and shorten the hospital stay.²⁹ Extensive use of IVIGs during the 2003 SARS outbreak in Singapore revealed that despite using low-molecular-weight heparin, around one-third of the patients developed thromboembolic complications.

To conclude, all patients with severe COVID-19 should be screened for hyperinflammation using laboratory trends (e.g., IL-6, platelet counts, or ESR etc.), to identify the subgroup of patients for whom immunosuppression could improve mortality. Therapeutic options include corticosteroids, intravenous immunoglobulin, selective cytokine blockade (e.g., tocilizumab), and JAK /STAT inhibition.

ANTICOAGULANTS

COVID-19 infection can be associated with coagulopathy. The initial presentation corresponds with elevation of D-dimer, Fibrin and FDP, whereas abnormalities in PT, aPTT, and Platelet counts are relatively uncommon at initial stages. Patients should be closely monitored for the development of thrombosis. The incidence of thrombotic disease in COVID-19 infections is reported to be as high as 31%. A significant mortality benefit has been observed with the use of anticoagulant therapy in high-risk individuals.³⁰ While mortality in COVID-19 can be largely attributed to hypoxemia secondary to ARDS, there is growing suspicion that thromboembolic events could also contribute to the overall picture.³¹ All admitted confirmed or suspected COVID-19 patients should be given anti-thrombotic prophylaxis unless contraindicated. It is important to remember that, when dealing with anticoagulants, it is always necessary to consider the risk/benefit balance, weighing the potential efficacy: prevention of thrombosis.

CLINICAL INDICATIONS FOR ANTI-COAGULANT THERAPY

For COVID-19 patients with other indications for anticoagulation, such as new or recent diagnosis of VTE, atrial fibrillation, mechanical cardiac valves, or long-term secondary VTE prevention, anticoagulation should be continued at a full dose or a dose equivalent to their

current dose. For critically ill inpatients, the use of LMWH or UFH is preferred over direct oral anticoagulants, the former having shorter half-lives and ability for parenteral administration.³²

Dose of anticoagulation

A prophylactic dose of UFH or LMWH (e.g., Enoxaparin 40 mg per day SC). For, obese patients, higher doses may be given.

ANTIVIRALS

Ribavirin

It is a broad-spectrum antiviral drug used to treat the respiratory syncytial virus, parainfluenza, measles, herpes, and hepatitis C virus infections. It acts via inhibition of RNA-dependent RNA polymerase enzyme. A few in-vitro studies have demonstrated its therapeutic potential in SARS-CoV-2. Its utility as an adjunct to lopinavir-ritonavir has been explored in clinical trials. Early triple antiviral therapy with lopinavir-ritonavir and ribavirin was safe and superior to lopinavir-ritonavir alone in alleviating symptoms and shortening the duration of viral shedding and hospital stay in patients with mild to moderate COVID-19.³³

INTERFERONS

Interferons (IFNs) are proteins produced by a variety of cells as an inflammatory response to viral infections. They are critical effectors of both innate and adaptive immune responses. They are considered to be a broad-spectrum antiviral agent through their interaction with toll-like receptors and inhibition of viral replication.³⁴ Interferon-alfa and beta both demonstrated an anti-SARS-CoV-1 activity in vitro. Interferon beta-1b has been shown to reduce viral load and improve lung pathology in marmoset model of MERS-Cov.³⁵

Treatment with IFN- α 2b with or without Arbidol significantly reduced the duration of detectable virus in the upper respiratory tract and in parallel, reduced duration of elevated blood levels of inflammatory markers like IL-6 and CRP.³⁶

ANTIBIOTICS

Macrolide antibiotics like azithromycin inhibit bacterial protein synthesis by binding to the 50S ribosomal subunit, causing the cessation of bacterial protein synthesis.

It has been reported by Gautret et al that azithromycin helps to reinforce the action of HCQ in reducing the viral load in patients infected with SARS-CoV-2.³⁷ However, the study had limitations of small sample sizes and concerns of cardiotoxicity. Doxycycline, in combination with HCQ, has also been used.

PHOSPHODIESTERASE INHIBITORS

Phosphodiesterase (PDE) inhibitors are a family of enzymes which prevent the degradation of cyclic nucleotides (cAMP/cGMP) the elevated levels of these cyclic nucleotides play a key role in regulating inflammation and smooth muscle relaxation. PDE4 and PDE5 isoforms are widely expressed in the airway.

Various PDE4 (Roflumilast, rolipram) and PDE5 (Tadalafil, vardenafil) inhibitors are approved for the treatment of bronchial asthma and pulmonary artery hypertension, respectively. PDE5 inhibition favors an anti-inflammatory response by modulating activated T cells, reducing cytokine release, lowering fibrosis, increasing oxygen diffusion, stimulating vascular repair.³⁸ Various animal models have demonstrated strong anti-inflammatory effects of PDE4 inhibitors in airway inflammation. The rationale for PDE4 inhibitors uses in COVID-19 patients comes from their multimodal mechanism of action with cytokine, chemokine, and other essential pathway inhibition all achieved with an excellent safety profile.³⁹ Thus the role of these agents which act via cAMP/cGMP pathway is currently being explored in mitigating airway inflammation associated with COVID-19

VITAMINS AND SUPPLEMENTS

Also, vitamin supplements; minerals; trace elements such as iron, selenium, Zinc and flavonoids have been recommended for the management of COVID-19.⁴⁰

HERBAL MEDICINES

Glycyrrhizin, an active constituent of liquorice roots, has been reported to prevent the replication of SARS-CoV in vitro. Baicalin, a flavonoid from *Radix Scutellaria*, showed in vitro antiviral activity against SARS-CoV. Diarylheptanoids extracted from the bark of *Alnus japonica* have been found to inhibit the papain-like protease in SARS-CoV. In India, there is a healthy complementary co-existence of modern medicine with Ayurveda, Homeopathy, Unani, and Siddha. The Ayurvedic specialists, through the Government of India, have suggested ten measures which through a possible and potential psychoneuroimmune mechanism can help boost the immunity against COVID-19. Some of these include, use of turmeric, coriander, and garlic; steam inhalation; and the use of clove powder for relief from sore throat in patients with COVID-19. The Unani traditional medicine generally suggests the use of some specific agents during epidemics to boost immunity. Herbal medicines can therefore be tried to enhance the immunity against COVID-19.⁴¹

CONVALESCENT PLASMA THERAPY

Lessons learnt so far from COVID-19 infection reveal that there is still no cure. However, several possible drugs

and novel agents, are available through compassionate use, or as repurposed antiviral and immunomodulating pharmacotherapies.⁴² One of the hopeful treatments that has emerged is convalescent plasma therapy (CPT), or immune plasma, which is plasma that is collected from a COVID-19 infected individual and then transfused into infected patients. CPT has shown limited and moderate success, previously for SARS-1 and MERS, and for COVID-19 in China, and other countries. It could serve as a short-term solution to suppress mortality rates. As the number of infections increases, the CP of infected patients could be donated or harvested for simultaneous treatment or future use until an effective antibody is discovered. On 24 March, 2020, the US Food and Drug Administration (FDA) approved the use of CP therapy for patients with severe COVID-19 infections.⁴³ The Indian Council of Medical Research (ICMR) has approved a trial for CP therapy, to be conducted by the Shree Chitra Tirunal Institute for Medical Sciences and Technology.⁴⁴

Indications: Convalescent Plasma (Off Label) may be considered in I) patients with moderate disease, II) who are not improving (oxygen requirement is progressively increasing) despite use of steroids III) age more than 18 years IV. Any of the two, PaO₂/FiO₂ between 200-300 or respiratory rate more than 24.min or, SaO₂ less than 93% on room air

Contraindications: I) Should be avoided in patients with IgA deficiency, II) immunoglobulin allergy, III) pregnant/breastfeeding woman, IV) hypersensitivity to blood products, V) critically ill patients, and VI) patient who has received immunoglobulin in last 30 days.

Dose: It varies ranging from 4 to 13 ml/kg (usually 200 ml single dose given slowly over not less than 2 hours.

COVID-19 VACCINE

The entire world is united in facing the emergency of the COVID-19 pandemic. Everybody together is at war, against a common enemy. Several countries of the world like USA, UK, Australia, Russia, China, Hong Kong, and India are working relentlessly to develop COVID-19 vaccine. In just six months since the virus came into existence, 140 vaccine candidates are in the pre-clinical trial stage, and 23 are in the clinical evaluation stage, according to WHO. US-based Moderna was the first company to be off the blocks with a vaccine candidate. With past experience from SARS and MERS it created the first dose of its mRNA vaccine in record time and launched the first human trial on a SARS-CoV-2 vaccine on 16 March. The vaccine encodes the spike (S) protein of SARS-CoV-2. Another vaccine (ChAdOx1) developed at Oxford University in collaboration with AstraZeneca is made from a weakened version of a common cold virus (Adenovirus) is currently into Phase-III trials in South Africa and Brazil. India has started Phase I trial of an inactivated virus vaccine called Covaxin on 15 July. Another plasmid DNA vaccine has also been initiated in

India and on trial. While vaccine development research continues, questions are already arising on the next steps and challenges concerning the manufacturing, distribution, and widespread accessibility of a possible vaccine. Of course, once an effective vaccine is available, it will be of the utmost importance to provide affordable and accessible protection from COVID-19 for all who need it. Right now, we celebrate the efforts of scientists, doctors, and individuals working around the clock to find a solution to this pandemic.⁴⁵

BACILLUS CALMETTE-GUÉRIN VACCINE

Based on its active role in SARS, Bacillus Calmette–Guérin (BCG) has been recommended for the treatment of COVID-19.⁴⁶ The Drug Controller General of India has permitted to start BCG trials in patients with COVID-19 in India.

CONCLUSION

With hospitals being overwhelmed with severely ill patients, treatment options for COVID-19 are essential.⁴⁷⁻⁴⁹ Rapid identification of such therapies is the need of the hour but challenging. Repurposing of existing antiviral and immunomodulating drugs is a crucial strategy because the safety profile of these drugs is well known. As the pathogenesis of COVID-19 is not yet well understood, and associations between clinical status and viral clearance, radiological or immunological evaluations are unclear, the use of clinical outcomes should be encouraged. Several clinical trials with COVID-19 patients are evaluating repurposed drugs for dosage and duration of treatment. In the trial launched by the WHO, only simple outcomes will be measured that are currently relevant for public health. In this pandemic context, it is essential that clinicians have rapid access to the information from clinical trials. Still, clinical trials and the reports on their results must be of high quality, as these results will guide clinicians in their decision on which drug to use, the dosing and duration of the treatment, and which patients to include and exclude. No treatment has been definitively proven to be effective against COVID-19 to date. The only FDA-approved drug is Remdesivir, and several others are under investigation. Corticosteroids and anticoagulant therapy have been recommended in patients with severe ARDS. With the limited proven efficacy of most of the drugs currently in use, it is of utmost necessity to investigate all the potential drug therapies in order to gather good-quality data amidst this pandemic.

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