International Journal of Basic & Clinical Pharmacology
Mohapatra M et al. Int J Basic Clin Pharmacol. 2020 Nov;9(11):1770-1777
http://www.ijbcp.com
pISSN 2319-2003 | eISSN 2279-0780

DOI: https://dx.doi.org/10.18203/2319-2003.ijbcp20204509

Review Article

An overview of treatment options for COVID-19

Madhusmita Mohanty Mohapatra*, Manju Rajaram, Dharm Prakash Dwivedi, Vishnukant Govindraj, Pratap Upadhya

Department of Pulmonary Medicine, Jawaharlal Institute of Postgraduate Medical Education and Research, Gorimedu, Puducherry, India

Received: 14 September 2020
Accepted: 13 October 2020

***Correspondence:**
Dr. Madhusmita Mohanty Mohapatra,
Email: drmadhusmita1@gmail.com

ABSTRACT

Severe acute respiratory syndrome- coronavirus-2 (SARS-CoV-2) which emerged in Wuhan initially as pneumonia of unknown origin in December 2019, later spread to whole world and became pandemic on 11th March, 2020. Many drugs have been proposed but are backed without clinical evidence. Scientific bodies are in the row to discover a reliable vaccine and effective drugs against the novel coronavirus. Many antiviral and anti-parasitic drugs which were thought to have some effect on Coronavirus disease 2019 (COVID-19) have been tried during the crisis but none have shown concrete evidence of action. Randomized clinical trials on the repurposed drugs are now registered under clinical trial registry to look at the safety profile and efficacy of the drugs to be used against SARS-CoV-2. Many meta-analyses are being conducted worldwide to frame evidence for the fight against this novel coronavirus. We are providing below a review of various drugs that have been tried for treatment of COVID-19 as well as different clinical trials which are underway.

Keywords: Antivirals, Convalescent plasma therapy, COVID-19, Immunosuppressant, Mesenchymal cell

INTRODUCTION

The 2020 novel coronavirus named as Corona virus disease-19 (COVID-19) emerged in China in late December causing severe respiratory infection in humans and was declared as a pandemic by World Health Organization (WHO) on 11th March 2020. Initially considered as pneumonia of unknown etiology in China, it started spreading to Asian countries and then worldwide. According to WHO, there are 15,107,950 confirmed cases of COVID-19 and 6,19,817 deaths with United States of America leading amongst the countries followed by Brazil, India, Russia by June 22, 2020.[1] The detection of SARS-CoV-2 is done by polymerase chain reaction test of samples obtained from throat and nasal swabs. The dynamics of the disease assessed using the reports of polymerase chain reaction (PCR) have raised serious concerns and urgent need for containing the pandemic. Given the magnitude of global health crisis, there is no effective prophylaxis or therapy, as of now, for the disease. We are providing below a review of various drugs that have been tried for treatment of COVID-19 as well as different clinical trials which are underway.

MOLECULAR MECHANISM FOR COVID-19 THERAPY

There are four genera of coronavirus named as α, β, δ and γ coronavirus. β- coronavirus has been further sub classified as A, B, C and D variety. So far, there have been seven coronavirus variants that causes human infection called human coronavirus (HCoVS). HCoV-229E and HCoV-NL63 belong to α- coronavirus, HCoV-OC43 and HCoV-HKU1are β- coronavirus subtype A, severe acute respiratory syndrome coronavirus (SARS-CoV) and SARS-CoV-2 are β- coronavirus subtype B while middle

east respiratory coronavirus (MERS-CoV) is a β-coronavirus C type.[2] SARS-CoV-2 has spike proteins which has two subunits, S1 and S2. S1 subunit has receptor binding domain which utilizes human angiotensin converting enzyme 2 (ACE-2) receptor present on epithelial cells of oral mucosa and type-2 pneumocytes of lung parenchyma while S2 subunit mediates membrane fusion process of virion and target cell. Drugs targeting this fusion protein may cause effective inhibitory action on SARS-CoV-2.[3] Soluble recombinant human ACE2 protein can also prove to be an effective therapeutic option.[4]

After entering the cell, SARS-CoV-2 utilizes cellular serine protease enzyme transmembrane protease serine 2 (TMPRSS2) to confer the virion infectivity. Ribonucleic acid (RNA) polymerase and protease inhibitors also affect intracellular virion assembly. Drugs targeting these enzymes should be evaluated for possible action against the virus. The mature virion enters endosomes and initiates inflammatory pathways by interacting with toll like receptor. Drugs that change the pH of the endosome and there by stop the inflammatory pathways are also helpful. The cytokine storm which results following virion entry to cell and thereby releases interleukins (ILs) by inflammatory pathway can also be targeted for management of COVID.[5-7]

SEARCH METHOD

We searched PubMed, Cochrane COVID-19 Study Register, LitCovid open database, World Health Organization (WHO) COVID-19 International Research Database, Centers for Disease Control and Prevention COVID-19 Research Article Database to identify studies published up to 20 May 2020. We also identified ongoing trials registered under ClinicalTrials.gov and WHO international clinical trial registry. Articles for this review were identified using filters to include clinical trials, randomized controlled trials, meta-analysis and systematic reviews. Only English language studies were identified and considered for this review. Further, relevant studies were identified through hand search of references of selected studies. We excluded case reports, studies involving other types of coronavirus, non-indexed studies and news reports. A total of 148 studies were identified after removing duplicates, and using the strategy outlined above, 99 studies relevant to this article were selected for review.

ANTIVIRAL THERAPY

Many of the antiviral drugs used for treatment of Human immunodeficiency virus (HIV-1) have been thought to be useful in treatment of SARS-CoV-2. Drugs that inhibit RNA polymerase and protease inhibitors are being tried in management of novel coronavirus. (Table 1) A randomized open labelled clinical trial done by Cao et al on 199 COVID-19 patients with lopinavir-ritonavir compared with standard therapy did not show significant reduction in viral RNA or mortality as opposed to standard therapy group.[8] However, Chen et al found no death when treated with lopinavir-ritonavir but the sample size was very small to reach a conclusion.[9] Two clinical trials are in phase 4 comparing the efficacy of lopinavir-ritonavir with other antivirals for novel coronavirus. Remdesivir is a nucleotide analogue which inhibits viral RNA polymerase that has been tried in both mild and severe COVID-19 patients. Grein et al found that compassionate use of remdesivir caused clinical improvement in 36 out of 53 SARS-CoV-2 patients (68%), mortality was 18% in patients on invasive ventilator and 5% without ventilator.[10]

Table 1: Summary of drugs and mechanism of action for COVID-19.

Group	Drugs	Mechanism of action
Viral protein synthesis inhibitor	Lopinavir/ritonavir	Protease inhibitor
Viral RNA polymerase inhibitor	Remdesivir	Adenosine nucleotide inhibitor
	Favipiravir	Guanosine nucleotide inhibitor
Viral entry inhibitors	Arbidol	Inhibits fusion and entry of virus by inhibiting trimerization of spike proteins
	Hydroxychloroquine	Increase endosomal pH and inhibit viral entry to host cell
	Chloroquine	
	Azithromycin	
Viral replication inhibitor	Ivermectin	Inhibit IMP α/β1 importin of viral proteins and replication
	Nitazoxanide	Inhibit viral replication by its metabolite in vitro
Viral particle release from host inhibitor	Oseltamivir	Neuraminidase inhibitor and inhibit viral particle release

Two clinical trials, NCT04257656 (severe) and NCT04252664 (mild) have been registered in ClinicalTrials.gov looking for the efficacy of remdesivir for novel coronavirus infection. Oseltamivir is a neuraminidase inhibitor used for influenza virus infection treatment and can inhibit release of virus from host cell. In a study done by Guan et al among 1099 COVID-19 patients, 393 patients received oseltamivir, showed that

oseltamivir is ineffective in reducing mortality and ventilator rates.[11] Clinical trials are underway with Oseltamivir used along with chloroquine and favipiravir.

Arbidol, a fusion inhibitor which blocks entry of virus into host cell is approved for SARS. Clinical trials have been registered comparing arbidol with standard treatment for COVID-19 treatment. Three more trials are in the pipeline comparing efficacy of arbidol with oseltamivir, lopinavir-ritonavir and carrimycin.[12-14] Favipiravir is an RNA dependent RNA polymerase inhibitor used for treatment of Ebola has been considered for treatment of SARS-Cov-2. Studies done on 80 patients of COVID-19 in China showed that favipiravir is more potent than lopinavir-ritonavir and had less side effects but the article has been withdrawn for unknown reason. In addition, patients with COVID-19 infection are being recruited for randomized trials to evaluate the efficacy of favipiravir versus hydroxychloroquine (NCT04373733) and favipiravir versus interferon-α (INF-α) (ChiCTR2000029600).[15-17] A systematic review done by Yousefifard et al concluded that the beneficial effect of currently used antiviral agents for COVID-19 is not clear due to few published data and lack of randomized clinical trials. Further ongoing clinical trials may bring out effective and potent antiviral drugs with less adverse effects of COVID-19.[17]

ANTIPARASITIC THERAPY

Chloroquine (CQ), an anti-malarial agent has also anti-viral and anti-inflammatory properties and is believed to play an important role in the treatment of novel coronavirus. Chloroquine is a weak base and it interferes with the glycosylation of ACE2 receptors of SARS-CoV-2 by increasing the endosomal pH and thereby inhibiting viral entry into host cell. Chloroquine also prevents viral exit from host cell and release of inflammatory cytokines. The clinical effectiveness of CQ for COVID-19 came from China where Gao et al tried CQ on 100 COVID-19 patients at different sites in China using different study protocols.[18] They reported reduction in the duration of illness, and improvement in COVID-19 pneumonia and appearances on chest imaging. No scientific data supporting these findings have been published and the evidence has therefore not been peer reviewed. A systematic review done by Andre et al suggested that CQ is effective in limiting SARS-CoV-2 replication in vitro but still more clinical trials is needed to mark its safety.[19] Hydroxychloroquine (HCQ), a derivative of chloroquine with hydroxy moiety has similar action as CQ in inhibiting entry, transport and post entry event of SARS-CoV-2. However, HCQ was found to be more potent than CQ against SARS-CoV-2 in one study by Liu et al and adverse effects like retinal toxicity were also less compared to CQ.[20] The first clinical trial of HCQ on COVID-19 was conducted by Chen et al. which was a randomized controlled trial on 30 patients.[21] Their primary outcome was nasopharyngeal test result on day 7 and the result of the trial was discouraging as there was neither a difference in negative test result between control and study group nor there was reduction in duration of illness. The adverse events were more in the treatment group. A second trial on HCQ was done by Guetret et al on 36 COVID-19 patients which was an open label non-randomized controlled trial.[22] The primary outcome was SARS-CoV-2 carriage at day 6, detected by PCR on nasopharyngeal swabs. Patients in the treatment group were significantly more likely to test negative for SARS-CoV-2 on day 6 than controls (70% versus 12.5% virologically cured, $p<0.001$). A systematic review and meta-analysis done by Sarma et al in which they included 7 studies with an objective to look at the virological cure found that treatment with HCQ resulted in fewer cases showing radiological progression of lung disease (Odds ratio (OR) 0.31, 0.11-0.9). However, there was no difference observed in virological cure (OR 2.37, 0.13-44.53), death or clinical worsening of disease (OR 1.37, 1.37-21.97) and safety (OR 2.19, 0.59-8.18), when compared to the control/ conventional treatment. Five studies reported either the safety or efficacy of HCQ + Azithromycin.[23] An updated systematic review and meta-analysis on use of HCQ in COVID-19 patients by Singh et al suggested that there was no viral clearance with the use HCQ and in fact there was there was two fold increase in mortality in COVID-19 patients due to HCQ compared to control.[24] However, clinical trials are on with HCQ is to establish its efficacy in SARS-CoV-2 management. Ivermectin, a broad spectrum anti-parasitic drug has been found to be effective in inhibiting the interaction of HIV-1 integrase protein and importin heterodimer for nuclear import and HIV-1 replication. Ivermectin was found to inhibit nuclear transport in SARS-CoV-2 virus. Leon et al demonstrated that ivermectin has antiviral activity against novel coronavirus clinical isolate and can control viral replication within 24-48 hours in human body.[25] Nitazoxanide another potent anti-parasitic drug also has antiviral activity by potentiating the interferon alpha and interferon beta production. It has been shown to be active against MERS CoV and other coronaviruses and has hence been suggested by few authors to be used synergistically with azithromycin.[26]

ANTIBIOTICS

Macrolides besides their antibiotic effects is also found to have immunomodulatory and anti-inflammatory action. Clarithromycin and azithromycin had already been tried on SARS-CoV-2 patients and has been found to be effective in combination with HCQ. Multiple mechanisms have been proposed for the antiviral properties of macrolides like azithromycin which was used in few trials. Azithromycin is a weak base and accumulates intracellularly in endosomal vesicles thereby increasing pH levels and blocks viral replication. The acidic environment required for the uncoating of enveloped viruses such as influenza and human immunodeficiency virus (HIV) is also required for coronaviruses. The antiviral effects of azithromycin may also be mediated by a host interferon mediated antiviral responses. In SARS-CoV-2 patients, it is suggested that azithromycin may act by interfering with viral entry by interacting between the

SARS-CoV-2 spike protein and host receptor ACE2 protein.[27] Many clinical trials are authorized to start up using various combination of azithromycin with other repurposed drugs in COVID-19 patients. Three important randomized trials of which two trials have started recruiting patients have been registered under clinical trial registry looking at efficacy of using azithromycin used in combination with HCQ.[28,29] Teicoplanin, a glycopeptide antibiotic used to treat bacterial infection was found to be active in vitro against SARS-CoV. It acts on the early step of the viral life cycle by inhibiting cleavage of the viral spike protein by cathepsin L and thereby preventing the release of genomic viral RNA and virus replication. A randomized controlled clinical trial looking at the efficacy of teicoplanin in coronavirus patient has been registered under WHO international clinical trial registry platform and patients are being recruited for the purpose (IRCT20161204031229N3).[30]

CONVALESCENT PLASMA THERAPY

The plasma obtained from blood of patients infected with novel coronavirus and had recovered from the disease is called convalescent plasma. The plasma contains large amount of antibodies which can be injected to a newly infected person to combat the viral antigen. This decade old technique has been tried earlier in many diseases including SARS and MERS. A systematic review was conducted by Rajendran et al on clinical effectiveness of convalescent plasma therapy for treatment of COVID-19 patients. They included critically evaluated five studies with 27 patients and the outcome of interest was clinical effects, survival benefits, viral load, antibody titre status and adverse events. All patients had good clinical effects and survival benefit and the viral load decreased between day 1 and day 30. This warrants a multicentric trial in this pandemic to further evaluate convalescent plasma therapy in management of COVID-19.[31] Nearly 74 clinical trials have been registered in the clinical trial registry among which the CONCOVID trial has started recruiting patients.[32]

ANTICOAGULATION THERAPY

Heparin has antiviral properties and it inhibits viral attachment by causing conformational change in spike protein-1 of SARS-CoV-2. Tang et al in his study found that disseminated intravascular coagulation and elevated D-dimer level were independent predictors for mortality in a cohort of 449 COVID-19 patients.[33] Low molecular weight heparin (LMWH) administered in COVID-19 patients were associated with lower level of IL-6 suggesting that it not only prevent thrombosis but also take part in reducing cytokine storm. Hence, it is justified to give heparin and LMWH as prophylaxis of venous thrombosis or as treatment where rapid respiratory deterioration is attributed to thromboembolism. A Chinese study of 81 patients and a Dutch study of 184 critically ill COVID-19 patient showed incidence of 25% and 31% of venous thromboembolism events respectively.[34,35] Hence, WHO and Sciensano guidelines recommended the use of prophylactic LMWH or heparin against venous thromboembolism in critically ill COVID-19 patients.[36] The International society on thrombosis and haemostasis recommended that all hospitalized COVID-19 patients should receive prophylactic LMWH.[37] Two randomized clinical trial has been registered and are recruiting COVID-19 patients to obtain evidence about the benefit of anticoagulation therapy in these patients (NCT04362085, NCT04359277).[38,39]

IMMUNOSUPPRESSIVE THERAPY

Cytokine storm refers to excessive and uninhibited release of pro-inflammatory cytokines. It is an important event that occurs once the viral infection cascade continues thereby releasing cytokines causing severe respiratory distress and organ damage with high inflammatory parameter in COVID-19 patients. Systemic corticosteroid: Glucocorticoids has been tried to suppress this cytokine storm in few trials. A meta-analysis done by Lu et al on use of systemic corticosteroid in COVID-19 patient showed that corticosteroid did not reduce the risk of mortality with (relative risk (RR) =2.0, CI-95%: 0.7-5.8), duration of pneumonia (weighted mean difference (WMD)=-1.0 day, 95%- CI: -2.9-0.9) and hospital stay (WMD=2.4days, 95%- CI: 1.4-3.4 days) in COVID-19 patients.[40] Tobaiqy et al in his systematic review found that the most common drug used in COVID-19 is corticosteroid and suggested that they are not recommended in guidelines.[41] Dexamethasone, a synthetic anti-inflammatory drug however showed promising result from the RECOVERY TRIAL conducted in UK and hence low dose of dexamethasone was recommended by Horby et al from the preliminary report obtained from this trial.[42] Interleukin-6 inhibitor (Tocilizumab): It is a humanized immunoglobulin that blocks IL-6 receptor. It has been used to block the cytokine storm in severe covid-19 patients. Two studies have been done using tocilizumab in severe COVID-19 patients. A case series published by Xu et al from China which included 21 patients with severe COVID-19 symptoms were given a trial of tocilizumab along with methylprednisolone.[43] They observed that the was significant improvement in clinical symptoms and oxygen saturation. Another study done by Roumier et al in France using tocilizumab on 30 critically ill COVID-19 patients concluded that significantly reduced the requirement of mechanical ventilation compared to controls (weighted odds ratio (WOR)=0.42; 95% CI: 0.20-0.89; p=0.025)) and reduced the risk of Intensive care unit (ICU) admission in those treated outside ICU (weighted OR=0.17; 95% CI: 0.06-0.48; p=0.001). However, there was no statistically significant difference in reduction of mortality after weighted analysis (OR=0.25; 95% CI: 0.05-0.95; p=0.04).[44] Both studies were published in a preprint server without peer review. However, the current evidence is insufficient to support the use of tocilizumab outside clinical trials. A multicentric phase 2 clinical trial to treat COVID-19 patients with tocilizumab had already started enrolling the subjects (NCT04317092).[45] Sirolimus: It is

an immunosuppressant used to prevent organ transplant rejection and treatment of lymphangioleiomyomatosis. It acts by inhibiting the mammalian target of rapamycin (mTOR) kinase which helps in viral replication. A randomized double-blind placebo-controlled trial (SCOPE) has been planned by University of Cincinnati to observe the effect of sirolimus in critically ill COVID-19 patients requiring respiratory support.[46] Zhou et al using a network-based drug repurposing obtained from data of other coronavirus found sirolimus to be one of the potential drug that can be used for novel coronavirus management.[47]

Interferon beta 1b

Type I IFNs (IFN-α and IFN-β) are the major contributors in innate immunity serving as the first line of defence against viruses as well as linking innate to adaptive immunity. Both IFN-α and IFN-β signal through a common receptor IFNAR that consists of IFNAR1 and IFNAR2 chains and binding to the receptor leads to the activation of JAK-STAT signalling pathway, which results in direct antiviral effects of type I IFNs and expression of interferon-inducible genes. An open label randomized phase 2 clinical trial conducted by Hung et al to look at the efficacy of interferon beta-1b on 127 COVID-19 positive patients admitted to six hospital in China. It was triple combination drug therapy trial that included in interferon beta-1b in combination with lopinavir-ritonavir and ribavirin compared to lopinavir-ritonavir alone. The primary outcome was time to SARS-CoV-2 RT PCR negativity and the secondary outcome was time to symptom resolution, duration of hospital stay, 30 day mortality and SOFA score 0. They found that in subgroup analysis there was a significant improvement in the triple combination group compared to control group.[48] Six clinical trials with interferon beta-1b in combination with various drugs has been registered in the clinical trial registry. One has been completed while others are in the stage of recruitment.

OTHER ADJUNCTIVE THERAPIES

Mesenchymal stem cells

Mesenchymal stem cells have immunomodulatory functions and can reduce cytokine storm caused due to the SARS-CoV-2 virus. SARS-CoV2 virus targets the angiotensin-converting enzyme (ACE)-2 receptors through their spike proteins but bone marrow which produces mesenchymal cells lack ACE-2 receptors making them immune to the effects of the virus. Clinical study using mesenchymal stem cell therapy on severely ill COVID-19 patients has been tried in China as a pilot study. Leng et al. performed a clinical pilot trial of mesenchymal stem cell treatment on 7 critically ill COVID-19 patients. Three patients with severe illness served as controls. There was reversal of symptoms with no adverse effects in trial group with the biochemistry demonstrating increase in lymphocytes and decrease of cytokines.[49] A clinical trial using mesenchymal stem cells in COVID-19 pneumonia has been registered and in the phase of recruitment (NCT04339660).[50]

Fluvoxamine

Fluvoxamine is an anti-depressant drug used for treatment of obsessive-compulsive disorder. The drug was found to be effective in preventing sepsis in mice and hence being interpreted that it will prevent cytokine storm. A clinical trial by University School of Medicine in St Louis, Missouri has been recruiting COVID-19 patients to evaluate the effectiveness of fluvoxamine (STOP COVID Trial) (NCT04342663).[51]

Vitamin C

It neutralizes free radicals and reverse cellular damage. Vitamin C not only inhibits reactive oxygen species production and cytokine storm syndrome but also involved in immune response to viral agents through lymphocytes and natural killer (NK) cells. China is conducting a clinical trial with high-dose IV vitamin C in severe COVID-19 patients and the results are still awaited (NCT04264533).[52]

Inhaled pulmonary vasodilators

Inhaled pulmonary vasodilator therapy has been suggested in mechanically ventilated COVID-19 patients with severe hypoxemia not responding to maximum ventilatory support. Inhaled epoprostenol and inhaled nitric oxide are two common pulmonary vasodilators that have been used. Clinical trials evaluating the efficacy inhaled nitric oxide for treatment and prevention of COVID-19 patients are ongoing (NCT04305457, NCT04312243).[53,54]

Chinese herbal medications

Chinese herbal medications were tried along with generic drugs in China during the pandemic and was found to be effective. This idea was drawn from the Cochrane systematic review which suggested the effectiveness of use of the herbal medication in SARS. A systematic review and meta-analysis done by Lin et al concluded that use of herbal medication along with western medications can reduce the symptoms.[55]

FUTURE PERSPECTIVES

Mycobacterium w

A vaccine containing heat killed *Mycobacterium w* previously used as a immunomodulator for leprosy and has been tried in sepsis was administered to four severe COVID-19 patients and the result was found to be remarkable with clinical and radiological resolution as well as the need for ventilator was also deferred. A randomized clinical trial has been registered to evaluate the efficacy of this vaccine in COVID-19 pneumonia (NCT04347174).[56]

Colchicine

Colchicine is a lipid-soluble alkaloid drug administered orally and has anti-inflammatory action. It is used in acute pericarditis as well as in various other conditions. In concern to COVID-19, majority of the patients suffer from acute respiratory distress syndrome (ARDS) and myocardial injury. This was from evidence obtained from study conducted in Wuhan, China on 150 patients in which 7% of deaths was attributed to myocarditis and 33% with myocarditis had adverse outcome.[57]

It has been shown in experimental models that inflammosome NLRP3 is a major pathophysiological component for development of ARDS while in dry lab model the SARS-CoV-2 proteins such as viroporins E, 3a and 8A plays important role in viral replication. These viral proteins provoke inflammosome NLRP3 and cause ARDS which can be inhibited by colchicine. The GRECCO-19 trial is recruiting patients and to evaluate the effect of colchicine in prevention of complication due to COVID-19 (ClinicalTrials.gov identifier: NCT043267-90).[58]

Vasoactive intestinal polypeptide

Vasoactive intestinal polypeptide (VIP) target the VAPC1 receptor of alveolar type II cells and prevent them from damage. It has been observed in animal models that VIP prevents from NMDA induced caspase-3 activation in lung, inhibits IL-6 and TNFα production and prevents pulmonary oedema. Synthetic form of VIP has been tried and found to be safe in treatment of sarcoid, pulmonary hypertension, ARDS and erectile dysfunction. A multi-center randomized placebo-controlled trial has been registered in clinical trial registry and patients with moderate or severe COVID-19 infection are being recruited for trial with intravenous synthetic VIP compared to standard treatment. The trial is in phase 2 and soon to be rolled to phase 3 (ClinicalTrials.gov Identifier: NCT04311697).[59]

Monoclonal antibodies

Anti-spike S monoclonal antibodies which target the spike proteins at two sites are being tried in critically ill COVID-19 patients. It has been found to give promising results in treating hospitalized adult patients. A randomized placebo-controlled trial is the process of recruiting patients for evaluating the safety and efficacy of monoclonal antibodies (ClinicalTrials.gov Identifier: NCT04426695).[60]

CONCLUSION

There is presently no definite treatment or prevention for COVID-19. Many drugs have been repurposed and are on clinical trials to evaluate the safety and efficacy in critically ill COVID-19 patients as well as for prophylaxis. Beside creating awareness about the global crisis about the virus, it is safe for policy makers and stake holders to follow expert opinion and draw conclusions based on evidence-based recommendations. While, WHO is awaiting the results of trials involving lopinavir-ritonavir and interferon beta 1b as well as effective vaccines, awareness of social distancing and maintaining hand hygiene seem to be the most important strategy against this virus for the time being.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. COVID-19 cases worldwide. 2020. Available at: https://www.worldometers.info/coronavirus/. Accessed on 22 June 2020.
2. Zhou P. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020;579:270-3.
3. Xia S. Inhibition of SARS-CoV-2 (previously 2019-nCoV). Cell Res. 2020;30(4):343-55.
4. Batlle D, Wysocki J, Satchell K. Soluble angiotensinconverting enzyme 2: A potential approach for coronavirus infection therapy? Clin Sci (Lond). 2020;134:543-45.
5. Colson P, Rolain JM, Raoult D. Chloroquine for the 2019 novel coronavirus SARS-CoV-2. Int J Antimicrob Agents. 2020;55:105923.
6. Gao J, Tian Z, Yang X. Breakthrough: chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. Biosci Trends. 2020;14(1):72-3.
7. Schrezenmeier E, Dörner T. Mechanisms of action of hydroxychloroquine and chloroquine: implications for rheumatology. Nat Rev Rheumatol. 2020;16:155-66.
8. Cao B, Wang Y, Wen D. A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19. N Engl J Med. 2020;382(19):1787-99.
9. Chen Q, Quan B, Li X. A report of clinical diagnosis and treatment of nine cases of coronavirus disease 2019. J Med Virol. 2020;10.1002/jmv.25755.
10. Grein J, Ohmagari N, Shin D. Compassionate Use of Remdesivir for Patients with Severe Covid-19. N Engl J Med. 2020;NEJMoa2007016.
11. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. The New England journal of medicine. 2020;382:1708-20.
12. Bethesda. A prospective, randomized controlled clinical study of antiviral therapy in the 2019-nCoV pneumonia. ClinicalTrials.gov. (MD): National Library of Medicine (US). Identifier NCT04255017. 2020. Available at: https://clinicaltrials.gov/ct2/show/NCT04255017?term=antiviral+therapy&cond=Covid19&draw=2. Accessed on 10 August 2020.
13. Bethesda. The efficacy of lopinavir plus ritonavir and arbidol against novel coronavirus infection (ELACOI). ClinicalTrials.gov. National Library of

Medicine (US). 2020. Identifier NCT04252885. Available at: https://clinicaltrials.gov/ct2/show/study /NCT04252885. Accessed on 10 August, 2020.
14. Bethesda. The clinical study of carrimycin on treatment patients with Covid19. ClinicalTrials.gov. National Library of Medicine (US). 2020. Identifier NCT04286503. Available at: https://clinicaltrials. gov/ct2/show/ NCT04286503. Accessed on 10 August, 2020.
15. Bethesda. A Randomised Controlled Trial of Early Intervention in COVID-19: Favipiravir Verses HydroxycholorquiNe & Azithromycin & Zinc vErsEs Standard CaRe (PIONEER). ClinicalTrials.gov. National Library of Medicine (US). 2020. Identifier NCT04373733. Available at: https://clinicaltrials. gov/c2/show/NCT04373733. Accessed on 10 August, 2020.
16. Clinical study for safety and efficacy of Favipiravir in the treatment of novel coronavirus pneumonia (COVID-19). Chinese Clinical trial registry. 2020. Identifier- ChiCTR2000029600. Available at: https:// www.chictr.org.cn/c2/show/ ChiCTR2000029600. Accessed on 10 August, 2020.
17. Yousefifard M, Zali A, Mohamed Ali K, Madani Neishaboori A, Zarghi A, Hosseini M et al. Antiviral therapy in management of COVID-19: a systematic review on current evidence. Arch Acad Emerg Med. 2020;8(1):e45.
18. Gao J, Tian Z, Yang X. Breakthrough: chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. Biosci Trends. 2020;14(1):72-3.
19. Cortegiani A, Ingoglia G, Ippolito M, Giarratano A, Einav S. A systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19. J Crit Care. 2020;57:279-83.
20. Liu J, Cao R, Xu M, Wang X, Zhang H, Hu H, et al. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. Cell Discov. 2020;6:16.
21. Chen J, Liu D, Liu L. A pilot study of hydroxychloroquine in treatment of patients with common coronavirus disease-19 (COVID-19). Journal of Zhe Jiang University (Medical Sciences). 2020;49(2):215-9.
22. Gautret P, Lagier J-C, Parola P. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open- label non- randomized clinical trial. Int J Antimicrob Agents. 2020;105949:105949.
23. Sarma P, Kaur H, Kumar H. Virological and clinical cure in COVID-19 patients treated with hydroxychloroquine: a systematic review and meta-analysis. J Med Virol. 2020;92(7):776-85.
24. Singh AK, Singh A, Singh R, Misra A. Hydroxychloroquine in patients with COVID-19: A Systematic Review and meta-analysis. Diabetes Metab Syndr. 2020;14(4):589-96.
25. Caly L, Druce JD, Catton MG, Jans DA, Wagstaff KM. The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. Antiviral Res. 2020;178:104787.
26. Kelleni MT, Nitazoxanide/Azithromycin combination for COVID-19: A suggested new protocol for COVID-19 early management. Pharmacological Res. 2020;157:104874.
27. Damle B, Vourvahis M, Wang E, Leaney J, Corrigan B. Clinical Pharmacology Perspectives on the Antiviral Activity of Azithromycin and Use in COVID-19. Clin Pharmacol Ther. 2020;10.1002/cpt.1857.
28. Bethesda. Randomized Comparison of Combination Azithromycin and Hydroxychloroquine vs. Hydroxychloroquine Alone for the Treatment of Confirmed COVID-19. ClinicalTrials.gov. National Library of Medicine (US). 2020. Identifier NCT04336332.
29. Bethesda. Hydroxychloroquine Plus Azithromycin Versus Hydroxychloroquine for COVID-19 Pneumonia (COVIDOC Trial) (COVIDOC). ClinicalTrials.gov. National Library of Medicine (US). 2020. Identifier NCT04345861.
30. Valuation the Effect of Ticoplanin in Patients With Coronavirus Disease. World Health Organization Database on clinical trials. Identifier IRCT20161204031229N3. Accessed on 27 May, 2020.
31. Rajendran K, Krishnasamy N, Rangarajan J, Rathinam J, Natarajan M, Ramachandran A. Convalescent plasma transfusion for the treatment of COVID-19: Systematic review. J Med Virol. 2020;10:1002/jmv.25961.
32. Bethesda. Convalescent Plasma as Therapy for Covid-19 Severe SARS-CoV-2 Disease (CONCOVID Study) (ConCoVid-19). ClinicalTrials.gov. National Library of Medicine (US). 2020. Identifier NCT04342182.
33. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost. 2020;18(5):1094-99.
34. Cui S, Chen S, Li X, Liu S, Wang F. Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. J Thromb Haemost. 2020;18(6):1421-24.
35. Klok FA, Kruip MJHA, van der Meer NJM. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res. 2020;S0049-3848(20)30120-1.
36. World Health Organization. Clinical management of severe acute respiratory infection when COVID-19 is suspected 2020. Available at: https://www.who. int/publications-detail/clinicalmanagement-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected. Accessed 28 May, 2020.
37. Thachil J, Tang N, Gando S, Falanga A, Cattaneo M, Levi M, et al. ISTH interim guidance on recognition

and management of coagulopathy in COVID-19. J Thromb Haemost. 2020;18(5):1023-6.
38. Bethesda. Coagulopathy of COVID-19: A Pragmatic Randomized Controlled Trial of Therapeutic Anticoagulation Versus Standard Care. ClinicalTrials.gov. National Library of Medicine (US). 2020. Identifier NCT04362085.
39. Bethesda. A Randomized Trial of Anticoagulation Strategies in COVID-19. ClinicalTrials.gov. Bethesda (MD): National Library of Medicine (US). 2020. Identifier NCT04359277.
40. Lu S, Zhou Q, Huang L, Shi Q, Zhao S, Wang Z, et al. Effectiveness and Safety of Glucocorticoids to Treat COVID-19: A Rapid Review and Meta-Analysis. medrxiv. 2020;04(17):20064469.
41. Tobaiqy M, Qashqary M, Al-Dahery S, Mujallad A, Hershan AA, Kamal MA et al. Therapeutic management of patients with COVID-19: a systematic review. Infection Prevention in Practice. 2020;100061.
42. Horby P, Lim WS, Emberson J. Effect of dexamethasone in hospitalized patients with covid-19: preliminary report. MedRxiv. 2020.
43. Xu X, Han M, Li T, Sun W, Wang D, Fu B, et al. Effective treatment of severe COVID-19 patients with tocilizumab. Proc Natl Acad Sci U S A. 2020;117(20):10970-5.
44. Roumier M, Paule R, Groh M, Vallee A, Ackermann F. Interleukin-6 blockade for severe COVID-19. medrxiv. 2020;04(20):20061861.
45. Bethesda. Tocilizumab in COVID-19 Pneumonia (TOCIVID-19). ClinicalTrials.gov. National Library of Medicine (US). 2020. Identifier NCT04317092.
46. Bethesda. Sirolimus Treatment in Hospitalized Patients With COVID-19 Pneumonia (SCOPE). ClinicalTrials.gov. National Library of Medicine (US). 2020. Identifier NCT04341675.
47. Zhou Y, Hou Y, Shen J, Huang Y, Martin W, Cheng F. Networkbased drug repurposing for novel coronavirus 2019-nCoV/SARSCoV-2. Cell Discov. 2020;6:14.
48. Hung IF, Lung KC, Tso EY, Liu R, Chung TW, Chu MY et al. Triple combination of interferon beta-1b, lopinavir-ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial. Lancet. 2020;S0140-6736(20)31042-4.
49. Leng Z, Zhu R, Hou W, Feng Y, Yang Y, Han Q, et al. Transplantation of ACE2- Mesenchymal stem cells improves the outcome of patients with COVID-19 pneumonia. Aging Dis. 2020;11(2):216-28.
50. Bethesda. Clinical Research of Human Mesenchymal Stem Cells in the Treatment of COVID-19 Pneumonia. ClinicalTrials.gov. National Library of Medicine (US). 2020. Identifier NCT04339660.
51. Bethesda. A Double-blind, Placebo-controlled Clinical Trial of Fluvoxamine for Symptomatic Individuals With COVID-19 Infection (STOP COVID). ClinicalTrials.gov. National Library of Medicine (US). 2020. Identifier NCT04342663. Available at: https://clinicaltrials.gov/ct2/show/NCT04342663?term=fluvoxamine&cond=Covid19&draw=2&rank=1.Accessed on 10 August 2020.
52. Bethesda. Vitamin C Infusion for the Treatment of Severe 2019-nCoV Infected Pneumonia. ClinicalTrials.gov. National Library of Medicine (US). 2020. Identifier NCT04264533.
53. Bethesda. Nitric Oxide Gas Inhalation Therapy for Mild/Moderate COVID-19 (NoCovid). ClinicalTrials.gov. National Library of Medicine (US). 2020. Identifier NCT04305457. Available at: https://clinicaltrials.gov/ct2/show/NCT04290858?term=nitric+oxide&cond=Covid19&draw=2&rank=8. Accessed on 10 August 2020.
54. Bethesda. NO Prevention of COVID-19 for Healthcare Providers (NOpreventCOVID). ClinicalTrials.gov. National Library of Medicine (US). 2020. Identifier NCT04312243.
55. Ang L, Song E, Lee HW, Lee MS. Herbal Medicine for the Treatment of Coronavirus Disease 2019 (COVID-19): A Systematic Review and Meta-Analysis of Randomized Controlled Trials. J Clin Med. 2020;9(5):E1583.
56. Bethesda. Clinical Trial of Mycobacterium w in Critically Ill COVID 19 Patients. ClinicalTrials.gov. National Library of Medicine (US). 2020. Identifier NCT04347174.
57. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med. 2020;46(5):846-8.
58. Deftereos SG, Siasos G, Giannopoulos G, Vrachatis DA, Angelidis C, Giotaki SG et al. The Greek study in the effects of colchicine in COvid-19 complications prevention (GRECCO-19 study): Rationale and study design. Hellenic J Cardiol. 2020;61(1):42-5.
59. Bethesda. Intravenous Aviptadil for Critical COVID-19 With Respiratory Failure (COVID-AIV). ClinicalTrials.gov. National Library of Medicine (US). 2020. Identifier NCT04311697. Available at: https://clinicaltrials.gov/ct2/show/NCT04311697?term=aviptadil&cond=Covid19&draw=2&rank=2. Accessed on 10 August 2020.
60. Bethesda. Safety, Tolerability, and Efficacy of Anti-Spike (S) SARS-CoV-2 Monoclonal Antibodies for Hospitalized Adult Patients With COVID-19. ClinicalTrials.gov. National Library of Medicine (US). 2020. Identifier NCT04426695. Available at: https://clinicaltrials.gov/ct2/show/NCT04426695?term=anti+spike+monoclonal+antibodies&cond=Covid19&draw=2&rank=2. Accessed on 10 August 2020.

Cite this article as: Mohapatra MM, Rajaram M, Dwivedi DP, Govindraj V, Upadhya P. An overview of treatment options for COVID-19. Int J Basic Clin Pharmacol 2020;9:1770-7.