Review Article

International Journal of Research in Pharmaceutical Sciences

Published by JK Welfare & Pharmascope Foundation Journal Home Page: www.ijrps.com

A search in the surge of treatment for COVID-19 patients: A narrative literature review

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Article History:

Received on: 05 Jul 2020
Revised on: 10 Aug 2020
Accepted on: 19 Aug 2020

Keywords:

2019-nCoV,
COVID-19,
novel coronavirus,
treatment,
nCoV therapies

Abstract

Today, our understanding towards COVID-19 pandemic is that it is contagious and based on the behaviour of the virus, the signs and symptoms of this viral resemble the viral infection like Severe Acute-Respiratory Syndrome-coronavirus (SARS-CoV) and Middle East Respiratory Syndrome (MERS-CoV). Currently, documented vaccines or drugs are not available for the treatment of COVID-19, SARS-CoV-2 viral infection. The main objective of this article is to compile the available literature on the treatment modalities for COVID-19, currently being advocated. Furthermore, there is no time to wait for evidence-based treatment, hence in such a scenario; an attempt has been made to collect the available scientific literature and understand the treatment of the disease with this insight. A MEDLINE-PUBMED search was performed in the surge of the treatment strategies for COVID-19 using the keywords "COVID-19", "nCoV", "novel coronavirus", "treatment of coronavirus" and "therapies". We have reviewed the multiple articles from recently published literature and various pre-print proofs from up-to-date journals. Based on the reviewed literature, various categories of drugs are under trial or have been tried for the treatment of nCoV infection, which are categorised as medications (anti-viral agents, chloroquine and hydroxychloroquine, ACE-2 inhibitors, etc.), immune therapy, traditional Chinese medicine, plasma exchange therapy, and blood purification therapy, etc. We attempted to go through the literature available for the treatment of COVID-19 and tried to compile it all together. Still, clinical trials are under process, and there are no evidence-based treatment strategies available to manage the cases of COVID-19 patients.

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ISSN: 0975-7538

DOI: https://doi.org/10.26452/ijrps.v11iSPL1.3088

Production and Hosted by

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INTRODUCTION

Across the world, there is a widespread infectious disease. This modern era has faced so many global issues in terms of either natural or man-made disasters nearly in a constant outbreak. Though not every outbreak is constant and reaches the pandemic level as the novel coronavirus. Currently, the world is facing a challenge from the outbreak of the novel coronavirus disease (COVID-19), which has spread from China, in December 2019, and became an alarming situation according to the World Health Organization (WHO). COVID-19, which is causing

severe respiratory tract infections in humans, is an enveloped, non-segmented, positive-sense ribonucleic acid (RNA) that belongs to the family Coronaviridae, order Nidovirales. The clinical symptoms of COVID-19 prominently look like viral pneumonia of SARS-CoV and MERS-CoV. Most of the COVID-19 cases have mild (81%) symptoms and are usually self-limiting with recovery in approximately two weeks. The onset of symptoms is usually nonspecific and may initiates with fever, dry cough, shortness of breath, and in a few cases, the involvement of gastrointestinal symptoms are also noted (Guan *et al.*, 2020). Nearly 20–25% of Covid -19 patients have developed diarrhoea, in comparison with MERS-CoV or SARS-CoV infection (Assiri *et al.*, 2013). Patients with systemic diseases of hypertension, heart diseases, cerebrovascular diseases and diabetes are at higher risk for this infection (Guan *et al.*, 2020), which is similarly found in MERS-CoV infection. Swab tests from the nasopharyngeal and oropharyngeal region have become standard diagnostic criteria for COVID-19 infection by using Reverse-transcription polymerase chain reaction (RT-PCR), real-time RT-PCR (rRT-PCR) and reverse transcription loop-mediated isothermal amplification (RT-LAMP), as founded by the China National Health Commission. In cases of negative results from the above tests of RT-PCR, any patients with a history of fever, sore throat, fatigue, coughing, or dyspnea and is also coupled with a history of recent exposure to COVID-19 positive patient, typical chest computerised tomography (CT) has to be performed (Xie *et al.*, 2020).

To condense the spread of this pandemic infection, preventive measures like isolation, quarantine, social distancing, and community confinements have been implementing (Wilder-Smith and Freedman, 2020). Individuals or family members with a history of close contact with the infected person are priorities for the detection of COVID-19 as most of them may be asymptomatic, and are more threatening to the community. A key route for transmission of this infection is found to be respiratory droplets and close contact. Also, literature states that 2019-nCoV RNA was noticed in the faeces of some confirmed patients, which is indicative of likely transmission through the faecal-oral route. This specifies the strong contagion nature of COVID-19 infection with high morbidity and mortality rates. Many researchers are going on to discover drugs with high-efficiency and low toxicity (Guan *et al.*, 2020). Many institutes randomised drug trials are still going on, but there is no current evidence to recommend any specific treatment protocol for patients with a suspected or confirmed COVID-19 infection. None of the known therapies is currently approved for COVID-19, although many trials have been going on so far, multiple investigations with treatment protocol are underway all around the world presently. The objective of this article is to compile the available literature on COVID-19, regarding the treatment currently being advocated. Further, there is no time to wait for evidence-based treatment modalities, hence in such a scenario; an attempt has been made to collect the available scientific literature and to understand the treatment of the disease with this insight.

MATERIALS AND METHODS

A MEDLINE–PUBMED database was used to review the literature using the keywords ”COVID-19”, ”nCoV”, ”novel coronavirus”, and ”treatment of coronavirus” and ”therapies till 07 April 2020. We have reviewed the multiple articles from recently published literature and various pre-print proofs from up-to-date journals and the full-text of the relevant cross-references. The articles published in other than English language and irrelevant articles with inadequate information were not included in the review.

RESULTS AND DISCUSSION

Based on the articles reviewed, various categories of drugs, their mechanism of action, testing mechanism, and benefits in the treatment of COVID-19 have been summarised in Table 1.

There are several inconclusive clinical issues and dilemmas in the clinical management and proper treatment strategy of COVID-19. Here, we attempted to summarise available drugs and treatment therapy for the management of COVID-19.

Anti-viral agents

Currently, few anti-viral drugs which are Nucleoside analogues, Protease inhibitor, and broad-spectrum category of drugs are under trials with no specific evidence of anti-SARS-CoV-2 treatment as it replicates by RNA dependent RNA polymerase. Nucleoside analogues like Remdesivir are an adenosine analogue, which integrates with nascent viral RNA chains and results in premature termination. Because of similar structure between 2019-nCoV and MERS-CoV coronavirus, Remdesivir has shown a great potential of anti-2019-nCoV as reported in the first case of new coronavirus pneumonia treated in the United States, where patient’s symptoms have improved significantly after being given the intravenous injection of Remdesivir for one day (Holshue *et al.*, 2020). Subsequently, phase II clinical trial by

Table 1: Drugs used in the treatment of COVID-19 patients

Group of Drugs	Mechanism of Action	Tested	Benefit in COVID -19
I. Antiviral agents			
Ribavirin	By inhibiting enzyme protease	Studies conducted in-vitro and on animals.	Requires high doses which are beyond human therapy.
Favilavir	By inhibiting RdRp (RNA dependent RNA polymerase)	In-vitro studies	Mixed efficiency and has shown positive response in China and Japan in COVID-19 patients.
Type-1 Interferons	By the secretion of inflammatory mediator cytokines which promote the activation of the adaptive immunity.	In-vivo studies	Doubtful if used as the only drug. Mixed efficiency was noted against SARS-CoV and MERS-CoV. Interferon-beta is better in COVID-19 patient treatment, and results are best seen in the early stages of the infection.
Lopinavir (LPV)	By inhibiting enzyme protease	Studies conducted in-vitro and on animals	Nil or doubtful, if used as the only drug.
Ritonavir	By inhibiting enzyme protease	Studies conducted in-vitro and on animals	Nil or doubtful, if used as the only drug.
Combination of LPV+ Ritonavir	By inhibiting enzyme protease	Studies conducted in-vitro and on animals	Nil or doubtful, if used as the only drug.
Remdesivir	By inhibiting the synthesis of RNA	In-vivo studies (limited)	Preventive & therapeutic.
II. Anti-Malarial drugs (Chloroquine and Hydroxychloroquine)	Altering the intracellular pH and increase in endoplasmic reticulum stress, leading to abnormal viral protein formation.	In-vitro and Human studies	Preventive & therapeutic.
III. Immune-therapy (Convalescent plasma transfusion, monoclonal anti-bodies, vaccines etc.)	Neutralises anti-body titers Anti-bodies are formed which recognise and block the spike protein that the virus uses to enter human cells.	Animal studies	Preventive & therapeutic.

Continued on next page

Table 1 continued

Group of Drugs	Mechanism of Action	Tested	Benefit in COVID -19
IV. Ibuprofen and other NSAID's	Non-selective COX-inhibitor	Nil	Harmful, instead, paracetamol can be used for symptomatic relief.
V. Anti-hypertensives (ACE-2 inhibitors)	S-glycoprotein conformational changes which allow proteolytic digestion by host cell enzyme proteases and leading to disruption of the virion.		Preventive & therapeutic.
VI. Corticosteroids	Anti-inflammatory action	Nil	Harmful effect
VII. Emetine and other Ipecac alkaloids or analogues	Acts as 5-HT3 antagonists	In-vitro studies for SARS and MERS-CoV. Lacking for COVID-19.	Higher concentration in the lungs may be useful for respiratory symptoms. Inhibits SARS and MERS-CoV
VIII. Interleukin-6 receptor (IL-6R) antagonist (Tocilizumab)	By blocking the signal transduction pathway of IL-6.	Clinical trial	Advisable for critically ill COVID-19 patients in significantly elevated IL-6.
IX. Traditional Chinese Medicine (TCM)	Unknown but maybe ACE-2 receptors antagonist.	Not available	Therapeutic effect.
X. Blood purification therapy	Control the cytokine storm.	Not available	Nil or doubtful.
XI. Therapeutic Plasma exchange therapy	By eliminating inflammatory cytokines, and by stabilising endothelial membranes, and re-setting the hypercoagulable state.	Not available	Promising results but still requires more data to validate.

the University of Nebraska Medical Centre, and a phase III clinical trial by the China-Japan Friendship Hospital were performed. The results of these clinical trials are mixed reviews and revealed significantly no clinical benefits (Wang *et al.*, 2020). Ribavirin is a broad-spectrum anti-viral guanosine analogue with a mechanism of interacting with virus RNA dependent RNA polymerase to inhibit RNA synthesis. In vitro experiments signifying that significant effective dose is not within the range of human therapies, the symptoms of MERS could be improved by the combination of drugs Ribavirin and type I interferons in a primate model, further clinical trials are still going on.

Another category of drug, Lopinavir (LPV)/ Ritonavir is Protease inhibitor, which has a mechanism of inhibiting the enzyme protease activity of coronavirus in vitro and animal studies. Based on the information accumulated for the SARS and MERS outbreak, protease inhibitors have indicated as a potential treatment option for COVID- 19 (Yao *et al.*, 2020a). The combination of Remdesivir and Interferon-b (IFNb) as prophylactic and therapeutic agents showed superior anti-viral activity than the LPV/Ritonavir in in-vitro studies. Also, treatment with Remdesivir has shown improvement in pulmonary function and reduction in viral lung loads as in contrast to LPV/RTV-IFNb. Thus, altogether results showed Remdesivir has a more potent effect than LPV/RTV-IFNb (Sheahan *et al.*, 2020). Assessment of the efficacy and safety of these anti-viral agents are currently under clinical trials only.

Chloroquine (CQ) and Hydroxychloroquine (HCQ)

The potential efficacy of CQ and HCQ are widely in use as off-label, for the treatment and prevention of COVID-19. The in-vitro activity of these drugs has recommended their use in a clinical setting against COVID-19 at the molecular level (Yao *et al.*, 2020b). However, with the in-vitro activity of these drugs, it should not be interpreted as proof of clinical efficacy against COVID-19. Two studies on human trials are available; both have shown very promising results. The very first was, a Chinese study, reported that a dose of 500mg twice a day, when used in 100 patients, the effects of CQ were found to be superior in terms of duration of symptom, improvement in radiological sign and the most critical being in achieving a virus-negative seroconversion without severe side effects) as compared to the control group (Gao *et al.*, 2020). An excellent second human study which is a non-randomised trial, n=36 was conducted in France (Gautret *et al.*, 2020) with HCQ alone and HCQ in combination with azithromycin, the study showed that plain HCQ was less effective but when used along with azithromycin showed a synergistic effect. The results showed

1. virological clearance which is measured by PCR during post inclusion period around day 6 of primary outcome with HCQ alone & combination of HCQ with Azithromycin in COVID-19 & control subjects was 100%, 57.1% and 12.5% respectively ($p < 0.001$).
2. an infected patient can be converted to a seronegative in 6 days. Few drawbacks of the study are a small sample size, a dropout of six patients with limited follow-up, apart from the non-randomised and open-label nature of the trial.

Moreover, CQ and HCQ may cause harm, with narrow therapeutic windows, and many side effects, including cardiac toxicity (QT prolongation, ventricular arrhythmia, etc.), which may be particularly problematic in the elderly with COVID-19 (Nord *et al.*, 2004). The off-label use of CQ and HCQ to treat or prevent COVID-19 must be cautious, considering its potential severe toxicities. Before the availability of robust data from RCTs, they are highly recommended that off-label use of medications to treat COVID-19, including CQ or HCQ, be accompanied by careful observation for potential toxicity (Keshtkar-Jahromi and Bavari, 2020).

Immune-therapy or Vaccines

Immune-therapy aims to improve the host adaptive and innate immune response to effectuate long-lived elimination of diseased cells. These therapies can be categorized into *passive* including adaptive and antibody-based and *active* including vaccine therapy and allergen-specific approaches. It is presumed that plasma collected from COVID-19 convalescent patients may provide therapeutic relief as the number of COVID-19 cases escalating steeply worldwide. Previous studies regarding plasma therapy could reduce mortality in other various viral respiratory diseases including SARS-CoV related pneumonia are still lacking. It may be challenging in an acute crisis to identify, collect, qualify, and prepare plasma from convalescent patients with adequately to neutralize antibody titres. Careful clinical evaluation should be performed at an early stage to proceed with the plasma transfusion to prevent mortality. Studies are suggesting that convalescent plasma can be transfused as early as in due course of the disease with a high risk of subsequent deterioration (i.e. age above 70 or dependence on oxygen with a baseline oxygen saturation of less than

94%) (Tiberghien *et al.*, 2020). It has been suggested that plasma transfusion can be initiated by day 5 of infection and the two units of 200 to 250ml of plasma, in patients weighing 50 to 80kg are advisable (Woelfel *et al.*, 2020). Serious adverse reactions are not observed but the safety and efficacy of convalescent plasma transfusion in SARS-CoV-2-infected patients should be studied within the context of a well-designed clinical trial (Zhang *et al.*, 2020a). Studies have reported that CR3022, SARS-CoV specific human monoclonal antibody can effectively bind to 2019-nCoV RBD and it has the potential to be used alone or in combination with other neutralizing antibodies for the prevention and treatment of 2019-nCoV infection (Tian *et al.*, 2020). Vaccines help a person to generate an immune response against infection without first being exposed to the pathogen. The structure of SARS-CoV-2 has S protein, and vaccines are being developed to target this spike glycoprotein or S protein (Du *et al.*, 2009). Team based in China, have studied about two rhesus macaques (Macaca mulatta) had recovered from SARS-CoV-2 infection on 14 March 2020, which caused them only mild illness. Later it was noticed that, there is no re-infection when exposed to virus for the second time over a period of four week after their initial exposure. Studies by researchers are going for similar evidence for humans to react. Later, on 24 Febuary 2020, Moderna vaccine which consists of an RNA molecule by Moderna Company was announced. This company's experimental mRNA COVID-19 vaccine, also known as mRNA-1273, is being ready for human trials. Similarly like other SARS-CoV-2 vaccines, it is designed to modulate the immune system in forming antibodies that recognize and block the spike protein, so that virus fails to integrate with the human cells. Researchers reported that by injecting Inovio's vaccine - a DNA molecule with S-protein into mice and guinea pigs has produced both antibodies and T-cells against the virus. Also,thers is a report for successful development of a new oral SARS-CoV-2 vaccine by Tianjin University, which utilises food-grade safe Saccharomyces cerevisiae as a carrier to targets the S protein.

Ibuprofen and other NSAID's

Treatment with NSAID's in young patients suffering from COVID-19 with no underlying health problems had developed severe symptoms in the early stage of the disease in France. This observation prompted the advice against the use of ibuprofen in this condition (Day, 2020). World Health Organization (2020) first recommended against using Ibuprofen in COVID-19, however, went back against its advice and updated its advice soon to say that "based on currently available information, WHO does not recommend against the use of Ibuprofen". A letter to *The Lancet* suggested that harmfulness of usage of drug Ibuprofen's in COVID-19 is due to its effect on an enzyme in the body called angiotensin-converting enzyme-2 (ACE-2)–although this has not proven yet. Despite no evidence to suggesting the ibuprofen worsens symptoms, at the moment, the NHS only recommends taking paracetamol for COVID-19 symptoms, according to *Updated. WHO 2020*. There is no conclusive evidence for / or against the use of NSAIDs in the treatment of COVID-19 patients.

Anti-hypertensives (ACE-2 inhibitors)

Studies noted that the Angiotensin-Converting Enzyme-2 (ACE-2) which is expressed in type-2 alveolar epithelial cells and endothelium; is known to act as the receptor for SARS CoV-2 as well as other coronaviruses. The mechanism behind this is, S-glycoprotein that is present on the surface of coronavirus binds to ACE-2 and leads to a conformational change in this protein which allows proteolytic digestion by host cell proteases (TMPRSS2) and ultimately leading to internalisation of the virion (Chen *et al.*, 2020; Hoffmann *et al.*, 2020). As it is noticed that, ACE-2 is the binding site for SARS CoV-2, its blockade is thought to be beneficial in preventing/treating this infection. A retrospective analysis done on patients with ACE inhibitors showed a reduced mortality rate and also a reduction in the requirement for endotracheal intubation for patients with viral pneumonia (Henry *et al.*, 2018). It is presumed that ACE-2 over-expression is most likely to be part of a defensive mechanism, and in the case of COVID-19, it might be induced by the severe down-regulation caused by SARS-CoV2 binding. Analysis of clinical records of SARS-CoV2 patients should be performed meticulously to retrospectively investigate the role of antihypertensive therapy and other confounders at the time of hospital admission (Zhang *et al.*, 2020c).

Corticosteroids

Studies have shown that administration of corticosteroids in the acute phase of infection may alleviate early pro-inflammatory response; however, prolonged administration may enhance the viral replication (de Simone and Mancusi, 2020). A recent study conducted on 41 positive COVID-19 patients showed the suppression of lung inflammation after administrating the corticosteroids. Later, current WHO interim guidance (released 28 January 2020) contradicted of the use of corticosteroids unless indicated for another reason, as the

clinical outcomes from the use of corticosteroids do not support the coronavirus and similar outbreaks. A retrospective observational study of critically ill 309 patients with MERS, showed the mandate for mechanical ventilation, vasopressors, and renal replacement therapy when corticosteroids are administered (Arabi *et al.*, 2018). There is no as such exceptional reason of benefit for the use of corticosteroids in COVID-19 patients, and therefore, such treatment may be harmful. As the evidence is not proven, so many clinical trials are undergoing to evaluate its efficacy in COVID-19 patients.

Emetine and other ipecac alkaloids or analogues

Many drugs have been tried for the treatment of COVID-19, including anti-amoebiasis drugs like Emetine and Ipecac alkaloids or analogues. Studies showed that the relative effective concentration (EC50) of Emetine towards the coronaviruses in comparison with *Entamoeba histolytica*, can be used much efficiently than against amoebiasis. But the adverse effect of cardiac toxicity should be considered and it the recommended, the dose used to treat coronavirus is one fifth to one-tenth, of that used for amoebiasis (0.1–0.2 mg/kg, intramuscularly; maximum 6-12 mg/day). These lower doses show effectiveness by maintaining its anti-viral activity along with significantly minimising or eliminating cardiac toxicity and nausea. Moreover, there is no evidence for the administration and benefits of using this drug, at which phase of the disease process, not mentioned anywhere. I -vitro studies are lacking in terms of their sensitivity against COVID-19 (Bleasel and Peterson, 2020). In conclusion, the use of these drugs as an anti-viral should be considered as one of the treatment options, but the existing literature does not provide any conclusive evidence.

Interleukin-6 receptor (IL-6R) antagonist Tocilizumab

It is noted from large of data that, mild to severe cytokine storms in COVID-19 patients might be a significant cause of death as CD-8 T cells are decreased, and the inflammatory cytokines such as IL-6, IL-10, IL-2 and IFN-γ increased in severe cases, in the peripheral blood. Subsequently, treatment of this cytokine storm recusing severe COVID-19 patients. Peripheral flow cytometry analysis showed a decline in CD-4 and CD-8 cell count in patients with bilateral diffuse alveolar injury, but an increase in Th17 cell proportion is found (Xu *et al.*, 2020). These Th17 cells are helper T cells, which are differentiated from Th0 cells when stimulated by IL-6 and IL-23 (Miossec and Kolls, 2012). As Interleukin-6 (IL-6) plays a vital role in cytokine release syndrome (CRS) blockage of this signal transduction pathway is probable a new method for the treatment of severe patients. When tocilizumab is administered to patients, rapid reduction in the fever and oxygen requirement along with improvement in clinical symptoms without any adverse effect was noted. As tocilizumab blocks the IL-6 signal transduction pathway effectively, and hence, researchers are appealing that tocilizumab is likely to be an effective drug for COVID -19 patients (Zhang *et al.*, 2020b). A clinical trial of Tocilizumab administration done for a small group in China (Clinical trial registration ID: ChiCTR2000029765) has shown promising efficacy. Against severe or critical COVID-19. Therefore, CRS occurs in many patients with severe COVID-19, IL-6 is the crucial molecule of CRS, so IL-6R antagonist Tocilizumab may be an essential drug to save patients' lives. Still, studies are lacking in the evidence-based support for this drug against COVID-19.

Traditional Chinese Medicine (TCM)

China's government has recommended using routine treatment of anti-viral and antibiotic drugs, nutritional supplements and mechanical ventilation, if necessary, along with the traditional Chinese medicines. Many herbs have been used for the treatment of COVID-19 patients, and these are divided into clearing heat, eliminating dampness and detoxification depending upon their mechanism of action. The Chinese herbalists prescribe these herbs after a thorough examination by using Chinese diagnostic patters. Some of the herbal formula used is San Wu Huangqin decoction, Lianhuaqingwen Capsule and Yinhuapinggan granule possess anti-viral properties and may help to decrease the damage to lung epithelium (Li *et al.*, 2020).

Even molecular docking has been performed to find out natural compounds. Hence, they proposed the five herbs, including Scutellarin, Baicalin, Hesperetin, Nicotianamine, and Glycyrrhizin which have the potential to target against the ACE-2 receptor and also exert anti-virus effects. Some herb, named Toujie Quwen granule was used to treat 50 mild symptoms COVID-19 patients, and it is showed to improve in overall symptoms including a reduction in fever and tendency to reduce pneumonia after a week, without any severe complications.

A study done on 214 patients consuming a 3-day course of treatment, showed 60% of improvement significantly clinical and radiological symptoms and 30% had smooth symptoms without any exacerbation (Li *et al.*, 2020). But the limitations of using these drugs is unclear evaluation indicators, lack of long-term efficacy and no high-quality evidence of the safety of drugs, no comparison studies with con-

trol groups were published. Because of the lack of proper evidence, these drugs are still under the process of investigation to be useful for the treatment of COVID-19 (Zhang, 2020).

Blood purification therapy

It has noted from the data that, cytokine storm or pathogenic anti-bodies after three weeks of the onset of COVID-19, which in turn correlated with the severity of the disease. Monitoring inflammatory mediator and anti-bodies are essential factors in patients with viral fever or abnormal coagulopathy. In the early phase of diseases, expeditious control of the cytokine storm would result to be beneficial to selective patients, and therefore, blood purification therapy would be useful. Although randomised trial data is lacking in this area and the efforts from multi-disciplinary units should be made so that the availability of blood purification therapy to patients is maximised (Ma *et al.*, 2020).

Therapeutic plasma exchange (TPE) therapy

Following the corona virus infection, host response involved a complex series of interaction such as cytokine storm, inflammation, endothelial dysfunction and pathologic coagulation and these have been described clearly by many investigators.This therapy uniquely offers the benefits by eliminating the inflammatory cytokines, by stabilizing endothelial membranes and re-setting the hypercoagulable state at multiple levels.

Trials performed as adjunct therapy or standalone, reviewed retrospectively, results are very encouraging and further more trial are needed to show promising results, particular in today's situation and researchers proposed that more randomized trials to be designed to investigate further (Keith *et al.*, 2020).

After, all the treatment strategies have been discussed here, the WHO solidarity trial, which compared four good COVID-19 regimens consisting of Remdesevir, Chloroquine, Lopinavir–Ritonavir, and Lopinavir–Ritonavir plus beta-Interferons. All these drugs were compared with the standard of care with mortality as the primary endpoint (Kupferschmidt and Cohen, 2020).

CONCLUSION

We have attempted to go through the data available at present and tried to compile it all together. Various clinical trials are undergoing, and no evidence-based treatment strategies available for the treatment of COVID-19 infection.

Funding support

The authors declare that they have no funding support for this study.

Declaration of conflict of interest

The authors declare that they have no conflict of interest for this study.

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