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Pharmacotherapy of COVID-19

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Abstract

Corona virus disease is a pandemic that first reported from Wuhan City of China and later spread to other parts of the world. It is a highly contagious disease though the mortality rate is less compared to other corona virus disease seen in the last two decades. Most of the infected individuals are asymptomatic and goes unnoticed. However, 5-10 percent requires hospitalization and 1-3 percent may need critical care management. There is no proven drug for the disease, but many existing drugs are repurposed for this disease with variable degree of success. Few clinical trials are completed and some are still undergoing. An attempt is made to give an overview of various drugs available at present for the management of COVID-19 and in various stages of their development.

Keywords: Corona Virus Disease; Pharmacotherapy; Cytokine Storm

Introduction

COVID-19 is the third corona virus disease in the last two decades, which emerged from the Wuhan city of China in December 2019 and later spread to other countries. As of 7th August 2020 there are 19,303,517 corona virus cases. Out of this, 12,393,763cases recovered and 6,191,241 cases died, and 6,191,241 active cases. Out of 6,191,241, about 6,126,022 (99%) are mild and 65,219 (1%) are critical [1]. The present corona virus disease is having low mortality compared to other two corona virus disease viz. the severe acute respiratory syndrome (SARS) corona virus outbreak in 2002 and the Middle East respiratory syndrome (MERS) corona virus outbreak in 2012. However, this virus is highly contagious hence spread to people all over the world in just six months' time which resulted in much higher number death due to COVID-19 [1]. The CODD-19 was declared as community health disaster and later as pandemic in the month of January and February respectively.

The causative agent is SARS-CoV2 which comes from the large family corona virus. It is diagnosed by laboratory tests such as a) Antigen test - PCR for viral RNA and b) Antibody tests-IgM and IgG. However, the test result should be correlated with clinical signs and symptoms before interpreting the results. The presenting symptoms are fever, malaise, headache, dyspnea, cough, sore throat, myalgia, nose block. Rare presentation may include altered taste, anosmia and diarrhea. Lymphopenia, increased prothrombin time, increased D-Dimer and LDH are seen. Abnormal chest imaging elevated Transaminases, Low-normal procalcitonin and elevated inflammatory markers (CRP, IL-6, Ferritin), Troponin, NT-proBNP elevation are also seen depending on the progress of the disease.

Management of COVID-19

There are no approved drugs or other therapeutics at present for COVID-19 for either prophylaxis or treatment. However, some drugs are tried and few are undergoing

clinical trials for COVID-19.

Antimcirobials with additional Anti-Inflammatory Activity: Chloroquine, Hydroxychloroquine (HCQ) and Azithromycin

Hydroxychloroquine and chloroquine have some anti-inflammatory activity and used mainly in malaria. Lupuserythematosus and rheumatoid arthritis [2]. Both have been shown to kill the COVID-19 virus in in-vitro study. There was faster improvement when either of them are given in critically ill COVID-19 patients with severe symptoms. The macrolide antibiotic Azithromycin is a routinely used antimicrobial for streptococcal sore throat and bacterial pneumonia. So far it was not used for viral infections. It was thought that azithromycin might be useful in hyperactive immune response to the COVID-19 infection. These drugs, alone or in combination with HCQ, was tried in COVID-19 viral infection with variable success. However, of late, the studies did not support this view and the mortality might have increased due to cardiac arrhythmia. However, the medical fraternity questions the authenticity of these studies

However, WHO on July 4th recognized the findings from the Solidarity Trial's International Steering Committee to stop the trial's hydroxychloroquine and lopinavir/ritonavir arms [2].

Convalescent Plasma

The plasma of patient recovered from COVID-19 can prevent spike protein from binding to ACE2 receptor of alveolus. When patients improve from COVID-19, their blood contains antibodies, which are produced to fight the coronavirus, and hence they recover. This method of treatment is also followed earlier for conditions such as measles, polio, chickenpox, including SARS. Convalescent plasma is given by transfusion to a patient of COVID-19 [3]. However, there are reports of some success of plasma treatment but there no randomized trials conducted to prove this. It is not clear when this plasma has to be administered during the course of the disease. Use should be avoided in patients with IgA deficiency or immunoglobulin allergy.

Low Molecular Weight Heparin

Increased coagulability is observed in COVID-19 and the patient will have a procoagulant state. There is considerable increase in D-dimer and prothrombin level and decrease in fibrinogen level. Periodic checking of their level has role in clinical judgement. Both low molecular weight heparin and unfractionated heparin [UFH] are tried in COVID-19 patient with variable results [4,5]. UFH has many issues including monitoring, it may still be preferred if kidney function is impaired [6].

Interferon Alfa-2b

Interferon Alfa-2b is used to treat several virus infections and. It is made up of proteins similar in characters to that of naturally produced interferon. Interferon Alpha-2b increases individuals' natural body defense mecahisnsm by different ways. Hence, it may help in patients with COVD-19 [7].

It was observed that interferon alpha-2b has reduced the time required to viral clearance in the upper respiratory tract and rapid reduction in inflammatory reaction all over the body. In many countries, the nebulized interferon alfa-2b formulations are in use. However, in the United States of America it is approved only for clinical trials [8].

Protease enzyme inhibitors

Lopinavir and Ritonavir are tried for COVID-19 infection. However, the available data is insufficient to support the use of them to treat COVID-19 [9].

Remdesivir

Remdesivir has secured a definite place in the management of COVID-19 because of the similarities between COVID-19 virus and SARS and MERS virus. Preclinical study suggested that remdesivir may inhibit the replication and spread of viruses inside the body. All the three viruses have a common target which is an enzyme that is needed for viral replication. Since remdesivir is drug already proved to inhibit that enzyme in both SARS and MERS viruses, it is reasonable to argue that it is likely to work against COVID-19 virus [10].

Data from a multinational, randomized, placebo-controlled trial (the Adaptive COVID-19 Treatment Trial [ACTT]) strongly supports the beneficial effect of remdesivir in COVID-19 patients. The median recovery time of COVID-19 patients in remdesivir treated group is reduced by four days when compared to placebo group [10].

Corticosteroids

Inhaled corticosteroids have been shown to suppress SARS-CoV-2 replication in in vitro study. Thus, corticosteroids have direct antiviral activity in addition to anti-inflammatory activity. Inhaled ciclesonide has been tried for treating Covid-19 [11]. Inhaled budesonide is also used in few countries. Systemic dexamethasone can be used for the treatment of COVID-19 in patients who require supplemental oxygen. Alternative glucocorticoids such as prednisone, methylprednisolone, or hydrocortisone can be used if dexamethasone is not available [12-14]. However, it is recommended not to use dexamethasone for patients who do not require oxygen supplementation. Because of the potent anti-inflammatory activity of corticosteroids, they may be

helpful in preventing multiorgan failure due to widespread inflammatory reaction during COVID-19.

Tocilizumab (IL-6 Inhibitor)

Interleukin-6(IL-6) is a pro-inflammatory cytokine. This is usually produced by lymphocytes, monocytes, and fibroblasts. Coronavirus infection prompts synthesis of dose-dependent production of IL-6 from respiratory epithelial cells. IL-6 plays an important role in severe systemic inflammatory responses due to COVID-19 infection [15]. The cytochrome storm seen in-patient with COVID-19 infection is associated with increased blood levels of IL=6, C-reactive protein, D-dimer and ferritin [16-18]. Tocilizumab, intravenously or subcutaneously, might reduce the risk of invasive mechanical ventilation or mortality in severe COVID-19 pneumonia [19]. The adverse effects associated with tocilizumab include increased liver enzyme levels.

Vitamin C supplementation

Vitamin C is routinely given for sepsis and ARDS in intensive care units. In COVID-19 patients, sepsis and ARDS are most common disorders leading to intensive care unit admission, ventilator support, or death. In view of this vitamin C is tried in patients with severe COVID-19 infections [20]. No data is available regarding the role of vitamin C in prevention of COVID-19 infection.

Zinc supplementation

High-level intracellular zinc inhibits viral replication [21]. In vitro studies have confirmed the cytotoxic effect of zinc by inducing apoptosis [22]. Zinc sulphate (220mg twice daily) alone or in combination with hydroxychloroquine for prophylaxis and management of COVID-19 is currently being evaluated.

Conclusion

The ongoing pandemic namely COVID-19 is highly contagious disease usually spread by droplet infection. At present, we do not have any approved medication, but many approved drugs for other condition are being used or undergoing clinical trials with variable degree of outcome. It may take some time before we get an approved drug or a vaccine for controlling COVID-19.

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