



INSIGHT ON POTENTIAL PHARMACOLOGICAL TREATMENT OPTION FOR COVID-19: A SYSTEMATIC REVIEW

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ABSTRACT Covid 19 has already being named as pandemic by the WHO affecting more than 1 lakh people worldwide and affecting more than 100 countries in a short span of time. It is very crucial to prepare the healthcare system worldwide to prepare for the global response to come. Globally about 3.4 % of reported COVID-19 cases have died according to WHO as of March 3. People at risk are those having underlying medical conditions like diabetes, heart diseases, hypertension, obese individuals and also older adults. So we have took up a systematic review to provide a current clinical scenario in the management of COVID-19. This review brief up the current pharmacological approach, treatment strategies and the drugs in pipeline to provide a summary of current clinical experience and treatment guidance for this novel corona virus.

KEYWORDS :**INTRODUCTION**

As Covid 19 continues its devastation across the globe, many scientists and health researchers are investigating various options to come up with a remedy which can fight covid 19. Initially identified in Wuhan, province of china, it is fast spreading across the globe. So this is a gentle attempt from our side to provide genuine information for the health workers and also for the public about the diverse potential pharmacological therapy acting against covid 19. Corona viruses are a group of enveloped, positive sense, single stranded RNA viruses. The incubation period of the virus is reported to be 5 days or may be as long as 14 days. The virus can cause respiratory, intestinal, hepatic or neurological disease of varying severity. The clinical manifestations are not very specific and in a majority of patients there is fever and dry cough and about one third of patients experiencing shortness of breath.

As of April 28, 2020 a total of 202733 deaths worldwide and 2959929 confirmed cases¹. In India 22629 active cases and 1007 deaths have been reported. Currently there are no verified antiviral drug therapy which is specific to covid 19 and no vaccines are currently available. Only preventive measures like social distancing, hand hygiene, use of masks, and limitation of movements are successful in breaking the chain of transmission.

1. Chloroquine and Hydroxychloroquine

No other drug have been recently debated like hydroxychloroquine and chloroquine in context of covid 19 treatment especially after announcement from the highest scientific body of India (ICMR) and also from the president of the USA. They have created a positive perception on the effectiveness of hydroxychloroquine among common public. This is a matter of concern for the health department as people may start widespread self-medication. In vitro studies shows good response in the antiviral activity of both drugs against SARS-CoV.

Chloroquine and hydroxychloroquine have proven efficacy in prevention and treatment of malaria since long time. Some other therapeutic uses include chronic inflammatory diseases including systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). These drugs act by increasing the pH of endosomes and prevent the interaction of virus with host cell. Virus binds to target cell through ACE-2. It prevents the binding of virus to ACE-2 by reducing the glycosylation of ACE-2.

No high quality studies exists for the efficacy of chloroquine/hydroxychloroquine treatment of SARS or MERS. A news briefing from china reported chloroquine was successfully used to treat covid19 resulting in improved radiological features and enhanced viral clearance. But the clinical data and outcomes have not yet been published. A study conducted in 63 patients of covid 19 at sinai grace and henry ford hospital in Detroit (USA). 32 patients received hydroxychloroquine with supportive treatment and 31 patients received only supportive treatment. Group of patient who have received hydroxychloroquine required more respiratory support than

the other group. Therefore according to some "HCQ not the magic drug you are waiting for". However ICMR has made guidelines for the prophylactic use of HCQ for high risk population.

Hydroxychloroquine is used in the dose of 400mg twice a day on day1 and then 200mg twice a day upto 5 days. Chloroquine phosphate is used in the dose of 1000mg on diagnosis and then 500 mg after 12 hours followed by 500 mg twice a day up to 5 days. Because of long elimination half-life, the duration of therapy is not recommended beyond 5 days. Chloroquine and HCQ are relatively well tolerated however both agents can cause serious adverse effects including QT prolongation, hypoglycaemia, neuropsychiatric effect and retinopathy. Baseline ECG is required before starting these drugs. There is an increased risk of ventricular arrhythmia when HCQ is used with amiodarone or moxifloxacin.³ A blanket recommendation for chemoprophylaxis in the absence of proper evidence might be controversial. Therefore for deciding efficacy, optimum dose and duration of therapy for covid 19 more extensive studies are required.

2. Lopinavir/ritonavir and other antivirals**a. Lopinavir/ritonavir**

Lopinavir/ritonavir, a fixed dose combination antiretroviral sold under the brand name Kaletra, has been approved by CDSCO. WHO has mentioned this combination as an agent that can be tried in covid 19. There are insufficient data about the In vitro activity of these drugs against SARS-CoV. Lopinavir/ritonavir is an FDA approved oral combination for treating HIV, which has also displayed in vitro activity against other novel corona viruses via the inhibition of 3-chymotrypsin like protease. No published SARS-CoV2 in vitro data is available for lopinavir/ritonavir. Some early report claiming the advantage of using lopinavir/ritonavir are small retrospective, non-randomised cohort studies, so it is very difficult to validate the research outcomes.

So the current data suggests a limited role for lopinavir/ritonavir in covid19 treatment. Dose is lopinavir (400mg) + Ritonavir (100mg) twice a day for 14 days or for 7 days after the patient become asymptomatic. Oral and liquid formulations are available. It has been tried with interferon alpha, interferon beta 1b or ribacvarin. However Chinese medical researchers (Bin cao et al)⁴, published in New England Journal of Medicine on march 18, concluded that lopinavir/ritonavir didn't deliver any observed benefits in a randomised controlled trial of 199 SARS CoV infected patients.

b. Remdesivir

This antiviral drug has shown in vitro activity against SARS-CoV2. It inhibits the viral replication. Researches have shown promising result during the Ebola virus outbreak. Dose is 200 mg loading dose followed by 100 mg daily infusion. The drug acts by premature termination of viral RNA transcription. It has been found to reduce pulmonary pathology in in vitro studies. Jiang Shibo of Fudan University⁷ (worked on corona virus therapeutics) says - "Remdesivir has the best potential to be used in clinics". Stanley perlman (a corona virus researcher)

from university of Iowa expressed the view on Remdesivir "What you really want to do is give a drug like that to people who walk in with mild symptoms. And you can't do that because it's an intravenous and expensive drug and 85 out of 100 patients don't need it". ICMR has given a nod for its use against covid19 by saying that they will consider using remdesivir, an experimental drug made by Gilead sciences, to treat covid 19 patients if domestic companies can manufacture it. "Initial data base on observational study shows that the drug is effective. We will wait for the results from the WHO solidarity trial" said Raman Gangakhedkar, head scientist at ICMR. Remdesivir is not currently FDA approved and must be obtained via compassionate use (only for children < 18 years and pregnant women).

3) Azithromycin

Azithromycin is semi synthetic macrolide antibiotic chemically related to erythromycin which effective against susceptible bacteria causing otitis media, tonsillitis, sinusitis etc. Some researchers have seen limited success in covid patients when added it to chloroquine or hydroxychloroquine in severely ill patients. As of now there is little evidence for this drug combinations effectiveness. A French study of 80 patients published in *International journal of Antimicrobial Agents*⁶ showed encouraging results for the addition of azithromycin to the drug cocktail.

4) Tocilizumab

It is IL-6 receptor inhibiting monoclonal antibody which has been tried to manage cytokine release syndrome (CRS) in severely ill patients of covid 19. Dose is 4-8 mg/kg infused in 60 minutes. If initial dose is ineffective the second dose is repeated after 12hrs. Not more than two doses are given. Important ADRs are GI perforation, hepatotoxicity, hypertension, dizziness and infusion related reactions. A trial in 21 severely ill patients of covid19 having extensive lung lesions and high IL-6 level indicated that there is improvement in terms of reduction in fever and need for oxygen.⁷

5) Ivermectin

Ivermectin is an FDA approved broad spectrum anti parasitic agent which also has shown to have anti-viral activity against a broad range of viruses. Even though the exact mechanism is not known ivermectin has shown to inhibit the viral proteins and prevent its replication. In a collaborative study led by Australia's Monash Biomedicine Discovery Institute of Infection and Immunity (Doherty institute), a joint venture of University of Melbourne and Royal Melbourne hospital, has shown that Ivermectin can kill the virus in 48 hours.⁸ Ivermectin might emerge as one of the most suitable drug candidate for COVID-19 but needs further clinical trials.

6) Adjunctive therapies

Corticosteroids, Anticytokine or immunomodulatory agents and immunoglobulin therapy

Corticosteroids is not indicated in treating SARS CoV2 as per evidence available. It might prolong viral shedding. It is used as per indicated in septic shock. It may also use to decrease the host inflammatory response in lungs, which may lead to ARDS. A recent retrospective study of 201 patients with covid 19 in china found that, for those who developed ARDS, treatment with prednisolone is associated with decrease risk of death.⁹

Significant organ damage in lungs and other organs is caused by an amplified immune response and cytokine release or 'cytokine storm'. IL-6 appears to be a key agent in this dysregulated inflammation. Tocilizumab, Sarilumab etc. are some monoclonal antibodies which can be tried for hospitalised patients with severe covid infection.

7) Ascorbic acid

Ascorbic acid has shown to improve mortality in the multi-centre CITRIC-ALI trial. There is extremely limited evidence suggesting any beneficial effects in treating covid patients. A dose of 1.5gm IV q6 ascorbic acid plus 200 mg thiamine IV q12 seems to be safe. As of now there is no strong evidence to support ascorbic acid in viral pneumonia.

8) Convalescent plasma therapy

It is based on the principle of passive antibody. In 2014, WHO had recommended the use of convalescent plasma (CP) therapy to treat patients with the antibody rich plasma of those who had recovered from Ebola virus disease. It was also used for the treatment of people infected with H1N1 in 2009 and also for MERS CoV in 2015. The convalescent plasma therapy aims at using antibodies from the blood of a recovery Covid 19 patient to treat those critically affected by the

virus. US FDA has approved convalescent plasma from patients recovered from Covid 19 for the treatment of life threatening covid 19 infection on trial basis.

In a pilot study in china, CP therapy is given for 10 patients.¹⁰ After CP transfusion, the level of neutralising antibody increased rapidly up to 1:640 in five cases. The clinical symptoms significantly improved along with increase of oxyhaemoglobin saturation within 3 days. Several parameters tended to improve as compared to pretransfusion including increased lymphocyte count and reduced CRP. India's first covid 19 patient who was administered CP therapy has fully recovered and was discharged from Delhi's Max hospital.

Lyophilised convalescent plasma (LCP)

Lyophilisation, also known as freeze-drying is a process used for preserving biological material by removing water from the sample, which involves first freezing the sample and then drying it, under vacuum at a very low temperature. Lyophilised samples may be stored much longer than untreated samples. It can be stored in pharmacies, readily reconstituted in normal saline within 10 min. US FDA has not approved LCP till date.

Stem cell therapy

Mesenchymal stem cell immunomodulation stem cell therapy has been proposed as a suitable therapeutic approach in various clinical trials. It has claimed to improve the pulmonary microenvironment, prevent fibrosis and cure lung dysfunction. However currently there are no approved approaches in stem cell therapy. Stempeutics, a stem cell company which is a part of Manipal education group has approached the Drug Controller General of India to offer a stem cell based product for treatment of severe COVID patients. The drug is expected to be in the market within next 12 months.

09) Anticoagulants

Recent studies has shown some benefit in using anticoagulants especially heparin in severely ill hospitalised COVID patients due to its anti coagulant, anti inflammatory and antiviral properties. A strong predictor of mortality in COVID is Disseminated intravascular coagulation. As an anticoagulant heparin may reduce thrombi formation in pulmonary vasculature. So the study suggests all patients with COVID-19 should be placed on prophylactic dose of LMWH, unless there is a contraindication.¹¹

10) Vaccination

Currently there are no vaccines available for Covid 19 till date. Scientists around the world are working on potential treatments and vaccines for covid 19. There are 120 projects around the world involved in development of vaccine. Five had been approved for clinical trials. Altimmune's intranasal corona virus vaccine, INO-4800 by Inovio pharmaceuticals, mRNA-1273 by modern, Avian coronavirus infectious bronchitis virus (IBV) vaccine by MIGAL are some projects under clinical trials.¹²

DISCUSSION AND CONCLUSION

WHO clinical management guidance document (as of march 13, 2020) states "there is no current evidence to recommend any specific anti-covid treatment for patients with confirmed covid 19. This shows the necessity of the preventable and containment options we should look into. Only preventive measures like social distancing, hand hygiene, use of masks and limitation of movement are successful in breaking the chain of transmission. The current clinical management for Covid emphasise mainly in giving supportive care based on severity of illness, ranging from mild flu like illness to ARDS requiring ventilation. More clinical studies are required for investigating potential therapies for Covid 19 as no therapy has shown conclusive evidence till date to cure Covid 19.

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