

Review Article

POTENTIAL THERAPEUTIC AVENUES FOR COVID-19 THERAPY

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ABSTRACT

Covid-19, an infectious disease caused by coronavirus spreads by salivary droplets or nasal discharge from an infected person during sneezing or coughing. This infectious disease is caused by a novel coronavirus, SARS CoV-2 shares the same structure with that of the virus that causes severe acute respiratory syndrome (SARS). Most of the people who are infected with Covid-19 will experience respiratory illness and can be treated with antiviral drugs and or a combination of antiviral drugs and supportive therapies. Many medical investigational approaches are being investigated to design possible treatment strategies and possible avenues for Covid-19 therapy. Potential strategies for the treatment of Covid-19 include antiviral medication, the combination of interferons and antiviral drugs, interleukin inhibitors. Recent studies show that the use of plasma from survivors can help patients in recovering from the disease. This approach of using plasma is termed as convalescent plasma therapy. Another newer technology that includes the construction of a recombinant vaccine is gaining importance for further investigation. The other major approaches include the therapeutic use of serine protease inhibitors, chloroquine, hydroxychloroquine, ammonium chloride in definite doses. New study approaches include investigation on the production of monoclonal antibodies has gained a way for further clinical research. An effective supportive therapy includes extracorporeal membrane oxygenation could be considered as rescued therapy for the patients having respiratory distress. After sufficient clinical data is obtained and by taking all these approaches into consideration, the treatment protocol can be designed to treat Covid-19 successfully.

Keywords: SARS CoV-2, Antiviral drugs, Chloroquine, Interferon therapy, Monoclonal antibodies, Vaccine therapy, Extracorporeal membrane oxygenation

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INTRODUCTION

Coronavirus disease, COVID-19, is an infectious disease caused by a coronavirus. Coronaviruses are a large family of enveloped, single-stranded RNA viruses that infect a broad range of vertebrates. Mostly people infected with the COVID-19 virus will experience mild to moderate respiratory illness and can be recovered with less special treatment. While the elderly people and the people with compromised immune systems like cancer and the people with underlying medical conditions like cardiovascular disease, diabetes and chronic respiratory diseases.

The COVID-19 virus spreads through salivary droplets or nasal discharge from an infected person during sneezing or coughing. The better way to prevent or slow down the transmission is by protecting oneself from the infection by washing hands or using an alcohol-based rub frequently and by not touching the face. It is important to practice respiratory etiquette like using a flexed elbow while coughing.

COVID-19 is the ongoing respiratory disease outbreak and was recognized in December 2019 [1]. The novel coronavirus has a structural similarity with the virus that causes severe acute respiratory syndrome (SARS) and has stood as critical challenge for public health, research and medical professionals. Children are less likely to get infected or their symptoms were so mild that their infection escaped detection. Many medical approaches are being investigated, which include supportive therapy along with antiviral medication. Potential developmental research of a vaccine is under the process against COVID-19 [2]. Another attractive investigational approach includes use of intravenous hyperimmune globulin obtained from recovered persons and monoclonal antibodies. These approaches need scientific and ethical evaluation. By considering the above treatment strategies, the following are the possible avenues for COVID-19 therapy.

Avenues for COVID-19 therapy

Repurposing old drugs against SARS-CoV occurs to be an interesting treatment strategy for the novel coronavirus as it shares a similar

structure. While focusing on treating viral infection, the treatment strategy should include prevention of secondary infections, respiratory and circulatory support, and preservation of physiological systems, which include renal, hepatic and neurological functions. Potential treatment strategies for COVID-19 include:

Antiviral medication

As the novel coronavirus has a structural similarity with SARS-CoV, the treatment done for SARS-CoV infection could be a possible treatment option, which includes a combination of 400 mg ritonavir and 100 mg of lopinavir which are potent protease inhibitors used in the treatment of human immunodeficiency virus infection. This combination was considered for the early treatment of SARS patients [3]. The china International Exchange and Promotive Association for Medical and Health care (CPAM) has recommended the oral administration of lopinavir and ritonavir in combination with nebulized alfa-interferon based on retrospective controlled studies [4].

Korean physicians have developed recommendations for the treatment of COVID-19, which include the use of a combination of lopinavir and ritonavir or chloroquine in older patients or patients with underlying conditions and serious symptoms. However, no use of antiviral medication in young, healthy patients with mild symptoms and no underlying comorbid conditions is recommended.

Another nucleoside analogue which is under investigation, Remdesivir, has shown significant activity against coronavirus and a high genetic barrier to resistance in preclinical trials. Remdesivir has shown prophylactic and therapeutic efficacy against 2002 SARS-CoV in a mouse model. Hence remdesivir stands out as one of the promising treatments for SARS-CoV-2.

Another promising combination of antiviral medication includes Sofosbuvir with ribavirin. The mechanism of action includes the tight binding of sofosbuvir and ribavirin to coronavirus RNA dependent RNA polymerase. However, much of the clinical data is awaited.

Favipiravir, another antiviral drug which is known to inhibit RNA viruses is under Phase III clinical trials has gained importance in potential possibilities for Covid-19 treatment [5].

Antiviral medication with steroids

Methylprednisolone in the dose of 250 to 500 mg per day for 3 to 6 d along with antiviral medication was found to be effective in critically ill SARS patients. However, high dose steroids in the absence of an effective antimicrobial agent could result in complications related to fungal infection and avascular necrosis [3].

A prospective observational study of 2002 SARS-CoV infected patients who received treatment with ribavirin and corticosteroids has shown improvement of initial pulmonary lesions in 45% of patients along with possible side effects and no survival benefit [4].

Interferon therapy

There is not enough data on *in vitro* activity of IFN preparations in the treatment of SARS and hence interferon (IFN) is not recommended as standard therapy in SARS.

A combination therapy with ribavirin and interferon (IFN)- α 2b has shown improved clinical outcomes in MERS-CoV-infected non-human primates [3]. However, various IFN dosage regimens in combination with ribavirin have been given to critically ill patients and the possibility for the patients to experience toxicities when the drug is given alone or in combination with interferon. Interferons can show systemic adverse effects, psychiatric disturbances and neutropenia [6].

A combination of lopinavir/ritonavir and interferon-beta-1b was used and the study has shown promising results in the treatment of MERS-CoV infection [7].

However, use of ribavirin and interferon may be considered if the treatment with lopinavir, ritonavir, chloroquine or hydroxychloroquine are ineffective [4].

Another promising treatment strategy includes the use of a combination of Interferon alfacon-1 with corticosteroids [8].

Interleukin Inhibitors

Interleukin 6 inhibitors (IL-6) could be suggested as possible treatment based on the clinical data of Covid-19 patients, which showed increased levels of interleukin 6 in the blood [5].

As some of the severely affected Covid-19 patients experienced hyper inflammation and a 'cytokine storm', Interleukin 1 inhibitors could be considered as a possible treatment strategy for Covid-19.

Convalescent plasma therapy

People who have recovered from the disease have antibodies that might help those still suffering from it. The idea of using plasma from survivors is known as convalescent-plasma therapy [9]. Doctors have transfused the blood of recovered patients into the patients with 1918 flu, measles, polio, chickenpox, SARS and Ebola and this convalescent plasma therapy has shown varying degrees of success. The blood of survivors contains antibodies (proteins) that can neutralize the coronavirus has to be pooled and purified to get a concentrated dose of antibodies.

However some evidence recommends the use of plasma antibodies early on in the immune response and found to be useful but less effective once the patient reaches the stage of organ failure that requires hospitalization. The antibodies in the plasma help to prevent virus from spreading from the nose and throat into the lungs. If these antibodies in plasma can lessen the severity of COVID-19, this could be one among the key possible treatment strategies. Pirofski says if the patients with respiratory symptoms like cough and chest pain are administered with antibodies, maybe they won't require supplemental oxygen and intubation.

Sarilumab (Keyzara) is a fully human monoclonal antibody that inhibits the interleukin-6 (IL-6) pathway by binding and blocking the IL-6 may render a role in driving the overactive inflammatory response in the lungs of critically ill patients with COVID-19.

Vaccine therapy

Immunization is achieved using live, attenuated forms of virus or part or whole of the virus once it has been inactivated by heat or chemicals. As these methods have drawbacks, newer technology has gained importance which involves the construction of a "recombinant" vaccine. This process involves extracting the genetic code for the protein spike on the surface of SARS-CoV-2. As it is the part of the virus that provokes an immune reaction in humans, genetic code for the protein spike plays a major role in the production of vaccine. By incorporating the genetic code of viral protein spike into the genome of a bacterium or yeast and then making these microorganisms to produce large quantities of the protein. Other approaches in developing a vaccine includes bypassing the protein and constructing vaccines from the genetic information alone. Thus, vaccines for Covid-19 can be constructed out of messenger RNA. Using a genetic platform, an investigational vaccine is developed based on mRNA [10]. This investigational vaccine is supposed to direct the cells in the body to express a viral protein, which in turn produces a robust immune response. However, different phases of clinical trials are to be carried out on the investigational vaccine to get complete safety data.

Role of serine protease inhibitors

During SARS CoV-2 virus entry, viral S protein needs to be cleaved by cellular proteases at two sites thus, resulting in S protein priming, which in turn results in the fusion of viral and cellular membranes. S-protein priming happens by TMPRSS2 activity. Hence, inhibiting TMPRSS2 activity blocks CoV-2 entry. Thus, serine protease inhibitors could be one among the potential avenues for Covid-19 therapy [11]. Camostat mesylate, a serine protease inhibitor, is under clinical trials for its efficacy against Covid-19.

Role of chloroquine/hydroxychloroquine and ammonium chloride in covid-19 therapy

Chloroquine and hydroxychloroquine are the two medicines currently approved to treat malaria and certain autoimmune diseases are under investigation for their potential to treat coronavirus disease. Both chloroquine and hydroxychloroquine can show serious side effects at high doses and when given in combination with other medicines. A robust data is being generated based on large clinical trials [12] to establish the efficacy and safety of chloroquine and hydroxychloroquine in the treatment of Covid-19.

Strong antiviral effects on SARS-CoV infected primate cells are exhibited by chloroquine when the cells are treated with the drug either before or after exposure to the virus. Thus, it suggests both prophylactic and therapeutic advantage of the drug, chloroquine. Chloroquine is known to elevate endosomal pH and interferes with terminal glycosylation of the cellular receptor, angiotensin converting enzyme-2 which in turn negatively influences the virus-receptor binding. Thus, by elevating vesicular pH, infection can be inhibited and thus the spread of SARS CoV [13].

Role of ammonium chloride in SARS CoV infection-treatment

Based on the inhibition of SARS-CoV infection by chloroquine when added before or after infection, another lysosomotropic agent, Ammonium chloride is anticipated to have similar mechanism of action. Ammonium chloride is found to reduce the transduction of pseudotype viruses having SARS-CoV spike protein. Hence, ammonium chloride has gained importance in clinical studies.

As intra-vesicular acidic pH regulates cellular functions, including N-glycosylation trimming, cellular trafficking and enzymatic activities, it has gained importance to demonstrate the effect of chloroquine and ammonium chloride on the cellular processes, glycosylation and cellular mechanisms involved in SARS-CoV spike glycoprotein and its receptor, Angiotensin-converting enzyme-2. Based on the flow cytometry analysis performed on Vero E6 cells which when treated with appropriate antiviral concentrations of chloroquine or ammonium chloride, it is revealed that drug has not shown any significant change in the levels of ACE2 receptors inferring that the inhibitory effects on SARS-CoV infection are not because of lack of available ACE2 receptors. Based on flow cytometry and

immunoprecipitation analyses, it can be concluded that ammonium chloride and chloroquine have impaired the terminal glycosylation of ACE2 thus making ACE2-SARS-CoV binding less effective inhibiting the virus entry. Thus the studies have confirmed that elevation of pH caused by chloroquine reduces the transduction of SARS-CoV pseudotype viruses. In addition to these studies, immunoprecipitation results of ACE2 has shown the effect of anti-SARS-CoV concentrations of chloroquine and ammonium chloride on impairment of terminal glycosylation of ACE2. Based on these results, chloroquine treatment prior to infection resulted in decreased binding affinities between ACE2 and SARS-CoV spike protein and thus negatively influencing the initiation of SARS-CoV infection. By considering the analyses, chloroquine and ammonium chloride have gained importance in Covid-19 therapy [12].

Monoclonal antibodies

A fully human polyclonal IgG antibody (SAB-301) was found to be safe and need further studies for its efficacy to be used in the treatment of MERS-CoV infection. As SARS-CoV-2 virus falls under same virus family, coronaviridae, the knowledge of this investigational monoclonal antibody used to treat MERS-CoV infection could be useful in fabrication of monoclonal antibodies against SARS-CoV-2 infection.

According to the study that is published in Science dated April 3, 2020 from the source, Scripps Research Institute, human antibody's interaction with the new coronavirus at near-atomic resolution is mapped. The antibody produced in response to SARS (severe acute respiratory syndrome) infection, which is caused by SARS-CoV virus has cross-reacted with the new coronavirus, SARS-CoV-2 [14]. Thus, the structural mapping revealed a closely identical site on both coronaviruses to which the antibody binds, which suggests it as a vulnerable site for the family of coronaviruses. These vulnerable sites can help in the structure-based design of vaccines and therapeutic agents against SARS-CoV-2. Few structural studies of antibodies bound to viruses, including HIV and influenza, have been carried out and these studies have played a major role in the design of vaccines, antibody drugs and other therapeutic agents.

New study centers have been set up on anti-SARS-CoV antibody called CR3022 which was originally isolated in 2006, by the pharmaceutical company, Crucell Holland B. V. in Netherlands. From the report given by the Chinese scientists earlier this year, shows that CR3022 cross-reacts against SARS-CoV-2. The key finding of this study using structural mapping includes the information about the similarity of antibody's binding site between the two coronaviruses, which differ by just four protein building blocks known as amino-acids [15]. The Scripps Research analysis concluded that the antibody binding site is relatively remote from the part of the virus that holds cell-surface protein receptors prior to cellular penetration in the lungs. Thus, suggesting that at least for SARS-CoV, CR3002 neutralizes the ability of viruses to infect cells. These findings suggest that the binding site for this antibody on SARS-CoV-2 is a site of vulnerability and the antibodies attaching to this site succeed in neutralizing the virus. If these neutralizing antibodies are developed into therapies, then these antibodies can be considered as a potential strategy in the treatment of Covid-19.

Recombinant human angiotensin-converting enzyme 2 (ACE2) is under clinical trials. As SARS-CoV-2 is known to enter cells through ACE2 receptor so binding to soluble ACE2 would prevent the virus from entering cells [16].

Hence, certain combination therapies are to be monitored to get sufficient clinical data to be used further in treating viral infection.

Extra corporeal membrane oxygenation

Extracorporeal membrane oxygenation (ECMO) has been proven to be an effective therapy in the treatment of respiratory failure or acute respiratory distress syndrome (ARDS) [17].

From the clinical database of patients with H1N1-related ARDS, it is known that ECMO-referred patients have shown lower hospital mortality when compared with non-ECMO-referred patients.

Based on the same mechanism of action, ECMO could pave away in the treatment of Covid-19. As per the interim guidance provided by World Health Organization (WHO), ECMO should be considered as rescue therapy for Covid-19 with refractory hypoxemia despite lung-protective ventilation [18].

As most of the studies did not report the clinical outcomes of ECMO, retrospective studies were conducted by Yang *et al.* and Guqin *et al.* showed that out of the considerable number of patients who received invasive mechanical ventilation (IMV) and ECMO support, a very few were benefited by ECMO support. Lack of clinical trial of ECMO on Covid-19, it gives incomplete data on the usage of ECMO in Covid-19 patients.

As a few approaches such as intubation [19], ventilator venting and sputum suction pose a high risk of infection to medical staff. Hence, it is challenging for the medical staff to encounter the pandemic with sufficient personal protective equipment.

CONCLUSION

The ongoing respiratory disease outbreak, COVID-19 caused by novel corona virus, SARS-CoV-2 which has structural similarity with the virus that causes severe acute respiratory syndrome (SARS) being stood as challenge for public health and medical researchers has laid a way for many investigational medical approaches. Though a few of the newest approaches need scientific and ethical evaluation, keeping into consideration, the possible treatment avenues for Covid-19 therapy include antiviral medication administered alone or in combination with other antiviral drugs and/or steroidal drugs, interferon therapy, interleukin inhibitors, convalescent plasma therapy, vaccine therapy, serine protease inhibitors, chloroquine or hydroxychloroquine, ammonium chloride, monoclonal antibodies. Another approach by which respiratory distress associated with corona virus infection can be effectively treated by extracorporeal membrane oxygenation for which considerable clinical data is to be obtained only of which it could be implemented. By considering these methods and by conducting research on the potential avenues for Covid-19 therapy, we can get complete clinical data of various drugs and treatment strategies that can be implemented for covid-19 therapy.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

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