Current Therapeutic Drugs with Potential for Treatment of COVID-19

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ABSTRACT

The current global pandemic of corona virus disease 2019 (COVID-19) has presented a enormous challenge to the healthcare systems around the world. Currently there is no widely accepted standard of care in the management of patients with COVID-19 or any prophylactic therapy. Many active clinical treatment trials are ongoing as urgent identification of potential treatment strategies is a priority. Therapies include novel agents available in clinical trials or through compassionate use, and other drugs, repurposed antiviral and immunomodulating therapies. Combination of Hydroxychloroquine / chloroquin and azithromycin is often considered for hospitalized patients with moderate to severe COVID-19. As such, the efficacy of this treatment is still questionable. Among antivirals, Remdesivir and Favipiravir have recently got approval for restricted emergency use in India for COVID-19 and could be a promising candidate. Other adjunctive therapies include ascorbic acid, corticosteroids, epoprostenol, and biologics like sirolimus, tocilizumab, sarilumab and convalescent plasma etc. The results of ongoing clinical trials testing single and combination therapies are needed to make definitive recommendations for the treatment of COVID-19.

Introduction :

The current global pandemic of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) has presented a enormous challenge to the healthcare systems in almost every country around the world. It began in Wuhan, China, in December 2019, and since then has spread worldwide.[1] As of June 5, 2020, there have been more than 8.25 million reported cases worldwide and a total of 3.95 lakh confirmed cases in India.[2] Similar to previously identified severe acute respiratory syndrome corona virus (SARS-CoV) and Middle East respiratory syndrome corona virus (MERS-CoV), SARS-CoV-2 is the third corona virus that severely infects humans or even causes death.[3] SARS-CoV-2 is a positive-sense single-stranded RNA virus named for their crown-like spikes on their surface.[4] COVID-19 can manifest as asymptomatic / mild disease to severe respiratory failure requiring intensive care unit admission. Fortunately, majority of SARS-CoV-2- infected individuals are asymptomatic or have mild symptoms. However, about 20% of SARS-CoV-2-infected individuals including the immune compromised, elderly, patients with underlying health conditions such as cardiovascular and pulmonary problems, diabetics, hypertension, obesity, chronic obstructive pulmonary disease would encounter more severe disease characterized by significant respiratory symptoms leading to acute respiratory distress syndrome (ARDS) and even death[5,6].

As the incidence continues to rise rapidly, critical care teams are faced with challenging treatment decisions. Currently there is no widely accepted standard of care in the management of patients with COVID-19 or any prophylactic therapy. No vaccine or approved drug is available to eradicate the virus, however, some drugs that are indicated for other diseases seems to be potentially beneficial to treat the infection though without clear evidence. Many active clinical treatment trials are ongoing as urgent identification of potential treatment strategies is a priority. Therapies include novel agents available in clinical trials or through compassionate use, and other drugs, repurposed antiviral and immuno-modulating therapies. Many have demonstrated in vitro or in vivo potential against other viruses that are similar to SARS-CoV-2. The WHO has embarked on an ambitious global "megatrial" called SOLIDARITY in which confirmed cases of COVD-19 are randomized to standard care or one of four

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active treatment arms (remdesivir, chloroquine or hydroxychloroquine, lopinavir / ritonavir, or lopinavir / ritonavir plus interferon beta-1a.[7] This review will summarize the most current drugs prescribed in the treatment of COVID-19 patients.

Antivirals

Remdesivir

Remdesivir is a potential drug for treatment of COVID-19. Remdesivir (GS-5734; Gilead Sciences, Inc) a broad spectrum antiviral is a nucleotide analog prodrug that is intracellularly metabolized to adenosine triphosphate that inhibits viral RNA polymerases. It has activity against Ebola virus and coronaviruses [e.g., SARS-CoV and MERS-CoV] and has shown prophylactic and therapeutic efficacy in nonclinical models of these corona viruses. On May 1, 2020, The US FDA issued Emergency use Authorization (EUA) of Remdesivir to allow emergency use of the agent for severe COVID-19 in hospitalized adults and children.[8,9] EUA for Remdesivir was based on preliminary data analysis of the Adaptive COVID-19 Treatment Trial (ACTT) was announced April 29, 2020. The analysis included 1,063 hospitalized patients with advanced COVID-19 and lung involvement, showing that patients who received Remdesivir recovered faster than similar patients who received placebo[10]. Several phase 3 clinical trials are testing Remdesivir for treatment of COVID-19 in the United States, South Korea, and China. Positive results were seen with Remdesivir after use by the University of Washington in the first case of COVID-19 documented on US soil in January 2020.[11] The drug was prescribed under an open-label compassionate use protocol, but the US FDA has since moved to allow expanded access to Remdesivir, permitting approved sites to prescribe the investigational product for multiple patients under protocol without requesting permission for each[12]. Ongoing clinical trials are studying Remdesivir with a loading dose of 200 mg intravenously followed by 100 mg/day intravenously for 5 to 10 days in adult patients[13].

In view of the crisis posed by the pandemic, India's drug regulator has granted Gilead Sciences marketing authorization for Remdesivir for "restricted emergency use" for a maximum of five-day period for treatment of suspected or laboratory-confirmed cases of Covid-19 in adults and children hospitalized with severe symptoms, subject to several safeguards. The approval process for Remdesivir was accelerated by invoking special provisions under the New Drug and Clinical Trial Rules, 2019[14] To expand the supply of Remdesivir across the globe, Gilead Sciences has signed non-exclusive voluntary licensing agreements with four Indian generic pharma manufacturers, namely; Cipla, Hetero Labs, Jubilant Life-Sciences and Mylan

Favipiravir

Favipiravir is a oral antiviral approved for the treatment of influenza in Japan and effective against RNA viruses such as Ebola. It selectively inhibits RNA polymerase, which is necessary for viral replication. Clinical trials testing Favipiravir against COVID-19 have been carried out vigorously in various countries including India.[4] On 15 March 2020, the drug was approved in China for the treatment of Covid-19.[15] The drug was approved for the treatment of COVID-19 in the hospital settings in Russia on May 29, 2020, after an ongoing open-label randomized clinical trial had recruited 60 subjects on Favipiravir.[16]

In India DCGI has approved Favipiravir drug for restricted emergency use for the treatment of mild to moderate cases of COVID-19. This approval has been granted based on the evaluation of data and in consultation with the Subject Expert Committee, as part of the accelerated approval process, considering the emergency situation and unmet medical need of the COVID-19 outbreak. It is only for restricted emergency use in India. DCGI has granted permission to Glenmark Pharmaceuticals to manufacture and market Favipiravir 200 mg tablet. The recommended dosage duration has been fixed for 14 days. On day 1, a dose of 1,800 mg twice a day is recommended, followed by 800 mg twice a day from day 2 up to 14th day[17]. Approval of Favipiravir has raised many questions. Many experts said the drug is not only expensive but still under trial in

most countries and its efficacy is yet to be proven. Others said the evidence cited for emergency use authorization by the Central Drugs Standard Control Organisation was rather weak. They said only an observational trial, not a clinical trial, had been conducted with 160 patients in 10 hospitals without any comparison with a placebo arm.[18]

Lopinavir-Ritonavir

The combination of lopinavir / ritonavir is used for the treatment of human immunodeficiency virus (HIV) infection; however, it has been observed that lopinavir has in vitro activity against corona virus. Ritonavir is also a protease inhibitor, but its primary role is to boost lopinavir concentrations and prolong its half-life.[19]

Lopinavir-ritonavir was investigated in an open-label, individually randomized, controlled trial, where patients with COVID-19 received either lopinavir-ritonavir 400 mg/ 100 mg, orally twice daily plus standard of care, or standard of care alone. No benefit was observed with lopinavir-ritonavir treatment beyond standard care[4].

Due to a lack of definitive evidence supporting the use of lopinavir / ritonavir and the high risk of adverse events, and significant drug-drug interactions, use of these agents is not recommended at this time. The results of a clinical trial through the World Health Organization (WHO), which includes lopinavir / ritonavir in one arm of the study, may provide more conclusive insight on the benefits of using these drugs for the treatment of COVID-19[19].

Other antivirals

Oseltamivir, aneuraminidase inhibitor is a drug approved for treatment of influenza A and B. Several clinical trials are still evaluating the effectiveness of oseltamivir in treating SARS-CoV-2 infection. Ribavirin, a guanine analogue, inhibits viral RNA-dependent RNA polymerase. It has activity against other corona viruses that makes it a candidate for COVID-19 treatment. The inconclusive efficacy data with ribavirin for other new CoVs and its substantial toxicity suggest that it has limited value for treatment of COVID-19.[20]

Hydroxychloroquine and chloroquine

Chloroquine and hydroxychloroquine are drugs with a long history of clinical use with similar chemical structures used in the treatment of malaria and autoimmune diseases. These agents have immunomodulatory effect and are also believed to have additional antiviral activity. They are found to inhibit SARS-CoV-2 in vitro. Furthermore, chloroquine was found to show some efficacy in treating COVID-19 associated pneumonia in a multicenter clinical trial with > 100 patients in China[21]. However later studies have found that hydroxychloroquine has more potency and a better safety profile when compared to chloroquine[22]. A recent nonrandomized clinical trial that compared hydroxychloroquine alone with combination of of hydroxychloroquine and azithromycin[23] found a substantial reduction in viral load and more rapid virus elimination in patients treated with a combination of hydroxychloroquine and azithromycin; however, the majority of patients treated with hydroxychloroquine alone continued to display symptoms of upper or lower respiratory tract infections[23]. Given the wider accessibility of antimalarials, as compared to the aforementioned antivirals, combination treatment with hydroxy-chloroquine and azithromycin is now recommended for many hospitalized patients with moderate to severe COVID-19. The FDA recently granted emergency authorization for hydroxychloroquine to treat COVID-19 infection[24]. There are several ongoing clinical trials that are investigating the efficacy of prophylactic and therapeutic use of these medications against SARS-CoV-2[22]. Chloroquine, hydroxychloroquine, and azithromycin each carry the warning of QT prolongation[25].

Miscellaneous and Supporting Agents

In the absence of vaccine or specific antiviral drugs been proven against SARS-CoV-2, many adjunctive therapies are used as supportive care for COVID-19 patients. The adjunctive therapies include azithromycin, ascorbic acid, corticosteroids, epoprostenol, sirolimus, tocilizumab, sarilumab etc.

Biologics

Tocilizumab and other interleukin-directed therapies are administered in an effort to blunt the cytokine stormoften seen in progressing disease. Tocilizumab and sarilumab are monoclonal antibodies against the IL-6 receptor that are currently being considered for use in patients with COVID-19, who develop cytokine release syndrome (CRS)[26]. It may have a potential role in severe and life-threatening illness. The proposed efficacy of this treatment involves the attenuation of the potentially fatal inflammatory response by reducing cytokine concentrations and inhibiting the production of acute phase reactants.[27]

Corticosteroids

As a potent anti-inflammatory and anti-fibrotic drug, low doses of methylprednisolone have the potential to prevent an extended cytokineresponse and may accelerate resolution of pulmonary and systemic inflammation in pneumonia.[4] The use of corticosteroids may be indicated in patients who desaturate, develop ARDS or refractory septic shock, and those with underlying respiratory conditions such as asthma or chronic obstructive pulmonary disease.[28] Recently Dexamethasone has been included in clinical trial protocol for managing moderate to severe cases of COVID-19 by Union Health Ministry. This was after the drug was tested in hospitalized patients with COVID-19 in the 'RECOVERY' clinical trial in the United Kingdom and was found to have benefits for the critically ill patients and reduce mortality by one-third for patients on ventilators and one-fifth for patients on oxygen therapy.[29]

Vitamin C

Vitamin C can neutralize free radicals and assist to prevent or reverse cellular damage as a potent antioxidant agent. It is also involved in some biological processes, many of which are associated with immune health. Moreover, vitamin C appears to be effective as an antiviral agent, especially against influenza viruses[4].

Ivermectin

Very recently, ivermectinapotent antihelminthic drug has shown inhibition against SARS-CoV-2 up to 5000-fold at 48 h in vitro. It will be interesting to know its inhibition effect against SARS-CoV-2 in vivo[4].

Convalescent plasma

The use of convalescent plasma has a long history in the treatment of infectious diseases. Casadevall and Pirofski proposed using it as a treatment for COVID-19, and Bloch et al laid out a conceptual framework for implementation.[4] To date, two small case series have been published.[30,31] These series reported improvement in oxygenation, sequential organ failure assessment (SOFA) scores, and eventual ventilator weaning in some patients.

Conclusion

Although there are currently no available therapies that are directly active against SARS-CoV-2, several medications have emerged as potential treatments. Due to the low cost, easy accessibility, and lack of alternative treatment options, treatment with a combination of hydroxychloroquine and azithromycin is often considered for hospitalized patients with mild to moderate COVID-19. As such, the efficacy of this treatment is still questionable, and the risk of significant adverse effects should be considered prior to initiating treatment with these drugs. Among antivirals, Remdesivir could be a promising candidate and may be more widely available in the upcoming weeks. Passive immunization has been successfully used in the past; however, the efficacy of convalescent plasma in the treatment of critically ill patients with COVID-19 is still largely unknown. Many institutions are beginning to use this treatment as more individuals recover from the disease and convalescent plasma becomes available. As the SARS-CoV-2 pandemic continues to evolve, some information has become available on the effectiveness of certain therapies. Still, the results of ongoing clinical trials testing single and combination therapies are needed to make definitive recommendations for the treatment of COVID-19.

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