COVID-19 Treatment: Current and Emerging Options

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Abstract

Coronavirus disease 2019 (COVID-19) which is caused by the Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2) has posed a clinical threat to the global population. Its resemblance to SARS-CoV along with several other bat coronaviruses have been established through genome sequencing- related studies. The disease spreads by human-to-human transmission via droplets or direct contact and presents flu-like symptoms. It can have poor prognosis in high-risk individuals having co-morbid conditions. Though currently, no proven effective therapies for SARS-CoV-2 exist, many therapeutic agents are being repurposed to treat patients with COVID-19. The key aspect determining the prognosis of COVID-19 patients is the early accurate diagnosis followed by the management of acute respiratory failure and hemodynamic instability in moderate-severe cases. COVID-19 presents an unparalleled challenge to identify potential therapeutic agents for prophylaxis and treatment. There is an explicit and urgent need to explore all the possible prophylactic and therapeutic strategies to curb the spread of SARS-CoV-2. A large number of clinical trials have been launched to investigate potential therapies for COVID-19 and to provide the clinicians accurate evidence regarding effective medical treatments for this infection. The current review closely examines the drugs that are being explored and also those drugs which have a potential for consideration. Though the therapeutic options have not undergone extensive pre-clinical and clinical testing, each has a known merit and identified mechanism against viral infection. The review is based on currently available information and as new evidence emerges, reappraisal of therapies is anticipated.

Keywords: COVID-19, management, SARS-CoV-2, potential therapies, evidence

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Introduction

Coronavirus disease (COVID-19), which appeared in December 2019, continues to remain a global challenge, particularly due to rapid increase in critically ill patients with pneumonia and absence of definitive treatment. COVID-19 is highly transmissible amongst individuals through respiratory secretions. The virus enters through mucus membrane of upper respiratory tract, further transcends into the lungs. In many cases, COVID-19 is a mild illness; while in some cases, patients develop serious or critical illnesses.[1]

The worldwide spread of the pandemic has resulted in a proliferation of clinical trials to curb the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections. The therapies range from vaccines to drugs for influenza, Ebola, and malaria. Preclinical evidence has proven the potential of several drugs, yet large scale clinical trials are still warranted.[2]

The Virology of SARS-CoV-2

SARS-CoV-2, a single-stranded RNA-enveloped virus possesses viral structural spike (S) protein. SARS-CoV-2 binds to the angiotensin-converting enzyme 2

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(ACE2) receptor on the host cells through the spike proteins and enters into the cell. Type 2 transmembrane serine protease (TMPRSS2) helps this entry via the S protein. SARS-CoV-2, once in the cell releases its RNA in the cytoplasm, which encodes replicase-transcriptase complex (RTC). The virus then synthesizes RNA via its RNA-dependent RNA polymerase. The RTC replicates the synthesized RNA into many RNA copies. Structural proteins like nucleocapsid, spike, envelope and membrane proteins all assemble to form mature virions. Mature virions are then released from cell surface through exocytosis.[3,4]

Symptoms in COVID-19 include cough, fever, dyspnea, fatigue, gastrointestinal symptoms (nausea, vomiting, and diarrhea). Severe respiratory symptoms include respiratory rate ≥30 breaths/min; blood oxygen saturation ≤93%; PaO_2:FiO_2 <300 and/or pulmonary infiltrates on >50% of lung fields on radiological imaging.

The viral life cycle provides cues for potential targets for drug therapy which includes:

- Viral entry
- Viral RNA synthesis and protein synthesis inhibitor
- Viral replication and survival in host cells
- Immune regulation pathways

Repurposed agents

Hydroxychloroquine: Hydroxychloroquine (HCQ) has the potential to inhibit SARS-CoV-2 as demonstrated by *in-vitro* and *in-silico* studies. Chatterjee P *et al* used COVID-19 testing database in India. The researchers telephonically interviewed around 365 healthcare workers (HCW) who had taken HCQ prophylaxis (A loading dose 400 mg bid followed by a maintenance dose for seven weeks once weekly for seven weeks). The results showed that odds of SARS-CoV-2 infecting the HCWs reduced by >80% (95% CI of OR 0.1-0.36, P <0.001). In an initial study in treatment of COVID-19 patients, use of HCQ was associated with reduction in viral load. Million *et al* treated 1061 COVID-19 patients with HCQ and Azithromycin and reported good clinical outcome in around 92% patients.[5,6] Sustained intake of HCQ prophylaxis in conjunction with personal protective equipment (PPE) should be considered to protect HCWs.[5]

Azithromycin: Azithromycin has been used as an adjuvant therapy to provide antibacterial coverage along with immune-modulatory and anti-inflammatory effects in viral respiratory tract infections. The dosing followed is 500 mg for 1 day followed by 250 mg per day for 4 days. Data from trials testing the effect of Azithromycin in conjunction with HCQ in COVID-19 patients are insufficient to evaluate possible clinical benefits of Azithromycin in such patients.[7]

Remdesivir: Remdesivir has been granted emergency use approval in India, US and Japan for the treatment of COVID-19. Cell culture studies have shown that Remdesivir is a potent inhibitor of SARS-CoV-2 replication in human nasal and bronchial airway epithelial cells. Case studies have reported benefit in severely ill patients with COVID-19.[8] In 1059 patients with COVID-19 with evidence of lower respiratory tract involvement, Beigel J.H *et al*, upon administering Remdesivir 200 mg on day 1 followed by 100 mg on days 2–10 in single daily infusions, reported shortened time to recovery with Remdesivir as compared to placebo (11 days vs 15 days). By day 14, mortality rate was 7.1% in Remdesivir group as compared to 11.9% in placebo group.[9] These preliminary findings suggest combination of Remdesivir with other antivirals, or SARS-CoV-2 neutralizing antibodies to further improve the outcomes.[10]

Favipiravir: Favipiravir has shown potent activity against enveloped, positive-sense, single-strand RNA virus SARS-CoV-2.[11]

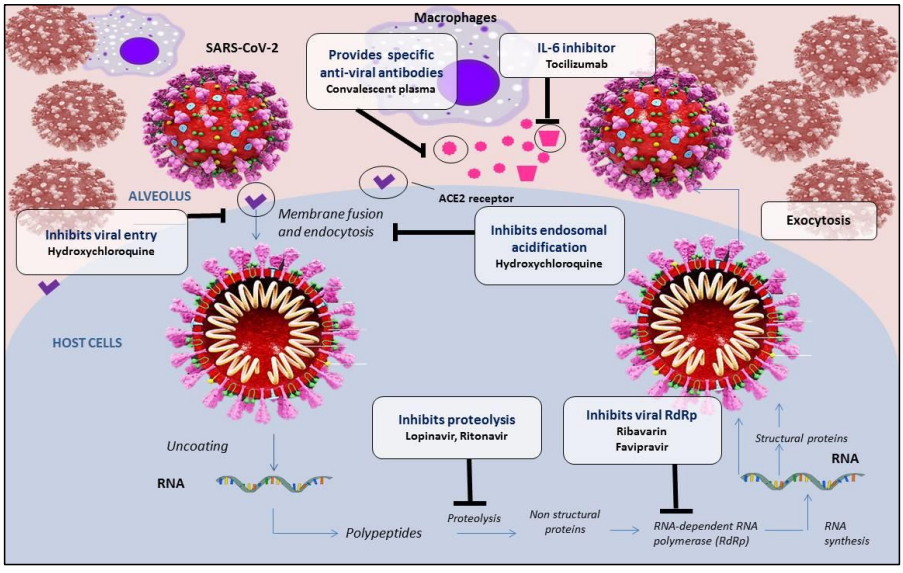

Figure 1: Possible targets of repurposed, investigational and adjuvant drugs

Chen C *et al* reported that COVID-19 patients treated with Favipiravir have superior recovery rate (71.43%) than that treated with Umifenovir (55.86%), and the duration of fever and cough relief time are significantly shorter in Favipiravir group than in Umifenovir group.[12] Cai *et al* compared the effects of Favipiravir against Lopinavir-Ritonavir in COVID-19 patients. Favipiravir cleared the viral load as well as improved the chest imaging rapidly as compared to Lopinavir-Ritonavir.[13] These trials are yet to be published in a peer-reviewed journal, and there are concerns about drug–drug interactions due to monoamine oxidase inhibitors (MAOIs).[14] Additional studies are needed for supplementary recommendation of Favipiravir in the treatment of COVID-19. The dosing followed for Favipravir is 1600 mg twice daily on Day 1 followed by 600 mg twice daily from day 2 to day 5.[15]

Ivermectin and Doxycycline: Apart from parasiticide and antibacterial action, Ivermectin has shown activity against a broad range of viruses. Experimental studies have shown that it inhibits SARS-CoV-2 with ~5000-fold reduction in viral RNA at 48 h.[16] Researchers from Bangladesh claim that off-label use of Ivermectin along with Doxycycline in sixty COVID-19 patients led to remarkable recovery rate within 4 days with minimal adverse reactions. A regulatory approved clinical trial involving the use of Ivermectin in COVID-19 patients is underway.[17] The use of Ivermectin in combination with HCQ is hypothesized to demonstrate synergistic action in the inhibition of SARS-CoV-2.[18] The dosing used in ongoing clinical trials for Ivermectin is 12 mg once daily for 2-7 days and for Doxycycline, 200 mg OD for 5-14 days.

Lopinavir-Ritonavir: The antiretroviral drug, Lopinavir is widely used for treating HIV and is a potential candidate for the treatment of COVID-19.[19] Ritonavir helps to stabilize Lopinavir and together they inhibit the replication of coronavirus *in vitro*.[20] Cao *et al*. carried out an open-label trial for Lopinavir–Ritonavir in 199 hospitalized patients with severe COVID-19 and administered Lopinavir–Ritonavir (400 mg and 100 mg, orally every 12 h for 14 days). The authors found no benefit with Lopinavir–Ritonavir therapy in terms of time to clinical improvement beyond the standard of care.[21] However, the analyses of secondary outcomes revealed that Lopinavir–Ritonavir may be associated with substantial lowering of overall mortality (19% in patients in Lopinavir–Ritonavir group vs. 25% in the standard-care group), reduced risk of severe adverse events (20% vs. 32%), and decreased risk of respiratory failure or acute respiratory distress syndrome (13% vs. 27%).[22] Though this therapy has not shown meaningful clinical improvement, Lopinavir–Ritonavir may not be abandoned by clinicians in the current scenario of shortages of alternative drugs.[21]

Ribavarin: Ribavirin has a well-established history of usage in emergency clinical management plans for novel coronavirus (nCoV), in which the greatest benefit has been reported with early administration upon presentation with pneumonia and before sepsis or organ system failure. The clinical utility is seen only in small research studies. However, no definitive clinical study has yet established a therapeutic benefit of Ribavirin in COVID-19.[23] A positive synergistic effect has been observed when clinicians combined Ribavarin with interferon beta-1b, Lopinavir–Ritonavir.[24] Hung *et al* randomized COVID- 19 patients to triple antiviral therapy i.e. Lopinavir/Ritonavir, Ribavirin and Interferon beta-1b and standard therapy. The combination therapy alleviated the symptoms, shortened the duration of viral shedding and hospital stay.[25] The dosing for Ribavarin is 2.4 g orally as a loading dose followed by 1.2 g orally every 12 hours for 10 days. [4]

Arbidol, Oseltamivir and other antiviral drugs: Arbidol is widely used in Russia and China against influenza infection. The clinical evidence for using Arbidol in the treatment of COVID-19 is scarce. A retrospective cohort study, case reports and case series revealed that Arbidol alone or combined with antiviral drugs produced certain benefits in the treatment of COVID-19.[26] The dosing followed for Arbidol is 200mg every 8 h orally for 7-14 days. [4]

Oseltamivir is being evaluated in clinical trials, mainly in combination with Chloroquine, Favipiravir and corticosteroids. The antiparasitic drug, Nitazoxanide and Bacillus Calmette–Guérin (BCG) vaccine, are being tested for their possible role in alleviation of symptoms amongst COVID- 19 patients.

Adjunctive therapies (Immunotherapy)

Convalescent Plasma: Passive immunization has been successfully used to treat infectious diseases.[27] The convalescent plasma derived from the patients with antibodies against COVID-19 can be effective in reducing the mortality rate of critically ill patients. Jenkins M *et al* demonstrated a significant reduction in mortality and viral load in studies using convalescent plasma for the treatment of severe acute viral respiratory infections.[28] Convalescent plasma treatment should be given to COVID-19 patients at the right phase (or severity) of illness and at the right time point. Based on

the limited scientific data, convalescent plasma treatment should probably be used in COVID-19 patients with severe and life-threatening symptoms.[29]

Tocilizumab: Tocilizumab is a monoclonal antibody against interleukin-6 (IL-6) being used for COVID-19 patients with a risk of cytokine storms. The dosing of Tocilizumab followed is 400 mg IV or 8 mg/kg × 1-2 doses.[4] Second dose can be given 8-12 h after first dose if inadequate response is seen. Tocilizumab needs to be tried in sufficient number of COVID-19 patients to establish its effectiveness.[30]

Vaccines: The complex process involved in vaccine development usually takes 4 years; the researchers are on a war footing to develop a vaccine within a year's time. Global COVID-19 vaccine R&D landscape includes candidates like mRNA-1273, Ad5—nCoV, INO-4800 and LV-SMENP-DC from five global vaccine manufacturers.[31] Five Indian companies are working on four types of vaccines namely, mRNA, attenuated, inactivated and adjuvant; 50 vaccine candidates have been shortlisted.[32]

Immunonutrition

A healthy and 'well-fed' immune system is one of the most important weapons against COVID-19. Though an array of micronutrients is required, a large body of evidence is seen for Vitamin C and Zinc.[33]

Vitamin C (Ascorbic Acid): Vitamin C, a potent antioxidant agent is an effective anti-viral agent against influenza viruses. It helps to develop and mature T lymphocytes and NK (natural killer) cells. In 50 moderate to severe COVID-19 patients, intravenous vitamin C (between 10 g and 20 g per day given over a period of 8–10 h) improved oxygenation index. All patients were cured and discharged. 11 Though high dose vitamin C is safe, large clinical studies are needed for bedside use.

Zinc: Zinc is a potential supportive therapy of COVID-19 owing to its immunomodulatory and antiviral effects. Zinc inhibits SARS-CoV RNA polymerase and decreases angiotensin-converting enzyme 2 (ACE2) (SARS-CoV-2 receptor). It also upregulates interferon α to improve antiviral immunity. In elderly individuals, 45 mg/day of oral zinc supplementation for a year has shown to lower the incidence of infections. It is hypothesized that Zinc supplementation in HCQ-treated patients may lead to improved outcomes in COVID-19 patients. HCQ has Zinc ionophore characteristics, leading to increased intracellular levels of Zinc specifically in lysosomes. This elevated intracellular concentration of Zinc is expected to result in better inhibition of replication process of SARS-CoV-2.[34]

Conclusion

COVID-19 represents the greatest global crisis since the pandemic influenza outbreak of 1918. Many clinical trials are being launched to investigate potential therapies for COVID-19. This simply suggests the pressing need to produce high-quality evidences since the currently used agents have yet to demonstrate consistent results. The available clinical options need to undergo intensive clinical testing. Hence, all the treatment options should be carefully considered in the right context at the time of application.

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