Treatment of COVID-19: A review of emerging treatment

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Abstract

COVID-19 has caused a devastating pandemic, infecting 3,090,445 people and causing 217,769 deaths, as of 30 April, 2020. The current evidence base for selected drugs repositioned to treat COVID-19 are summarized here. Chloroquine (CQ) and hydroxychloroquine (HCQ) block the entry of the SARS-CoV-2 virus into cells and have immunomodulatory effects. Early, poor quality studies pointed to benefit with CQ and HCQ treatment in COVID-19 infection, but no further evidence supporting their use is available to date, and the drugs cannot be recommended for treatment or prophylaxis. However, several countries use CQ or HCQ for compassionate treatment. Lopinavir-ritonavir, which is effective against HIV, was evaluated in one clinical trial which showed no benefit. Remdesivir, a drug developed for EBOLA, has been shown to have in-vitro efficacy against SARS-CoV-2, and the treatment has been used on compassionate grounds in severe cases. Limited studies have shown clinical improvement with remdesivir which is approved for emergency use in severe COVID-19. The RNA polymerase inhibitor favipiravir has been shown to improve clinical features, hasten viral clearance, and improve HRCT findings. Corticosteroids have shown no benefit. Trials are underway with the IL-6 receptor blocking monoclonal antibody tocilizumab, with retrospective data showing reduction in inflammatory markers and clinical improvement. Convalescent plasma has been shown to be of some benefit in severe cases of SARS, MERS and H1N1 influenza, and is recommended by the FDA for those with serious or immediately life-threatening infection with COVID-19. Several large randomized controlled trials are underway, evaluating these repositioned therapies as well as many other treatments. No effective specific treatments are available for COVID-19 infection as yet.

Key words: COVID-19, SARS-CoV-2, chloroquine, hydroxychloroquine, remdesivir, favipiravir, lopinavir-ritonavir

The virus SARS-CoV-2 emerged in December 2019 in Wuhan, China and spread rapidly worldwide. As of April 30, 2020, the virus has spread to 213 countries, infecting 3,090,445 and causing death in 217,769¹. The SARS-CoV-2 is a single stranded RNA beta-corona virus, similar to SARS and MERS². Therefore, drugs which were effective against SARS and MERS were repositioned for SARS-CoV-2. On behalf of the Ceylon College of Physicians’ “Subcommittee for Guidance on Treatment and Prophylaxis against COVID-19”, we herein summarize the current evidence as of May 2, 2020 for selected repositioned drugs which have been used in the current COVID-19 pandemic.

Antiviral agents

Chloroquine and hydroxychloroquine

Chloroquine (CQ) has been used effectively against malaria and hydroxychloroquine (HCQ) against systemic lupus erythematosus and rheumatoid arthritis for a long time. They appear to block the entry of SARS-CoV-2 virus into cells by inhibiting glycosylation of host receptors, proteolytic processing, and endosomal acidification. They also appear to have immuno-modulatory effects through attenuation of cytokine production³⁴. CQ was shown to be effective against SARS-CoV-2 in vitro with a low half maximal concentration (EC50)⁶. HCQ, a less toxic derivative of CQ, has an in vitro activity with a lower EC50 for SARS-CoV-2 compared with CQ⁶ and by reducing the production of cytokines,
is postulated to attenuate the cytokine storm associated with COVID-19.

No high-quality evidence exists for in-vivo efficacy of CQ/HCQ against COVID-19. A news conference in China held on February 15, 2020 reported the successful use of CQ in more than 100 COVID-19 cases who showed improved radiologic findings, enhanced viral clearance, and reduced disease progression. The clinical trial designs and outcome data, however, have not been presented yet nor published for peer review.

Many of the clinical trials that appear to show an efficacy of HCQ against COVID-19 have been open-labelled non-randomized ones, performed without a control arm and underpowered to detect a significant clinical effect. While some show an early virologic clearance measured from nasopharyngeal swabs and reduced body temperature recovery time and cough, others show no benefit with HCQ when compared with standard care. The claim of increased clearance when HCQ was combined with azithromycin, was not shown in a randomized controlled trial conducted by Molina et al. HCQ also showed no benefit when given to those with COVID-19 hypoxic pneumonia.

There is limited data regarding the optimal dose of CQ and HCQ to ensure the safety and efficacy when prescribed to those with COVID-19. The trials have used different regimens which make comparisons difficult. While both these drugs are known to prolong QTc, in many trials this does not appear to be a problem. Higher doses of CQ in COVID-19 however, have been associated with prolongation of QTc and reduced body temperature recovery time and cough. Others show no benefit with HCQ when compared with standard care. The claim of increased clearance when HCQ was combined with azithromycin, was not shown in a randomized controlled trial conducted by Molina et al. HCQ also showed no benefit when given to those with COVID-19 hypoxic pneumonia.

Investigational antiviral agents

Remdesivir

Remdesivir (previously GS-57340), is an adenine analogue, which incorporates into nascent viral RNA chains and results in pre-mature termination. It showed promise during the Ebola outbreak and is currently under development for treatment of Ebola infection. Remdesivir was considered a potential therapeutic agent for COVID-19 as it has shown in-vitro efficacy against SARS-CoV and MERS. Some patients with severe disease have been given a 10-day course of remdesivir on compassionate grounds. Analysis of data from these patients showed a significant improvement in oxygen-support class, reduction in the need for mechanical ventilation and a reduction in mortality in those given remdesivir. Interestingly, coexisting conditions and duration of symptoms before remdesivir treatment was initiated, were not significantly associated with clinical improvement. Mild-to-moderate elevation of liver transaminases was seen in those given remdesivir and this needs to be carefully monitored in view of hepatic dysfunction seen in those with COVID-19. As viral load data was not collected, the antiviral effects of remdesivir and any association between baseline viral load and viral suppression, and clinical response could not be confirmed. Preliminary results from the Adaptive COVID-19 Treatment Trial (ACTT) sponsored by the National Institute of Allergy and Infectious Diseases, National Institute of Health, USA showed that remdesivir accelerates recovery from advanced COVID-19. However, a randomized, double-blind, placebo-controlled, multicenter trial conducted in adults with severe COVID-19 in Hubei, China, remdesivir was not associated with significant clinical benefit. Based on current evidence, US FDA has
issued an emergency use authorization (EUA) of remdesivir for treatment of hospitalized severe COVID-19 patients 27.

**Favipiravir**

Favipiravir (FPV) is a new type of RNA-dependent RNA polymerase (RdRp) inhibitor. High concentration of favipiravir (EC50 = 61.88 μM, half-cytotoxic concentration (CC50), > 400 μM, selectivity index (SI)) > 6.46) has been shown to inhibit SARS-CoV-2 infection in Vero E6 cells 5. An open-label nonrandomized controlled study of FPV vs lopinavir-ritonavir in COVID-19 patients with mild to moderate disease, has shown significantly shorter median time of viral clearance and better CT resolution in FPV group 28. A prospective, multi-center, open-label, randomized superiority trial comparing umifenovir (Arbidol) and FPV showed a higher clinical recovery rate at 7 days and more effective reduction of fever and cough 29. This study also showed a non-significant benefit with favipiravir in COVID-19 patients with multiple comorbidities. Currently favipiravir is approved in Japan for influenza 30 and is investigational for use in COVID-19.

**Adjuvant therapies**

In the absence of proven therapy for SARS-CoV-2, supportive care remains the cornerstone of management for patients with COVID-19. These range from symptom management, mainly as outpatients in many parts of the world to full intensive care support for those with critical disease. Of the many that have been tried, corticosteroids, immunomodulatory agents, and immunoglobulin therapy have shown some promise. In these too, the small numbers of patients who have received the therapies and the multiple treatment modalities tried, make data interpretation difficult.

**Corticosteroids**

The pathological similarity between COVID-19 pneumonia and those seen in SARS and MERS, with changes suggestive of acute respiratory distress syndrome (ARDS) 31 makes the use of methylprednisolone (MPP) an attractive therapeutic option. In these patients MPP is expected to attenuate lung inflammation, a result of the "cytokine storm" seen in those with severe COVID-19 32. However, patients with MERS-CoV 33 or influenza 34 who were given corticosteroids were more likely to have prolonged viral replication, receive mechanical ventilation, and have higher mortality. A retrospective study on a cohort of patients with severe COVID-19 pneumonia with and without MPP showed that early, low-dose and short-term application of MPP was associated with shorter time for normalcy of body temperature, faster improvement of SpO2 with significantly shorter interval of using supplemental oxygen therapy and a significantly better absorption degree of the focus in chest CTs 35. The authors recommend the early use of MPP is those with severe pneumonia as worsening occurs during 5th to 7th day of the illness. However, due to methodological limitations of the studies, delayed viral clearance and complication, corticosteroid treatment for COVID-19 lung injury remains controversial 36. Guidelines issued by the World Health Organization, Royal College of Physicians (London) and Indian Council of Medical Research recommend against the routine use of steroids in those with severe COVID-19 pneumonia.

**Immunomodulatory agents**

The cytokine storm syndrome seen in those with severe COVID-19 pneumonia is the potential target for immunomodulatory therapies 37. Tocilizumab (TCZ), a monoclonal antibody against IL-6 receptors, has been evaluated in few clinical trials of those with severe COVID-19. Retrospective analysis of data from patients treated with TCZ showed a gradual reduction of acute phase reactants and IL-6 with improved clinical stability 38,39. Early, repeated dosing of TCZ appear to be beneficial in severe COVID-19 38,40. Several RCTs of tocilizumab, alone or in combination, in patients with COVID-19 with severe pneumonia are being conducted and TCZ is included in the current edition of the Chinese national treatment guidelines for COVID-19 41.

**Convalescent plasma or hyperimmune immunoglobulins**

It has been postulated that antibodies from those recovered from the infection may help with immune clearance of the free virus and infected cells. Convalescent plasma (CP) has been used as salvage therapy in SARS 42, MERS 43 and H1N1 influenza 44. In those with severe H1N1 influenza, treatment with CP was associated with a reduction of viral load and reduced mortality 45. Use of convalescent plasma in those with severe respiratory infections was not associated with adverse events or complications after treatment 46. In a limited number of patients with severe COVID-19 treated with CP in addition to antivirals and MPP, an increase in neutralizing antibodies, improvement in clinical symptoms and radiological evidence
for absorption of lung lesions without severe adverse events was observed. Key factors associated with efficacy of CP therapy are neutralizing antibody titre and treatment time point. The FDA has also approved the compassionate use of convalescent plasma to those with serious or immediately life threatening COVID-19 infections. Dipyridamole

Experimental models of SARS-CoV infection, showed that Spike protein engagement decreases ACE2 expression and activates the renin-angiotensin system (RAS). RAS activation promotes platelet adhesion and aggregation and increases the risk for pulmonary embolism, hypertension and fibrosis. Dipyridamole was shown to suppress HCoV-19 replication in vitro and significantly increased platelet and lymphocyte counts and decreased D-dimer levels in comparison to controls when given as adjuvant therapy to patients with COVID-19.

Prophylactic therapy

Despite being used, no evidence exists for prophylactic use of either CQ or HCQ for COVID-19. In Annals on Call, the COVID-19 Global Rheumatology Alliance reports that about 25% of those who were already on HCQ for rheumatological diseases had got COVID-19.

Problems with interpreting trial data

COVID-19 saw an unprecedented number of publications related to different aspect of the disease. In relation to treatment modalities a significant number were pre-publications which have not undergone peer review. Most studies are conducted in small numbers of patients and lack a control arm. Therefore, it is not possible to determine the true clinical effect of this intervention or whether patients might have recovered without these therapies. The baseline characteristics differ widely making comparisons between similar therapeutic modalities difficult. Those of adjuvant therapies are confounded by the concomitant use of different combinations of antivirals and adjuvant therapies. As such all these treatment options must be further investigated in randomized clinical studies. At present, 681 interventional clinical trials looking at the repositioned drugs for COVID-19 are registered with https://clinicaltrials.gov and better evidence is likely to be available during the course of the year.

Conclusions

The COVID-19 pandemic remains the biggest global public health crisis to date. Despite rapidly conducted clinical trials and observational studies, no strong evidence exists for the efficacy of any of the repositioned drugs in the treatment of COVID-19. All studies conducted to date have methodological flaws which make claims of data questionable. The use of multiple medications, lack of uniformity among patients enrolled and diverse treatment regimens even with the same drug make comparison of results difficult. These issues highlight the need for good quality, randomized clinical trials even in the midst of a pandemic. For the moment management of COVID-19 rests with prevention of infection, case detection and monitoring and supportive care in those with severe illness. Any medicine or treatment modality for COVID-19 is only on compassionate/emergency use or in the setting of a clinical trial.

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