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# CONTAINMENT AND PHARMACOLOGICAL THERAPIES FOR COVID-19 MANAGEMENT

**[1]*Dr. Shweta Sharma, [2]Dr. Meghna Pandey and [3]Dr. Vinod Kapoor**

[1]MD Pharmacology, Assistant Professor, Faculty of Medicine and Health Sciences, SGT University, Budhera, Gurugram, 122505.

[2]MD Pharmacology, Associate Professor, Faculty of Medicine and Health Sciences, SGT University, Budhera, Gurugram, 122505.

[3]Professor, Faculty of Medicine and Health Sciences, SGT University, Budhera, Gurugram, 122505.

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***Corresponding Author**
**Dr. Shweta Sharma**
MD Pharmacology, Assistant Professor, Faculty of Medicine and Health Sciences, SGT University, Budhera, Gurugram, 122505.

## ABSTRACT

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) caused by coronavirus 2019 (COVID-19) is spreading all over the world as a pandemic. It has a significant impact on global public health and economies. The biological agents/ vaccines of proven efficacy to treat or prevent this human coronavirus infection are in dire need and are being investigated worldwide. In this article, we review the recent advances in COVID-19, including the response by the host cells, the cytokine release syndrome, and the therapeutic approaches to inhibit the virus and alleviate the cytokine storm.

**KEYWORDS:** COVID-19, SARS-CoV-2, Management, Therapies.

## Containment of SARS-CoV-2

The SARS-CoV-2 is a new virus which shares 79.5% sequence similar to genome sequence of SARS-CoV.[1] The virus exhibits a high reproduction number[2,3], is more infectious and spreads easier between people than the SARS virus.[4] Some people doubted that this virus might be uncontainable and a “let go” policy might be suitable for this pandemic since the cost will be too high to afford strict social distancing and isolation. This approach may be inappropriate for some reasons. Firstly, the historic experience with both SARS and MERS demonstrated that coronavirus with high virulence do have tendency of self-limitation. Secondly, recent studies reported that the asymptomatic cases with transmissibility account

for only a small proportion (889/72314, 1.2%) of COVID-19 patient.[5] Thirdly, preliminary data on the recovered cases showed the presence of a very high titre of neutralizing antibodies (39/40 with titre of at least 1:640 while the remaining one had a titre of 1:32[6]), indicating the high probability of viral clearance in the great majority of infected populations. Hence, providing firm evidence that this virus is containable. In our country, the policy-makers recognized China's experience in combating COVID-19 and decided to apply sound policy of well-designed containment strategy. In extreme cases, use of national force including police and armed force is necessary to meet this unprecedented public health crisis. Anti-virus approaches in addition to oxygen and other supportive therapeutics are being tested in clinical trials including convalescent patient plasma.[6,7] In some COVID-19 patients who had viremia, the transfusion of convalescent plasma (CP) from recovered patients significantly reduced the viral load. Recent studies provided evidence that even after viremia, the viral infection may persist in the target organs including lungs, necessitating the CP therapy even in the relatively late stage of severe disease.[8] On the other hand, Cytokine Releasing Syndrome (CRS)-clearing drugs represent another key remedy to save severe cases. A monoclonal antibody against IL-6 receptor, tocilizumab, is shown to be effective in treating COVID-19. To achieve maximal efficacy, combined usage of anti-viral drugs, CP and drugs against cytokine storm, should be considered in clinical trials for severe cases.

**Therapeutic Targets and Agents**

Despite advances in Drug Discovery, the viral infections always remain the major challenge for the Scientists across the globe. Due to novelty of this virus, it will take minimum of a year or so to develop a vaccine or cure. But the increasing mortality rate across the countries demands an early cure. So, drug repurposing could be an alternative.

**Chloroquine and Hydroxychloroquine**

Chloroquine is extensively utilized in anti-malaria and autoimmune diseases, has been found to be a potential broad-spectrum antiviral agent.[9] It can prevent viral infections via elevating the endosomal pH needed for virus-cell fusion and disturbing the glycosylation of SARS-CoV cell receptors.[10] Gao et al. revealed that chloroquine was effective in the therapy of COVID-19-associated pneumonia.[11] Wang and team also conducted *in vitro* study, and they found that it is an ideal candidate antiviral drug against SARS-CoV-2 infection in Vero E6 cells with EC50 value of around 1 μM.[12] Although several trials had verified that

chloroquine suppresses the exacerbation of COVID-19, the optimal dosage of chloroquine will require to be evaluated in future trials.[11]

Hydroxychloroquine is an analog of chloroquine. In early trials, it has shown the efficacy as a potent antiviral against this infection. It helps in causing the increase in endosomal pH and makes the environment unfavorable for the fusion of virus/cell. However, recent clinical trials are proving that it has no benefits on mortality, lymphopenia or neutrophil-to-lymphocyte ratio improvement when used alone. Neither the evidence of antiviral activity of its combination with azithromycin for the treatment of hospitalised patients with severe COVID-19 was found in a recent trial by Molina et al.[13] Azithromycin itself does not usually cause clinically significant prolongation of the QTc interval,[14] but its use in combination with either chloroquine or hydroxychloroquine could theoretically increase the risk of Torsades de pointes.

According to latest guidelines from Indian Council of medical research (ICMR), there is a significant dose-response relationship between the number of prophylactic doses taken and frequency of occurrence of SARS-CoV-2 infection in symptomatic healthcare workers who were tested for SARS-CoV-2 infection. They have streamlined the dosage for the asymptomatic healthcare/ frontline workers, i.e., 400 mg twice a day on Day 1, followed by 400 mg once weekly for next 7 weeks; to be taken with meals.

**Remdesivir**

Remdesivir which is an adenosine analogue, incorporates into nascent viral RNA chains of the virus and results in its premature termination. Further trials of the drug are being carried over in patients of COVID-19 on the priority basis. Measurement of its efficacy would require ongoing clinical trials. Notably, intravenously administration of Remdesivir after development of pneumonia remarkably improved clinical condition, reported in the first case of novel coronavirus infection in the united states[15], though this could not be definitely ascribed to the effect of the drug. Currently, clinical trials are ongoing evaluating the efficacy and safety of Remdesivir in patients hospitalized with mild, moderate (NCT04252664) and severe (NCT04257656) COVID-19. Up to now, several results of clinical trials on the efficacy of Remdesivir for COVID-19 have published. Beigel et al. have reported a multicenter trial enrolling 1063 patients that conducted in 60 sites and 13 subsites globally.[16] In the remdesivir treated group, the time to recovery was significantly shorter compared to the placebo (NCT04280705). Gilead Sciences company reported the improved clinical

outcomes of the patients with severe COVID-19 treated with remdesivir in a compassionate-use program. No new safety signal was observed during the therapy.[17] In contrast, in a multicenter trial conducted at ten hospitals in Hubei, China, use of remdesivir in severe COVID-19 patients was not statistically significantly correlated to improve the time to clinical improvement, mortality, or time to eliminate virus.[18] The opposite clinical outcomes resulting from various studies may mainly ascribe to different clinical parameters setting, outcome measures, and eligibility criteria for enrollment. Larger sample sizes and more rigorous clinical trial designs are required to further confirm the potency of remdesivir against SARS-CoV-2 infection.

**Tocilizumab**

Tocilizumab, an immunosuppressive agent, is found to be efficacious *in vivo* in the patients of COVID- 19 in China.[19] It is a recombinant humanised monoclonal antibody against interleukin-6 (IL-6) and can be used as an alternative treatment for patients with a risk of cytokine storms. Also, for critically ill patients with elevated IL-6, the repeated dose of the Tocilizumab is recommended.[20] This drug is primarily used to treat rheumatoid arthritis. When it was tested in COVID 19 patients. it effectively improved the clinical symptoms of viral infection, but the count of patients included in the study were very less. Its mechanism could be explained by the important role of Interleukin-6 (IL-6) in cytokine release syndrome (CRS). If it can block the signal transduction pathway of IL-6, it is expected to become a new method for the treatment of severe patients. Tocilizumab is a blocker of IL-6R, which can effectively block IL-6 signal transduction.

One study in China recruited 21 patients who were severely or critically ill due to COVID-19. Reduction in the need for oxygen supplement after receiving tocilizumab (400 mg once through IV infusion; three patients had another dose administered due to continued fever within 12 hours) was observed in 75 percent of the patients. Nineteen patients were discharged on average 13.5 ± 3.1 days hospitalization time after the use of tocilizumab.[21] The US Food and Drug Administration (FDA) has approved a phase III clinical trial for evaluation of tocilizumab in hospitalized patients with severe COVID-19 pneumonia (NCT04320615). Meanwhile, one more IL-6 receptor antagonist, Sarilumab is also under investigation. Phase II/III clinical trials have been launched to evaluate its efficacy in curing the COVID-19 infection (NCT04315298). But still the data on the use of these molecules in the treatment of SARS-CoV-2 infection are still preliminary.

**Baricitinib**

Baricitinib can also be used for the treatment of COVID-19 patients.[22] It might target the process of endocytosis, because the receptor that SARS-CoV-2 uses to infect lung cells might be ACE2, which are prone to viral infection. The AP2-associated protein kinase 1 (AAK1) could be one of the known regulators of endocytosis. Disruption of AAK1 might interrupt the passage of the virus into cells and also the intracellular assembly of virus particles.[23] Again, the data is too less to establish the facts, still repurposing the use of this drug might help in current scenario.

**Convalescent Plasma Technique**

The convalescent plasma (CP) extracted from the patients who have recovered and having antibodies against 2019-nCoV can be effectively used in turning down the mortality rate of critically ill patients with this virulent disease.[24] The antibodies from CP might suppress viremia via free viral clearance, blockade of new infection and the momentum of infected cell clearance.[25] Also, the use of serum and CP was also suggested by World Health Organisation (WHO) under Blood Regulators network until vaccines and antiviral drug are unavailable for this novel virus. Association with the occurrence of Serious adverse events is also not established yet.[26] Convalescent plasma, if available, can be used for the treatment of critically ill patients with COVID-19 after the assessment of the count of antibody. It could be useful to test the efficacy and safety of CP transfusion in COVID-19 patients.

In India, the ICMR has approved 21 institutions for participating in a randomised controlled trial to assess the safety and efficacy of convalescent plasma to limit complications associated with COVID-19.

## CONCLUSION

Currently, there is no specific treatment for the cure of this new Corona virus. All the drugs in options are repurposed, i.e., previously they are being used for treatment of other diseases. But in lieu of structure of the virus and pre-clinical studies, they are incorporated. Extensive clinical trials are being performed. Health care professionals and scientists are working day and night to treat the patients and find the cure. Pharmacological interventions are being given on compassionate grounds. To completely halt the disease, a vaccine is urgently needed. For better awareness of this new virus, vigorous research work is required to be done and optimal strategies for the treatment shall be established.

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