TREATMENT FOR A PANDEMIC: AN ONGOING SEARCH

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Is there a cure for COVID-19? Does everyone with the disease require treatment? At what stage of infection does treatment become essential? What are the different approaches that are used to treat COVID-19 patients? What are some of the key concerns, side-effects, and limitations of each approach?

The ongoing COVID-19 pandemic, caused by the SARS-CoV-2 virus, has affected millions around the globe, and caused thousands of deaths. Until large-scale vaccination becomes a possibility, the outbreak is being managed through public health measures to slow the spread of infection and supportive measures to treat the infected. How do we treat a disease caused by a 'novel' pathogen?

Approaches to treatment

Not everyone infected with COVID-19 requires treatment. The immune response that SARS-CoV-2 virus triggers in our body is, in most cases (~ 81% of people), enough to resolve the infection with no (asymptomatic), or a few mild symptoms. More severe or critical symptoms are seen only when damage caused by the virus is combined with a dysfunctional (out of proportion) immune response.

Based on how host-virus interactions correlate with clinical symptoms, three phases of COVID-19 disease progression have been proposed — an incubation or early infection phase, a pulmonary phase, and a hyperinflammatory phase (see **Fig. 1**). While these phases can show much overlap, their identification can help in more effective treatment. For example, containment of the virus would be more important in the first phase, whereas immunosuppressive treatment would be more helpful in the second and third phases.

As of now, no specific drug is known to prevent or treat this infection. But researchers across the world are working on two strategies — designing new drugs, and repurposing existing drugs (see **Box 1**). Based on how they act, these pharmacological approaches are of two kinds:

- **Those that target the novel virus:** This includes drugs that prevent viral invasion, and protect host cells from infection. For example, inhibitors of cellular enzymes (like proteases and furins) help prevent the assembly of new viruses, while endosomal entry inhibitors may prevent the entry of the virus into host cells. Drugs affecting viral replication can prevent the spread of infection within our body.
- **Those that can help treat symptoms of the disease:** This includes drugs that can reduce disease severity and risk of death. For example, people with ongoing inflammation (due to hypertension, cardiovascular conditions, or diabetes) tend to be at greater risk of developing severe illness. Also, severe cases of COVID-19 show a strong inflammatory response (hyperinflammatory phase) with an overwhelming release of cytokines (called a cytokine storm). This plays a critical role in respiratory failure. Drugs that target this irregular inflammatory response can help manage such symptoms.

Antiviral drugs

Unlike antibiotics (which act against bacteria), antiviral drugs do not 'kill' the virus. They only inhibit its development within the host, giving the host's immune system time to mount a response against the virus. Most antiviral drugs are directed against virus-specific replication processes. Since virus replication occurs within host cells and uses the host cellular machinery, the challenge is to develop drugs that inhibit the virus without harming the host. Hence, drugs against other coronaviruses like SARS-CoV and MERS-CoV, or viruses like HIV, are being explored for COVID-19 treatment. Repurposing antivirals is not simple — a drug that works against SARS-CoV or MERS-CoV may not necessarily work against SARS-CoV-2. Despite these limitations, antivirals like remdesivir, lopinavir-ritonavir, favipiravir, tenofovir, and ribavirin have shown some promising results against SARS-CoV-2 (see **Box 2**). Clinical trials will help determine their safety and efficacy in COVID-19 treatment.

Convalescent Plasma Therapy (CPT)

This approach, also known as **Therapeutic Plasma Exchange** (TPE), was found to be useful during the SARS pandemic. It is based on

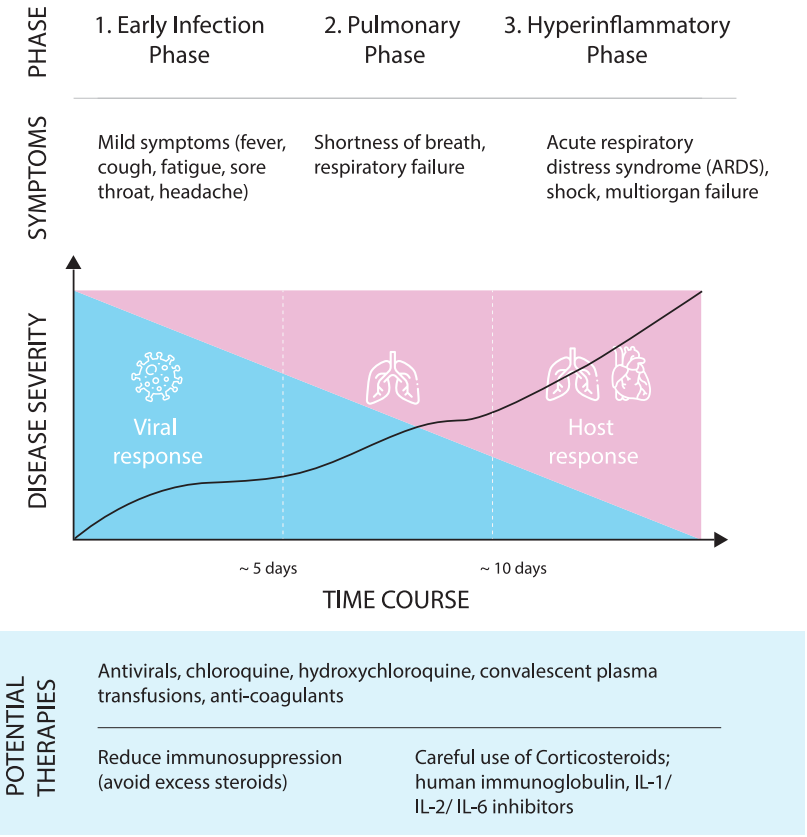

Fig. 1. COVID-19 progression with common symptoms and likely treatment strategies. Each phase is characterized by a different type of biological interaction between SARS-CoV-2 and the body's immune response. In Phase I, or the early infection or incubation phase, the SARS-CoV-2 virus infects cells in the respiratory tract, replicates within them, and releases new viral particles. In Phase II, or the pulmonary phase, the infection reaches the lungs and the body's immune system is strongly affected by it. In Phase III, or the hyperinflammatory phase, the virus moves from the lungs to the blood, reaching and infecting other body organs. The body's response against the virus is amplified to an extent where it may cause injury to its own organs. All three phases are seen only in severe cases.

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Box 1. New and old drugs:

The design of new drugs is affected by limitations in our understanding of SARS-CoV-2 biology, and the host-pathogen interactions that lead to COVID-19. Also, the process of drug development, like that of new vaccines, is expensive, time-consuming, and has a very low success rate. Some reports suggest that only 1 out of 10,000 preclinical compounds reaches the market.[1] In contrast, repurposing existing drugs (developed against similar viruses, or with the ability to treat the same/ related symptoms) requires tests for safety and efficacy in treating different disease phases. Since this is relatively faster, many existing drugs and treatment regimens are currently undergoing clinical trials.

Box 2. Repurposing antivirals:

Remdesivir, a drug against Ebola (also an RNA virus), affects RNA dependent RNA polymerase — an enzyme that is essential for RNA virus replication and protein synthesis.[2] It is active against SARS-CoV-2, SARS-CoV, and MERS-CoV in laboratory *(in vitro)* tests and in animal *(in vivo)* studies. But its adverse effects include skin rashes, loose stools, rise in liver enzymes (indicating liver damage) and creatinine (indicating poor kidney function), and low blood pressure. In some cases, it can lead to more serious conditions, like multiple-organ-dysfunction syndrome, septic shock, and acute kidney injury.[3] The Drug Controller General of India (DCGI) has approved the use of remdesivir for emergency use to treat hospitalised patients with severe COVID-19.

Lopinavir–ritonavir combinations have been used during SARS and MERS outbreaks. Lopinavir, an anti-HIV drug, inhibits the folding of viral proteins by inhibiting the virus-specific enzyme aspartate protease. Ritonavir acts by increasing the serum concentration of lopinavir. Adverse effects of the lopinavir-ritonavir combination include severe skin eruptions, anaemia, lower blood WBC count, inflammation of the pancreas, and liver injury.[4] The Indian Council of Medical Research (ICMR) advises restricted public health emergency use of lopinavir-ritonavir combination therapy for severe COVID-19 patients.

Favipiravir, an anti-influenza drug, is undergoing clinical trials for treatment against SARS-CoV-2, especially in combination with drugs like chloroquine phosphate and tocilizumab.

the principle that a person who has recovered from a COVID-19 infection would have neutralizing immunoglobulins (antibodies) against SARS-CoV-2 in their blood plasma (convalescent plasma). When this plasma (the liquid part of blood minus the blood cells) is transferred to an infected person, the anti-SARS-CoV-2 antibodies would neutralize the virus in the recipient (see **Fig. 2**).

The challenge for this therapy lies in finding healthy donors with high titres of neutralizing antibodies. The plasma donors need to have had COVID-19, but been completely symptom-free for at least 14-28 days before donation. They need to test negative for COVID-19, and have high SARS-CoV-2 neutralizing antibody titres. They also need to be healthy enough to donate plasma. The potential risks of convalescent plasma therapy include transfusion-related allergic reactions and pathogen transmission.[5]

Preliminary studies have shown a decrease in nasopharyngeal SARS-CoV-2 viral load, reduction in COVID-19 disease severity, and improved blood oxygenation after 12 days of CPT.[6] However, these studies are limited by small sample sizes and lack of robust data. In India, the ICMR has approved a multicentric phase-II clinical trial to test the efficacy of CPT on COVID-19 patients with moderate illness.

Drugs against other pathogens

Drugs against other pathogens can act in ways that could help treat viral infections. For example, the antimalarial drugs chloroquine and hydroxychloroquine, the antiparasitic drug ivermectin, and the antibiotic azithromycin are now being studied for anti-SARS-CoV-2 activity (see **Box 3**).

Monoclonal antibodies/ IL-6 pathway inhibitors

In critically ill patients, mild or severe cytokine release syndrome (CRS) could lead to Acute Respiratory Distress Syndrome (ARDS). A cytokine can only act on a cell if it can bind to specific membrane receptors, and drugs like tocilizumab, itolizumab, sarilumab, and siltuximab can inhibit these receptors. Thus, the DCGI has approved the use of tocilizumab, and a similar drug itolizumab, for emergency use in severe COVID-19 patients. Tocilizumab is a humanized monoclonal antibody (monoclonal antibodies are produced by a single cell and bind to the same region of an antigen) that blocks the IL-6 receptor. Originally developed for rheumatoid arthritis, it is recommended for use in CRS.[15] Results of clinical trials to evaluate the safety and efficacy of tocilizumab and sarilumab in severe COVID-19 pneumonia are awaited.

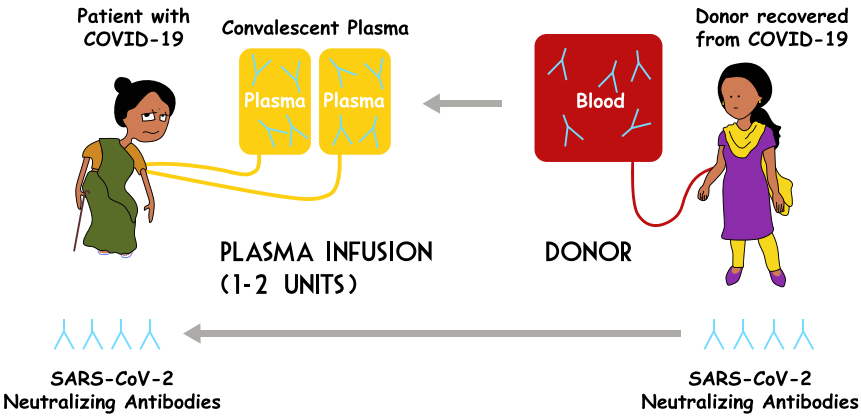

Fig. 2. How does Convalescent Plasma Therapy work?

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Box 3. Repurposing drugs against other pathogens:

Chloroquine (CQ) and its analogue Hydroxychloroquine (HCQ) inhibit SARS-CoV-2 *in vitro*. HCQ is possibly the more potent of the two.[7] Their antiviral mode of action is not clear, but could involve inhibition of pH-dependent steps of viral replication. They are also believed to act as immunomodulators, inhibiting tumour necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) — cytokines that in excessive amounts lead to hyperinflammation.[8] Initial studies on COVID-19 patients claimed that HCQ use was associated with faster recovery time, decreased nasopharyngeal shedding of the virus, improved lung health, and a lower chance of progression to severe illness. These studies have been questioned due to their small sample sizes, lack of double blinding (that minimises risk of bias), and lack of placebo control (that eliminates the possibility of therapy due to psychological processes rather than physiological ones). Recent studies suggest that HCQ has no beneficial effects in patients hospitalized with COVID-19. A few preliminary studies even suggest that treatment with CQ/HCQ may be associated with similar or even increased risk of death, especially when used in combination with azithromycin.[9] In India, the ICMR has advocated the supervised prophylactic use of CQ/HCQ in high-risk populations like health care workers, and therapeutic use in severely ill COVID-19 patients.

Ivermectin, used against HIV and dengue viruses, acts by inhibiting the replication and assembly of new virions. *In vitro* studies have shown that high concentrations of this drug can inhibit SARS-CoV-2 replication.[10] It has been suggested that combination therapy of ivermectin with other drugs may be beneficial.

Azithromycin has been shown to have anti-inflammatory activity *in vitro* and in clinical studies[11], as well as antiviral activity against Zika and Ebola viruses *in vitro*.[12] It induces the same cytokines (like IFN-α, IFN-β and IFN-λ) that the body produces in response to viral infection and are known to inhibit viral replication in host cells.[13] Preliminary studies in COVID-19 patients have shown that azithromycin can influence the course of viral infection and clinical outcomes for the better.[14] But further studies and validation will be needed before its use in COVID-19 treatment can be recommended, especially in combination with HCQ.

Systemic corticosteroids

Corticosteroids are steroid hormones that regulate inflammation and the immune response. Though systemic corticosteroids are not recommended for the treatment of viral pneumonia or ARDS, glucocorticoids such as methylprednisolone may be of limited help in severe COVID-19 induced ARDS. A recent study showed that dexamethasone, another glucocorticoid, reduced fever and mortality among critically ill COVID-19 patients.[16] However, evidence from the use of systemic corticosteroids in treatment of SARS and MERS indicates a likelihood of harmful side effects to the body without clear benefit in treating symptoms of infection. The Ministry of Health and Family Welfare, Govt. of India, advises the use of dexamethasone as an alternative to methylprednisolone in moderate to severe COVID-19 cases.

High-dose intravenous immunoglobulin (IVIg)

IVIg are polyclonal immunoglobulins or antibodies that are produced by different B cells and can bind to different parts of the same antigen. Extracted from healthy donors, IVIg is used in many autoimmune, infectious, and neuromuscular disorders for its immunomodulatory effects.[17] Since it was reported to have benefits with tolerable side-effects in SARS and MERS patients, IVIg therapy is now being used on a case-by-case basis for COVID-19 patients. Trials are underway to evaluate the efficacy of high-dose IVIg in severe COVID-19 patients.

Cell and biological therapy

Mesenchymal Stem Cells (MSCs) are stem cells from our bone marrow that form and repair skeletal tissues like bones and cartilages. They have been shown to have strong immunomodulatory effects. Hence, MSCs have been used for treatment of immune-mediated disorders like systemic lupus erythematosus (where the immune system attacks healthy tissue) and graft-versus-host disease (where the recipient of a transplant is attacked by cells of the graft).[18] Today, scientists are exploring the possibility of using MSCs to reduce the cytokine storm caused by a dysfunctional immune response to the SARS-CoV-2 virus. One concern regarding this line of treatment is the possibility of causing adverse long-term effects on the immune system.

Anticoagulants

COVID-19 patients have been reported to have a higher incidence of venous thromboembolism. In this condition, blood clots from leg and arm veins travel to the lungs and cause blockage. The use of anticoagulants (commonly called blood thinners) has been associated with reduced ICU mortality. Hence, the use of anticoagulants like enoxaparin or heparin to prevent clot formation in COVID-19 is being explored.[19] The World Health Organization (WHO) recommends the use of prophylactic heparin against venous thromboembolism in severe to critically ill COVID-19 patients, unless they are suffering from active bleeding or low platelet count etc.

Parting thoughts

Finding a cure for COVID-19 is a matter of great urgency. But it is important to note that many pharmacological therapies that have shown potential need to be studied extensively, especially for adverse effects and their long-term consequences. Clinical trials are underway in multiple countries to address some of these issues. The need of the hour is to coordinate research efforts across the globe for effective anti-SARS-CoV-2 drug design.

Key takeaways

- The immune response that SARS-CoV-2 triggers in our body is enough to resolve disease in most cases. Treatment is necessary only for those with severe or critical symptoms.
- Identifying the phase of disease progression — early infection, pulmonary or hyperinflammatory — can help in more effective treatment.
- Two strategies — designing new drugs, and repurposing existing drugs — are being explored to find drugs that can help prevent or treat COVID-19.
- Depending on their mode of action, pharmacological approaches to COVID-19 treatment either target the novel virus, or help treat symptoms of the disease.
- Treatment strategies involving the use of antiviral drugs, Convalescent Plasma Therapy, and repurposed drugs against other pathogens are being explored for their ability to target the novel virus.
- Treatment strategies involving the use of monoclonal antibodies/IL-6 pathway inhibitors, corticosteroids, high-dose intravenous immunoglobulins (IVIg), cell and biological therapy, and anticoagulants are being explored for their ability to treat symptoms of COVID-19.
- Many promising pharmacological therapies need to be studied extensively, especially to understand their adverse effects and long-term consequences.

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References:

1. Moreno L., Pearson A.D. How can attrition rates be reduced in cancer drug discovery? Expert Opinion on Drug Discovery. 2013; 8:363–368.
2. Mulangu S, Dodd LE, Davey RT Jr, Tshiani Mbaya O, Proschan M, Mukadi D, et al. A randomized, controlled trial of Ebola virus disease therapeutics. N Engl J Med. 2019;381(24):2293–303.
3. Grein J, Ohmagari N, Shin D, Diaz G, Asperges E, Castagna A, et al. Compassionate use of remdesivir for patients with severe Covid-19. N Engl J Med 2020. doi: 10.1056/NEJMoa2007016.
4. Kaplan SS, Hicks CB. Safety and antiviral activity of lopinavir/ritonavir-based therapy in human immunodeficiency virus type 1 (HIV-1) infection. J Antimicrob Chemother. 2005;56(2):273–6.
5. COVID-19 Treatment Guidance Writing Group. JHMI clinical guidance for available pharmacologic therapies 2020 [updated 25 March 2020]. Available from: https://www.hopkinsguides.com/hopkins/view/Johns_Hopkins_ABX_Guide/540747/all/Coronavirus_COVID_19__SARS_CoV_2_.
6. Shen C, Wang Z, Zhao F, Yang Y, Li J, Yuan J, et al. Treatment of 5 critically ill patients with COVID-19 with convalescent plasma. JAMA 2020. doi: 10.1001/jama. 2020.4783.
7. Yao X, Ye F, Zhang M, Cui C, Huang B, Niu P, et al. *In vitro* antiviral activity and projection of optimized dosing Design of Hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Clin Infect Dis. 2020.
8. Savarino A, Boelaert JR, Cassone A, Majori G, Cauda R. Effects of chloroquine on viral infections: an old drug against today's diseases? Lancet Infect Dis. 2003;3(11):722–7.
9. Andrea Cortegiani, Mariachiara Ippolito, Giulia Ingoglia, Pasquale Iozzo, Antonino Giarratano, Sharon Einav Update I. A systematic review on the efficacy and safety of chloroquine/hydroxychloroquine for COVID-19. J Crit Care. 2020 Oct; 59: 176–190.
10. Wagstaff K.M., Sivakumaran H., Heaton S.M., Harrich D., Jans D.A. Ivermectin is a specific inhibitor of importin α/β-mediated nuclear import able to inhibit replication of HIV-1 and dengue virus. Biochem. J. 2012;443(3):851–856.
11. Jaffé A., Bush A. Anti-inflammatory effects of macrolides in lung disease. Pediatr. Pulmonol. 2001; 31:464–473.
12. Retallack H., Di Lullo E., Arias C., Knopp K.A., Laurie M.T., Sandoval-Espinosa C., Mancia Leon W.R., Krencik R., Ullian E.M., Spatazza J., Pollen A.A., Mandel-Brehm C., Nowakowski T.J., Kriegstein A.R., DeRisi J.L. Zika virus cell tropism in the developing human brain and inhibition by azithromycin. Proc. Natl. Acad. Sci. U. S. A. 2016;113(50):14408–14413.
13. Menzel M., Akbarshahi H., Bjermer L., Uller L. Azithromycin induces anti-viral effects in cultured bronchial epithelial cells from COPD patients. Sci. Rep. 2016; 6:28698–28709.
14. Damle B., Vourvahis M., Wang E., Leaney J., Corrigan B. Clinical pharmacology perspectives on the antiviral activity of azithromycin and use in COVID-19. Clin. Pharm. Therap. 2020.
15. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020;395(10229):1033–4.
16. Cinzia Solinas, Laura Perra, Marco Aiello, Edoardo Migliori, Nicola Petrosillo. A critical evaluation of glucocorticoids in the management of severe COVID-19. Cytokine Growth Factor Rev. 2020 Jun 24.
17. Ferrara G, Zumla A, Maeurer M. Intravenous immunoglobulin (IVIg) for refractory and difficult-to-treat infections. Am J Med 2012; 125:1036. e1-8.
18. Leng Z, Zhu R, Hou W, Feng Y, Yang Y, Han, et al. Transplantation of ACE2(-) mesenchymal stem cells improves the outcome of patients with COVID-19 pneumonia. Aging Dis 2020; 11:216-28.
19. Kollias A, Kyriakoulis KG, Dimakakos E, Poulakou G, Stergiou GS, Syrigos K. Thromboembolic risk and anticoagulant therapy in COVID-19 patients: emerging evidence and call for action. Br. J. Haematol. 2020 Jun;189(5):846-847.

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