Editorial

A brief account of various treatment modalities for COVID-19 infections

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COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus and has a case fatality rate of 2-3%, with higher rates among elderly patients and patients with comorbidities. It was determined in a study that the viral load peaked during the first week of illness and then gradually declined over the second week. Viral load also correlates with age and the existent of comorbidities. Furthermore, both IgG and IgM antibodies starts to increase by around day 10 after symptomatic onset and most patients had seroconversion within the first 3 weeks. This hints at the fact that the patients are most infectious during the first week of infection and also accounts for the high transmissibility of SARS-CoV-2 during this period.

Various drugs ranging from immunosuppressive agents to antimalarials have been used in an effort to counter the symptoms of COVID-19. Apart from the drugs, asymptomatic and mild to moderately symptomatic patients have been treated with palliative care ranging from artificial respiration to bi-level positive airway pressure (BiPAP) to over the counter immunity boosters like zinc and vitamin supplements.

The following article summarizes various drugs and their pharmacokinetics in order to reduce viral load and provide symptomatic relieve to COVID-19 patients.

Vaccine and treatment for COVID-19

The SARS-CoV-2 invades the body when one breathes it in or touches a surface contaminated by the virus and then touches the face. It infects the cells lining the throat, airways and lungs and turns them into "coronavirus factories" that spew out huge numbers of new viruses that go on to infect even more cells. At this early stage, the person will not be sick and most people will be asymptomatic. The incubation period varies with age and comorbidities but is 5 days on average.

The mild symptoms in the initial infection are a result of the immune system fighting the infection leading to fever, cough and sore throat due to release of cytokines. The SARS-CoV-2 cough is initially a dry one and is due to irritation of the infected cells. Some people eventually start coughing up sputum containing dead lung cells killed by the virus.

When the infection progresses, it is due to the body overreacting to the infection. The chemical signals to the rest of the body cause inflammation, but it needs to be delicately balanced. Too much inflammation can cause collateral damage throughout the body. Inflammation of the lungs leads to pneumonia where the alveoli start to fill up with fluids and eventually cause shortness of breath and dyspnoea.

In critical COVID-19, the body's immune system is spiralling out of control and causing damage throughout the body. It might lead to septic shock, when the blood pressure drops to dangerously low levels and the organs stop working properly or fail completely. Acute respiratory distress syndrome caused by widespread inflammation in the lungs stops the body from getting enough oxygen. It may also damage the kidneys or the intestinal lining.

Certain drugs given against COVID-19 include: hydroxychloroquine, tocilizumab, favipiravir, remdisivir, plasma therapy and dexamethasone.

Hydroxychloroquine

This is an antimalarial drug which was one of the first drugs recommended by various institutions against COVID-19. It is used not only for malaria but also for several rheumatic diseases due to its anti-inflammatory properties, affordability and the fact that it has a good safety profile. In March 2020, the United States (US) food and drug administration (FDA) issued an emergency use authorization (EUA) to allow hydroxychloroquine (HCQ) sulphate and chloroquine phosphate to be distributed and used for hospitalized COVID-19 patients. Both the drugs are associated with an anti-viral, anti-inflammatory and an anti-thrombotic effect. Chloroquine is a potent inhibitor of autophagy and cell death, affecting distant cell function and survival. Its derivative, HCQ, has similar properties inhibiting autophagy. In vitro studies have shown that both these drugs can increase endosomal pH, prevent virus-cell fusion and interfere with glycosylation of the angiotensin converting enzyme-2 (ACE-2) receptor thus the binding of the SARS-CoV-2 protein to ACE-2. The anti-inflammatory effects of these drugs, prevents autoimmune flare-ups and organ damages and hence plays an important role in managing SARS-CoV-2 infection.
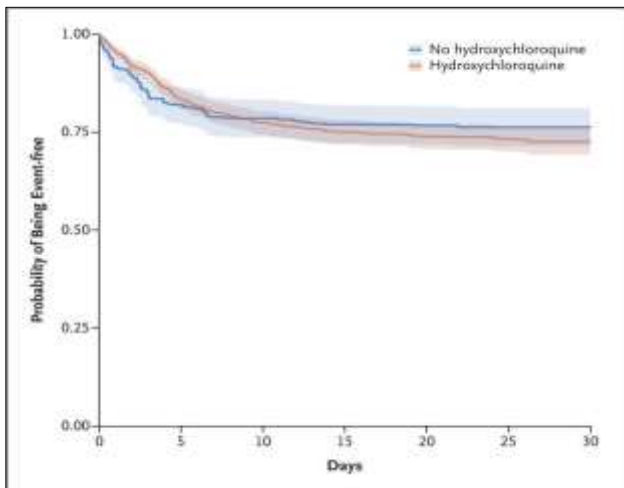

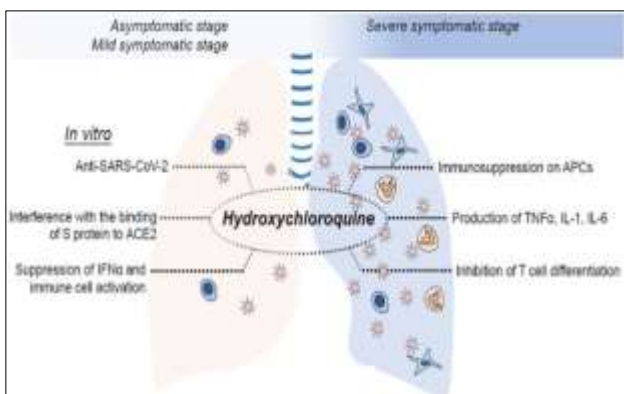**Figure 1: Effect of hydroxychloroquine on hospitalized patients.**

Figure 2: Action of hydroxychloroquine.

The mechanism of action of the anti-inflammatory effect is mainly related to preventing antigen processing and interrupting molecular pathways involved in immune activation causing reduced pro-inflammatory cytokine secretion. However, recent observational studies suggest that administration of HCQ was not associated with either a greatly lowered or an increased risk of composite end point or death. Still, HCQ treated patients were more severely ill at the baseline than those who did not receive HCQ. Eventually HCQ was discontinued from majority of the treatment programs because various studies found no potential benefits of the drug towards combatting SARS-CoV-2.

Tocilizumab

Tocilizumab is a humanized monoclonal antibody capable of interfering with the interleukin-6 (IL-6) soluble and membrane binding site of receptor (IL-6R), thereby blocking the assembly of the activated complex with transmembrane proteins. Tocilizumab is also able to block the IL-6 trans-signalling which is strongly related to pro-inflammatory effect of IL-6. Tocilizumab was initially introduced in the early 2000s for the treatment of autoimmune diseases like refractory rheumatoid arthritis and systemic juvenile idiopathic arthritis and is also approved for the treatment of cytokine release syndrome (CRS). Tocilizumab use is justified because in a cell model of sepsis (human monocyte cell line THP-1), tocilizumab reduced the expression of tumor necrosis factor (TNF) and IL-10, down regulated inflammasome activation and inhibited monocyte phagocytic activity. The current systemic data shows that although indirect pre-clinical data suggests rationale for using tocilizumab and observational studies suggest that treatment with it may be associated with more favourable outcomes compared to the standard care in severely infected patients, there is not documented and verified proof regarding its efficacy against the SARS-CoV-2 and the ensuing COVID-19. The effects of tocilizumab against IL-6 related pro-inflammatory and pro-coagulant status partially explain its potential role in COVID-19, however there is no evidence that suppressing the physiological inflammatory response to the virus is beneficial for the patient. Several clinical practice guidelines include tocilizumab as a therapeutic option for COVID-19. However the world health organization (WHO) recommends administration of tocilizumab only within the context of a clinical trial.

Favipiravir

Favipiravir is a prodrug of a purine nucleotide, favipiravir ribofuranosyl-5'-triphosphate. The active agent inhibits the ribonucleic acid (RNA) polymerase, halting viral replication. It has been extensively used for treatment of Ebola and influenza infections and has also demonstrated broad activity against other RNA viruses. A report from Wang et al showed that favipiravir was effective in reducing the SARS-CoV-2 infection in-vitro. Early findings of trials of this drug show that improvement of the

disease, which depends on the inhibition of SARS-CoV-2, is in fact facilitated by favipiravir. The adverse effects observed in patients given experimental doses of the drug were rare and tolerable and none of the patients needed to discontinue favipiravir.

Remdisivir

Remdesivir is a prodrug of a nucleotide analogue that is intracellularly metabolised to an analogue of adenosine triphosphate that inhibits viral RNA polymerases. Remdisivir has broad-spectrum activity against members of several viral families including filo viruses (Ebola) and even SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV) and has shown prophylactic and therapeutic efficacy in nonclinical models of these coronaviruses. *In-vitro* testing has also shown that remdisivir has activity against SARS-CoV-2. It appears to have a favourable clinical safety profile, as reported on the basis of experience in approximately 500 patients, including healthy volunteers and patients treated for acute Ebola virus infection. In the various trails with remdisivir, numerous positive results were obtained. In 68% patients, improved oxygen-support status was found and overall mortality was 13% over a median follow-up of 18 days. Remdisivir is advised only in severely infected patients and oxygen-support, invasive oxygen administration, ventilators or ECMO. No new safety signals have been detected during various trials. Although nonclinical toxicology studies have shown renal abnormalities, there is no clear evidence of nephrotoxicity due to remdisivir therapy. Patients may sometimes show mild to moderate elevations in alanine aminotransferase (ALT), aspartate aminotransferase (AST) or both. However considering the frequency of liver dysfunction in patients with COVID-19, attribution of hepatotoxicity to either remdisivir or the underlying disease is challenging.

Plasma therapy

Convalescent plasma (CP) has been used successfully to treat many types of infectious diseases, and has shown initial effects in the treatment of COVID-19. Convalescent plasma therapy is a type of passive immunization in which antibody-rich blood is collected from recovered patients and then processed to transfuse into other infected patients. Neutralizing antibodies are the key factors as they block the entry of the virus into the cell by binding to the virus proteins. In this way convalescent plasma therapy has been effective in treating diphtheria and tetanus since the early 19th century. Convalescent plasma therapy has also been used in treating Ebola, SARS, MERS and even pandemic influenza. The FDA has approved the use of plasma therapy to treat severely ill COVID -19 patients. As per initial results of various clinical trials, convalescent plasma therapy has been found effective in reducing mortality rate and can even have a significant effect on adjusting the immune system and decreasing the viral load. Analysis of hospital stay indicates that convalescent plasma therapy can also shorten the course of the disease and contribute to

patient recovery. There has been a low incidence of adverse events, most of which are controllable. The curative effect of convalescent plasma therapy is attributed to the protective antibodies that block the virus persistently and efficiently. Although the antibodies probably have an impact on the disease severity, there are potential risks resulting from the complexity of blood products, such as allergic reactions and pathogen transmission.
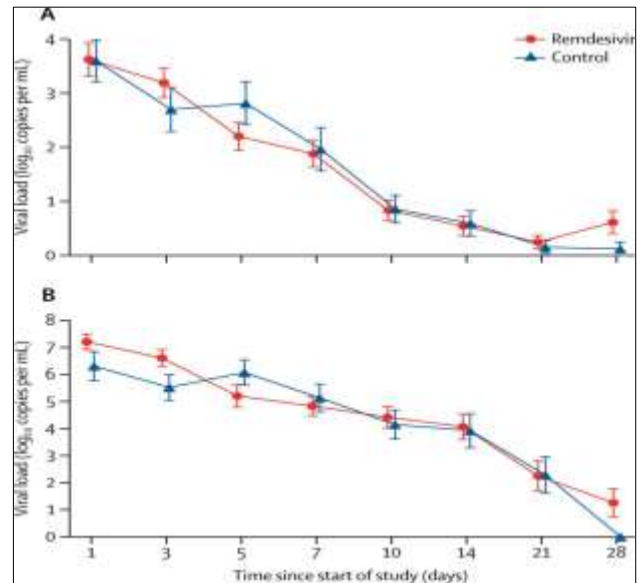

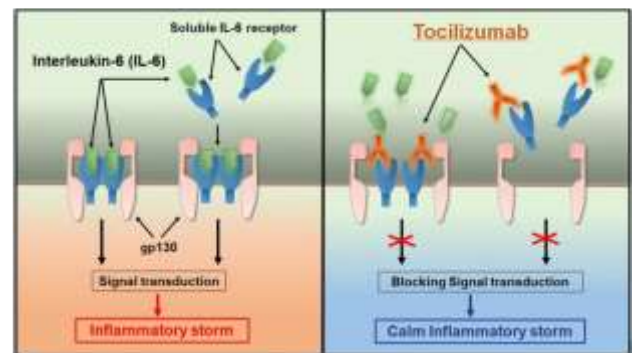**Figure 3: Effect of remdesivir on viral load.**

Figure 4: Action of tocilizumab.

Dexamethasone

It is a corticosteroid that is widely used for the treatment of several diseases and infections including rheumatic diseases, skin infections, hypersensitivity reactions, chronic obstructive pulmonary disorder (COPD) and also in combination therapy with antibiotics for tuberculosis treatment. Its effects are based on its anti-inflammatory responses and suppression of the body's immune responses. It binds to specific nuclear steroid receptors to initiate the mechanism of action of anti-inflammation and immune suppression. It also interferes with the activation of natural killer cells and apoptotic pathway. Dexamethasone was one of the drugs selected for trials at

the Oxford University (recovery trials). It was found to reduce death by one-third in ventilated patients and by one-fifth in patients with only oxygen support. They did not seem to have any effect on patients who did not require oxygen support. COVID-19 causes rapid accumulation of cytokines, majorly IL-6, in the lungs. IL-6 causes increased inflammation in the lung cavity which causes production and accumulation of fluid in the lungs. Dexamethasone, a steroid, causes decrease in the inflammation and supresses immune activation of immune agents, causing reduction in the level of cytokines in the lungs. This drug was approved by the WHO and the FDA for use in severely ill patients. Some of the promising vaccine candidates include Gam-COVID-Vac, BNT162, AZD1222, CoronaVac and Covaxin.

Gam-COVID-Vac

Gam-COVID-Vac, nicknamed Sputnik V, developed by Gamaleya Research Institute of Epidemiology and Microbiology, Russia is the forerunner in the race towards a potential vaccine against COVID-19. It has been claimed to be effective and has even been registered in Russia. It was tested only on 76 people; 38 in phase 1 and 38 in phase 2 and both the trials were in Moscow. It is a two dose vaccine with the second dose being administered 21 days after the first one. In the trials however, only one dose was administered. Its trials have not been published and hence it lacks peer reviews. Its phase 3 trials were to start on august 12 on 2000 people in Russia, the UAE, Saudi Arabia, Brazil and Mexico. Completion date of the Sputnik V are not known but it has been stated that it acts by using

inanimate particles created on the basis of adenoviruses that cause no harm to the patient. It claims to provide immunity to the recipient for at least 2 years.

BNT162

BNT162 is a potential vaccine candidate developed by BioNTech and Pfizer industries jointly in continental Europe. There are four vaccine candidates, each representing different mRNA formats and target antigens. Two of the four vaccine candidates include a nucleoside modified mRNA, one includes a uridine containing mRNA and the fourth vaccine candidate utilizes self-amplifying mRNA. Each mRNA format is combined with a lipid nanoparticle formulation. The larger spike sequence is included in two of the vaccine candidates and the smaller optimised receptor binding domain from the spike protein is included in the other two candidates. The RBD-based candidates contain the piece of the spike that is thought to be the most important for eliciting antibodies that can inactivate the virus. Its phase 1 trials indicated that their vaccine candidate elicited SARS-Cov-2 neutralizing geometric mean titres in younger and older adults, demonstrating strong immunogenicity in all participants. The vaccine was also found to be well tolerated across populations with mild to moderate fever in less than 20% of the participants. The vaccine is in a global phase 2/3 large scale safety and efficacy evaluation involving close to 30,000 people. The companies are on track to seek a regulatory review for the vaccine candidate as early as October 2020.
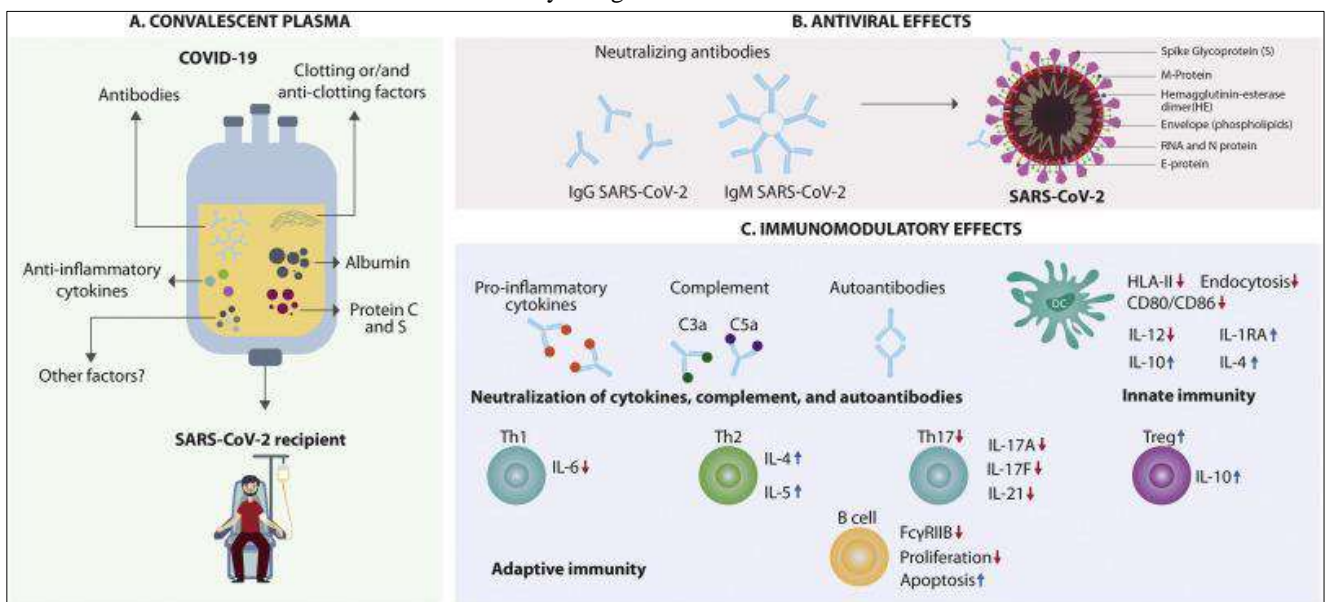

Figure 5: Effect of plasma therapy on COVID-19.

AZD1222

AZD1222 is a potential vaccine candidate developed by the Oxford University along with AstraZeneca and The Jenner Institute. Findings from a phase ½ clinical trials of

this candidate vaccine are quite promising. This vaccine elicited robust immune response against the virus in study participants, with minor side effects. The AZD1222 is a viral-vectored vaccine, which uses a non-infectious chimpanzee virus (vector) as a vehicle to deliver the gene

for the SARS-CoV-2 spike protein into human cells. The phase ½ clinical trials were carried out in 1077 healthy adults, aged between 18-55 years old. The vaccine was able to produce protective antibody and t-cell responses against SARS-CoV-2. The levels of antibodies peaked 28 days after vaccination and levels of t-cells peaked after 14 days. Although there were no serious adverse reactions to the vaccine, mild to moderate side-effects were observed. About 70% of the patients developed mild fever or headache which was easily treated with paracetamol. Researchers observed the elicitation of protective antibodies in 91% of the study subjects who received one dose and 100% of the subjects who received two doses. These results indicate that antibody response can be increased with a second dose but further validation of the phase 3 trials is necessary to ascertain the efficacy and safety of the vaccine.

CoronaVac

CoronaVac is a potential vaccine candidate being developed by Sinovac Biotech, China. The vaccine has elicited an immune response in phase ½ clinical trials. The vaccine has also said to have caused no adverse effects in almost 90% of the trials subjects. The company claims to have induced antibodies in the subjects a mere two weeks after inoculation. In phase 1 and phase 2 trials in china, a total of 743 healthy people between 18 and 59 years old received two shots of the vaccine or a placebo. The results claim to have shown development of antibodies in majority of the patients who received the vaccine. The vaccine contains a killed version of the vaccine. Its phase 3 trials are now underway in various countries across the world including Brazil. Ultimate determination of the efficacy and safety of the vaccine can be made after the completion of phase 3 trials and when the results are published and peer reviewed.

Covaxin

Covaxin is an indigenous vaccine candidate developed by Bharat Biotech India Limited in collaboration with the National Institute of Virology (NIV). NIV isolated a strain of the virus from an asymptomatic patient during the early stages of the pandemic and transferred it to Bharat Biotech, which then developed an inactivated vaccine. The vaccine once injected into human, does not infect or replicate but only serves to develop immunity and mounts an antibody response towards the virus. The firm is currently conducting a phase ½ trials across the country on 1125 patients and the firm has also ensured that the vaccine would be affordable to the common man. Ultimate determination of the efficacy and safety of the vaccine can only be made after phase 3 trials are published and peer reviewed.

Until there is a successful vaccine against COVID-19, doctors and medical professional across the world are at the moment only able to provide palliative care to patients infected with SARS-CoV-2. There are various criteria of patients depending on the severity of their infection.

At home

This is only applicable if the patient is either asymptomatic or is mildly symptomatic without any other existing comorbidities like diabetes, hypertension or any other lung pathology. In such scenarios the patient is advised to: rest at home and isolate himself from everyone including his family members to not only speed his recovery but also contain the spread of the virus; consume as much fluids as possible to prevent dehydration; take over the counter drugs like zinc tablets and vitamin supplements after consulting with his physician to counter his fever and to boost immunity; monitor his symptoms closely and keep his physician well informed of his health developments at all times so that he can be administered proper and timely care whenever necessary; wear a mask and sanitize his hands at all times to avoid infecting his family members and those in his close proximity.

In the hospital

Moderately symptomatic and severely symptomatic patients are often admitted to the hospital and in such case the attending doctor must insist on checking the patients oxygen saturation status as well as his breathing sounds on both sided of the lung to check for congestion. This helps to give an idea of the progress and the severity of the infection.

The doctor must also recommend a COVID-19 test as soon as possible along with a chest X-ray or chest computed tomography (CT) scan; in case of troubled breathing where oxygen saturation on room air drops below a designated limit, the patient may be given assisted respiration through oxygen cylinder or the patient may be intubated for assisted respiration; in severe cases of respiratory distress the patient may also be connected to a ventilator; the patient is also given IV fluids to prevent dehydration; and the protocol for providing experimental drugs is followed depending on the severity of the patient after considering his age and his other comorbid health conditions.

For the COVID-19 vaccine, the ideal candidate would be able to establish immunity in at least 70% of the population including those in the high risk category. The WHO says that the minimum acceptable for a vaccine would be one that was 50% effective. Assuming a COVID-19 vaccine meets the WHO standards including the one that "its benefits outweigh the risks", convincing the people to take the vaccine and guaranteeing its safety is another difficult task altogether.

In May, a survey of more than a thousand people conducted by the Associated Press-NORC Centre for Public Affairs Research found that 50% of the respondents were willing to take the a COVID-19 vaccine when one becomes available. 31% people were undecided on taking

a vaccine and a large proportion of the people were worried about the side effects of the COVID-19 vaccine.

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