Review

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Treatment of SARS-CoV-2: How far have we reached?

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SUMMARY The virus severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) is currently affecting more than 200 countries and territories worldwide. It has been declared as pandemic by World Health Organization (WHO) and the whole world is suffering from corona virus disease 2019 (COVID-19). Currently, no treatment for SARS-CoV-2 are approved because of lack of evidence, but a number of clinical trials are in process and we are expecting fruitful results very soon. This review focuses on various approaches of treatment and few of the most recent clinical trials carried out in this field.

Keywords SARS-CoV-2, pandemic, antiviral, corona virus, clinical trial

1. Introduction

The SARS-CoV-2 earlier called as 2019-nCoV (2019 novel corona virus) is known to cause corona virus disease 2019 (COVID-19) and has been declared pandemic by WHO. As of April 18, 2020 (20:50 GMT), total 2,322,033 cases have been reported so far worldwide causing 159,659 deaths. Currently, 1,512,066 patients are in mild conditions, whereas, 55,218 are in critical condition (*1*). There are several ways to combat the corona virus infection which include development of vaccine, but developing a vaccine can take at least 12-18 months in extraordinary circumstances and the first human clinical trial for corona virus vaccine has already started in US. The National Institute of Allergy and Infectious Diseases (NIAID) has already developed the vaccine in collaboration with Moderna Inc., a biotechnology-based company. There are other efforts to develop the vaccine too which include the major pharma giant GlaxoSmithKline in collaboration with Clover Biopharmaceuticals, China. Sanofi and Johnson & Johnson are working with the Biomedical Advanced Research and Development Authority for the same cause. But, in any case, the vaccine for human use would be available in at least 18 months and in the view of developing COVID-19 cases, we need to have a fast and effective treatment.

The other method to combat the virus is to develop a new drug that could target the virus or the host cell, but again this would take several years and we can not wait for that long. A new drug takes at least 14 years to get introduced to the market from the research and development phase and this remains an unlikely solution for this major problem. The third and most likely way to control the corona virus pandemic is to test the SARS-CoV-2 using existing drugs as most of the viruses share similar genome. In an attempt to treat the corona virus using this method, a number of different antiviral and other drugs are used and fortunately few drugs have shown a ray of hope as far as the reduction in duration of therapy and viral load is concerned. We summarized few important recent findings here.

2. Treatment approaches

2.1. Interferon-α (IFN-α)

The IFN-α, a broad spectrum antiviral drug approved for the treatment of viral hepatitis, is used to treat the COVID-19 at a dose of 5 million units through vapor inhalation two times a day alone or in combination with ribavirin (500 mg 2-3 times a day) and antiviral drugs lopinavir/ritonavir (400 mg/100 mg) for a period of 10 days (*2-4*). Previously, the combination of IFN-α 2a, ribavirin and lopinavir/ritonavir was used as a triple therapy for MERS-CoV in South Korea (*5*). It was seen that the SARS-CoV-2 is more susceptible to IFNs as compared to SARS-CoV as the inhalation of IFN-α 2b reduced the infection rate significantly (*6*) and it can be used for prophylaxis of SARS-CoV-2 infection (*7*).

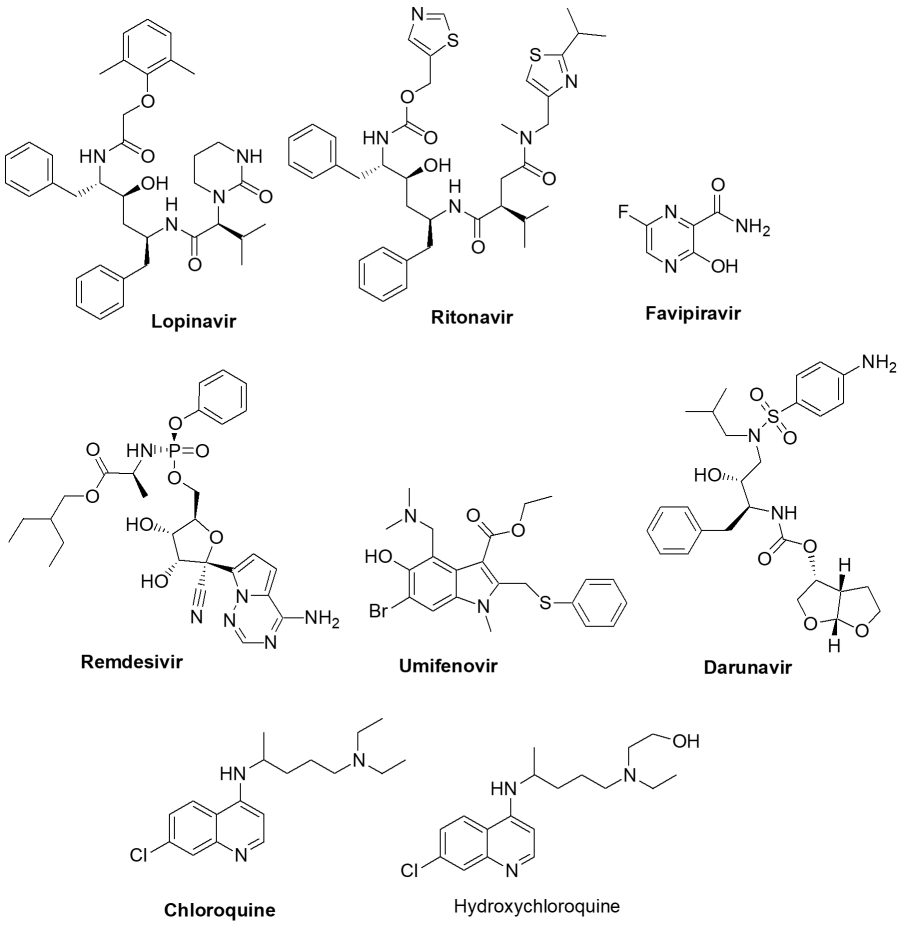

Figure 1. Structures of few drugs tested for anti-SARS-CoV-2 activity.

2.2. Interferon-β (IFN-β)

The other interferon, IFN-β was originally developed for chronic obstructive pulmonary disorder (COPD) and is known to improve the lung's condition and enhance its ability to fight the viral infections. Previously, it was reported that a decrease in the production of INF-β is directly linked to increased susceptibility of people to develop severe respiratory diseases resulting from viral infections (*4*). It was also observed that the SARS-CoV-2 infection suppresses the production of INF-β in body which results in protection from immune system (*2*). Recently, a UK biotechnology firm, Synairgen has been given approval to conduct a trial using IFN-β on patients with COVID-19 (*8*). The advantage with IFN-β is that it can be inhaled similar to IFN-α and can be administered by patients themselves.

2.3. Lopinavir/ritonavir

Lopinavir is an antiretroviral drug which inhibits the protease enzyme and can be formulated together with another protease inhibitor ritonavir which decreases the metabolism of the former by inhibiting the cytochrome (CYT) P4503A enzyme. Lopinavir/ritonavir drugs (Figure 1) combination (Kaletra) was approved for the treatment of human immunodeficiency virus (HIV) and was found to have *in vitro* anti-SARS-CoV efficacy (*9*). However, in a recent clinical trial conducted in China on the patients with severe COVID-19, the drug did not show any promising benefit as compared to the standard care. This randomized, controlled and open-labeled trial was conducted between January 18, 2020 and February 3, 2020 on 199 patients with confirmed SARS-CoV-2 infection. Out of the 199 patients, 99 patients were given the combination of lopinavir/ritonavir, whereas, 100 patients received standard care only. No significant clinical improvement and no reduction in mortality were observed for the lopinavir/ritonavir group along with standard care in comparison to the group receiving standard care only (*10*). Another trial on lopinavir was carried out on 44 participants with mild to moderate infection. Out of 44 patients, 21 patients received lopinavir for 14 days, 16 received umifenovir and 7 received standard care only (*11*). No significant differences in the clinical outcomes were observed for all three groups. The lopinavir group even showed deterioration of diseases conditions in 38.1% of patients compared to 12.5% and 14.3% for umifenovir and control groups respectively. However, Kaltera

can be useful in the early stages of the SARS-CoV-2 infection and might be beneficial for the milder disease conditions and a multi-country clinical trial is to be conducted for this combination.

2.4. Favipiravir

Favipiravir (Avigan) also known as T-705 was first approved for treatment of influenza virus in this February and is the inhibitor of RNA-dependent RNA polymerase in RNA viruses such as SARS-CoV-2 (*12*). Earlier, in February, a preliminary clinical trial on favipiravir was conducted in China on 80 patients and indicated better results for favipiravir in comparison to lopinavir/ritonavir with lesser adverse effects (*13*). Favipiravir was first developed in Japan by Fujifilm and was subjected to another clinical trial on 340 patients in China recently and resulted in very encouraging results as the patients receiving favipiravir with standard care showed cleared viral load in four days as compared to eleven days in patients receiving standard care only (*14*). Another multicentre, open labeled, randomized trial in China was conducted to compare the efficacy of favipiravir (1,600 mg × 2 on the first day followed by 600 mg × 2 for 9 days) and umifenovir (200 mg × 3 per day for 10 days) and the results revealed a higher recovery rate and better clinical outcomes in the patients treated with favipiravir at day 7 (*15*). A phase III trial is ongoing in Japan involving 100 patients and is expected to be completed in June. Another phase II trial is being conducted in the US at Massachusetts General Hospital, Brigham and Women's Hospital, and the University of Massachusetts. However, Avigan was not that much useful in severely ill patients and did not show much promising results. It has to be given before the viral load peaks in the body. Favipiravir would require government approval for usage against COVID-19 as it was earlier approved for the treatment of flu.

2.5. Remdesivir

Remdesivir is an antiviral drug originally developed for Ebola virus, but now is among the front runners for the therapy of novel corona virus, SARS-CoV-2. This drug has earlier shown very promising activity against SARS and MERS (Middle East respiratory syndrome), the two other forms of corona viruses which are more lethal but less contagious than SARS-CoV-2 (*16*). It is an inhibitor of viral replication and is much effective especially in the early stages of infection when the virus multiplies in the upper respiratory part of the body. It was invented by Gilead Sciences and had shown broad spectrum of activity against RNA viruses. Remdesivir resembles the RNA base adenosine and has several important features in its structure making it a strong inhibitor of viral RNA polymerase. It resembles the RNA building block and is taken up by the virus into its RNA strands causing chain termination. The results of compassionate-use of remdesivir were published recently by Gilead Sciences. This trial was conducted on 61 severely ill patients from the US, Canada, Europe and Japan who received intravenous remdesivir at a dose of 200 mg on first day followed by 100 mg for 9 days. Out of 61 patients receiving remdesivir, 8 patients were excluded from the study due to dosing error (1 patient) and lack of post-treatment data (7 patients). Out of the treated patients, 30 who were on mechanical ventilation showed significant improvement and 17 (57%) were extubated. A total of 25 patients (47%) were discharged and 7 (13%) died. Among the dead, 6 were on invasive ventilation, while 1 was not (*17*).

2.6. Umifenovir

Umifenovir (arbidol) was first invented by Pharmstandard and has shown efficacy in the treatment of influenza virus infection. It is claimed to be a viral entry inhibitor to the target cells. Interestingly, it does not have significant side effects and is patented for the treatment of SARS infection. It has shown very promising activity against SARS-CoV-2 *in vitro* showing inhibition of the virus at concentration as low as 10-30 μM (*18*). A randomized, open-labeled, multi-centered clinical trial was conducted in China during the period February 20, 2020 to March 12, 2020 to compare the efficacy and safety of favipiravir and arbidol on COVID-19 patients on 7 day's clinical recovery rate. 120 patients were assigned to each group receiving favipiravir and arbidol along with conventional therapy. The results were published on March 20, 2020 which revealed that the 7 day's recovery rate for arbidol group was 55.86% in comparison to 71.43% for favipiravir group (p = 0.0199). Patients with hypertension or diabetes also showed better improvement in case of favipiravir group in comparison to arbidol (*15*). Currently, three more phase IV clinical trials are planned for arbidol in the treatment of COVID-19. One clinical trial will compare the efficacy of arbidol on 380 patients at Jieming QU, Ruijin Hospital, China in comparison to the standard treatment (*19*), whereas, the other two would compare the efficacy of arbidol with oseltamivir (*20*) on 400 patients at Tongji Hospital, China, and carrimycin on 520 patients at Beijing Youan Hospital, China (*21*).

2.7. Darunavir

Darunavir (Prezista) is another antiviral drug used as HIV-1 protease inhibitor that was shown to have promising anti-SARS-CoV-2 activity *in vitro* earlier in February in a test carried out in China (*18*). It was shown to inhibit the viral replication at a concentration of 300 μM. However, Johnson and Johnson announced on March 18, 2020 that there is no any evidence to support the activity of darunavir against SARS-CoV-2.

Darunavir, marketed by its inventor company Janssen as Prezista was approved with a boosting agent such as ritonavir or cobicistat (*22*). A single center open labeled randomized and controlled phase III trial was conducted at Shanghai Public Health Clinical Center (SPHCC) for the evaluation of efficacy of darunavir/cobicistat combination on 30 COVID-19 patients and the results revealed that the combination was not effective in reducing the symptoms or the duration of treatment (*23*).

2.8. Sarilumab

Sarilumab (Kevzara) is a human monoclonal antibody against the interleukin-6 (IL-6) receptor. As IL-6 is the host target for SARS-CoV-2, its activation could result in severe respiratory symptoms due to lung inflammation. Sarilumab was first developed by Regeneron Pharmaceuticals Inc., US and has collaborated with Sanofi has announced on March 16 to conduct phase II/III clinical trials for the evaluation of Kevzara in around 400 patients hospitalized with COVID-19 infection. It is expected to reduce the overactive inflammatory response of the lungs by blocking the IL-6 receptor (*24,25*). The Feinstein Institute has also collaborated with Gilead Sciences and Regeneron Pharmaceuticals to conduct three clinical trials who are admitted to the Northwell Health Hospitals, US having moderate to severe infections. These trials would be conducted to test the efficacy and safety of sarilumab and remdesivir which is the investigational new drug (*26*).

2.9. Chloroquine (CQ) and hydroxychloroquine (HCQ)

Chloroquine is a widely used antimalarial drug that has shown good activity as antiviral drug in the year 2006 (*27*). In the *in vitro* studies carried out recently, CQ has shown good potential in inhibiting the SARS-CoV-2 at EC_{50} 1.13 μM and CC_{50} > 100 μM (*28*). CQ was reported to be superior in comparison to the control in inhibiting the exacerbation of pneumonia, improving the lung images as well as shortening of the duration of treatment (*29*) when tested on 100 patients. At least 16 clinical trials have been registered to check the efficacy and safety of CQ and HCQ in the treatment of COVID-19 patients.

A clinical trial is being planned in US to see the efficacy and safety of CQ on COVID-19 patients. A clinical study in France revealed that CQ derivative, HCQ when given alone and in combination with macrolide antibiotic azithromycin, have shown significant reduction in the duration of therapy (*30*). The study published on March 17, 2020 in the International Journal of Antimicrobial Agents confirmed that a clinical trial on COVID-19 patients during the period early March to March 16, 2020 showed significant reduction of the viral carriage and reduction of patients with PCR-positive samples for the HCQ treated patients at day 6 as compared to the control. Inclusion of azithromycin to the treatment further decreased the viral load significantly. Hydroxychloroquine was administered at a dose of 200 mg three times a day during ten days. However, this study had a smaller sample size as the HCQ was administered to 26 patients and 16 patients were kept as control. Out of those 26 patients, six patients were lost due to early cessation due to various reasons. Therefore, the data was reported for 20 HCQ administered patients and 16 control patients. However, use of both CQ and HCQ are questioned owing to the cardiovascular complications posed by both the drugs. Recently, worrying results came from Brazil where they needed to stop the high dose arm of CQ in six days as several patients died in the group. Two groups of COVID-19 patients were enrolled in the Manaus Public Hospital in Brazil, in which the high dose group of CQ were planned to receive 12 g total dose (600 mg × 2 × 10) over 10 days, whereas, the low dose received 2.7 g over 5 days (450 mg × 2 on the first day followed by 450 × 1 for 4 days). All the patients received antibiotics ceftriaxone and azithromycin also along with CQ. Unfortunately, 11 patients died in the study forcing the team to halt the high dose group as it caused more lethality. It revealed that high CQ dose for 10 days is not recommended for COVID-19 treatment due to potential toxic effects (*31*).

Similar results have emerged from France, where a University Hospital Centre of Nice has to stop the experiment involving HCQ as it posed a major risk leading to cardiac death. The trial which started on March 22 was experimenting four possible treatments of COVID-19, one of them was HCQ. The HCQ group of patients showed abnormally prolonged QTc resulting in abnormal heart rhythm as seen in the ECG of patients and one of the patients even died due to sudden cardiac arrest (*32*). Another study on HCQ and azithromycin revealed little difference in the clinical condition of COVID-19 patients receiving the combination with those receiving standard care only with a greater risk of cardiac rhythm related side effects (*33*).

2.10. Convalescent plasma (CP)

The plasma of recovered patients can be used to treat the severely ill COVID-19 patients as it contains the antibodies developed by the body in response to the viral infection. It was tried earlier for SARS and doctors were successful in improving the condition of some patients (*34*) whose condition continued deteriorating despite treatment with methylprednisolone. Shorter hospital stay and lesser mortality rates were observed for the patients treated with CP as compared to the patients without receiving it (*35*). Similar resorts were employed for Ebola in the year 2014 (*36*) and MERS patients in the year 2015 (*37*). Therefore, it would be worthwhile to test the efficacy of CP taken from the recovered patients on the COVID-19 patients.

Since, CP has not yet been approved for use against COVID-19 by FDA, it is being regulated under the investigational product. Recently, a clinical trial was conducted between January 23, 2020 and February 19, 2020, where the plasma of 40 recovered COVID-19 patients were collected. For the study, 10 COVID-19 patients with severe infections were selected and were given the transfusion of 200 mL of CP with neutralizing antibody titre values above 1:640 in addition to standard care and other antiviral drugs (*38*). Safety of CP transfusion was kept the primary endpoint, whereas, the improvement in the clinical symptoms within 3 days of CP transfusion remained the second endpoint. Out of 10 patients, 5 showed rapid increase in the antibody titre values to 1:640 and the other four also showed high titre values. Importantly, the clinical symptoms improved significantly including better oxyhaemoglobin saturation, increased lymphocytes count and reduced level of C-reactive protein with no adverse effects.

However, there are various downsides to this approach which includes the difficulty in scaling up for widespread use as well as the risk of transmission of other diseases that would come along with the plasma of recovered patients. Also the antibodies present in the plasma generally are in lesser concentration that may not be sufficient for the treatment. Regeneron company from US is about to introduce two antibodies that could act against COVID-19 which can be synthetically produced and their clinical trial would be started later. This would be helpful as both prophylactic and as a treatment measure especially for high risk groups.

3. Conclusions

A number of trials have been and are being conducted to come up with a drug which shows significant efficacy and safety in the treatment of COVID-19. Few have shown encouraging results and few are in pipeline. Hopefully, we would be able to identify the most suitable approach to combat this deadly virus very soon and make this world a healthy place to live again.

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