HEALTH EDUCATION

The Pharmacological Treatment of COVID-19

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ABSTRACT

Objective: **The present paper aimed at discussing the advances of pharmacological treatment of COVID-19 and highlighting the recent findings reported by either international medical bodies or specialized pharmacological research groups.**

Method: **The study adopted the narrative review approach through exploring and analyzing the findings reported in literature during the period of COVID-19 pandemic, in addition to providing commentary notes regarding the released statements of pharmacological research groups.**

Findings: **The findings of the study revealed that there is a significant advancement in COVID-19 therapy. However, still there is a significant lack of a single research-based evidence that the released or suggested drugs are effectively eradicating the COVID-19 viral infection.**

Conclusion: **The study concluded that commitment to the announced precautionary measures at the meantime remains the most appropriate action to be taken until a reliable research-based evidence is released regarding the effectiveness of the pharmacological treatments of COVID-19 infection.**

KEY WORDS

COVID-19, pharmacology, treatment, remedesivir, review

INTRODUCTION

The World Health Organization (WHO) has declared COVID-19 a pandemic. COVID-19 stands for Corona Virus Disease 2019, and is caused by the severe acute respiratory syndrome corona virus-2 (Cascella, Rajnik, Cuomo, Dulebohn, & Di Napoli, 2020).

Corona viruses are a large family of viruses that are common in people and many different species of animals including cats and bats. Common human Corona virus typically causes an upper respiratory tract infection like the common cold. Most people get infected with one or more of these viruses at some point in their lives (Holshue *et al*., 2020). The human corona virus infection typically resolves on its own with basic rest while feeling miserable. Rarely, the corona viruses that infect animals can evolve and become a new corona virus, which then infect and spread between people. Important examples of these include severe acute respiratory syndrome corona virus or SARS in 2003 and the Middle East Respiratory Syndrome Corona Virus, also known as MERS (Novel, 2020).

In 2019 in Wuhan, a city in China noticed a number of unusual cases of Pneumonia in the hospital. These patients most notably presented with clinical symptoms of dry cough, dyspnea, fever and bilateral lung infiltrates on imaging. The corona virus cases were eventually reported to the World Health Organization (WHO) country office in China on the 31st of December 2019. Many of the cases were reported and searches for the source have shown the one of seafood markets, a wet market as the origin, the market was where a large variety of vertebrate and invertebrate animals, wild court and farm raised are sold. On January 1st , markets were closed (Nishiura *et al*., 2020).

Furthermore, on January 12th 2020, China shares the genetic sequence of the novel Corona virus, which will be very important for the other countries as they developed specific diagnostic tests. At the end of January, the corona virus was found to have originated from wild bats and belonged to the similar group as SARS. Hence, this corona virus is also known as SARS Corona virus 2 (Song *et al*., 2020).

By January 30th, the novel corona virus outbreak was declared an emergency. On February 11th, 2020, the World Health Organization (WHO) announced that the official name of the disease would be COVID-19; a shortened version of Corona Virus Diseases 2019. By March 1th, COVID-19 was declared a pandemic. A pandemic is a global outbreak of a disease, something not to be taken lightly (Perlman, 2020).

As of March 15th, COVID-19 has affected more than 150.000 people worldwide, and carries a mortality rate of around 3%. To put into perspective, if you compare these figures to the other Corona viruses outbreaks, for example SARS in 2003 had just over 8.000 cases with a mortality rate of 9.5%, and MERS in 2012 had a roughly 2.500 cases with a mortality rate of about 35%. Despite having a lower mortality rate than its predecessors, 3% is still very significant, especially with the rapidly growing number of cases. One can imagine for every one hundred cases three people may die. If we compare these statistics of corona virus to the seasonal flu caused by the influenza virus, which affects millions each year, the mortality rate of the influenza seasonal flu is less than 0.2% (Holshue *et al*., 2020)

FDA CLINICAL TRIAL GUIDELINES OF COVID-19 DRUGS

During the advent of COVID-19 pandemic, the social distancing isolation, quarantine, FDA really does recognize how challenging this is for stakeholders and sponsors for conducting the trials, there are a suite of guidance that FDA has released trying to balance the subject safety with maintaining the integrity of the study and the ability with the clinical trials to actually generate results that can be interpreted at a future date to support a biological license application (Tanne, 2020).

The challenges faced by the FDA included site closures, travel limitations for site visits, patients may not be able to travel, the sites actually may not have appropriate number of staff to conduct the specified procedures at the site there, supply chain interruptions, the risk of exposure when patients are coming to sites, all of these caused limitations with institutional review board, in addition to the continuous protocol

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limitations (Kandeel & Al-Nazawi, 2020).

A number of drugs are floating around in the social media and news as possible treatment options for COVID-19 patients. Among these drugs are Remdesivir, Chloroquine, Hydroxychloroquine, Lopinavir, Ritonavir and Tocilizumab. These are the drugs used right now for the patients who are suffering from COVID-19. None of these drugs are used as prophylactic treatment of COVID-19, but they are used once the patient get infected by this novel corona virus or suffering from the disease (Venkatasubbaiah *et al*., 2020).

Remdesivir is still under the trial, it is an investigational intravenous drug which has a broader antiviral activity that inhibits the viral replication by means of premature termination of RNA transcription. This drug has a retroactivity against SARS CoV-2, severe acute respiratory syndrome corona virus-2, in addition to in vitro and in vivo activity against related beta-corona viruses. So, this drugs actually blocks RNA-dependent polymerases and there are several randomized clinical trials, which are in the process or underway to evaluate the efficacy of Remdesivir for moderate or severe COVID-19, but as of today, its clinical efficacy is not well understood (Cao *et al*., 2020).

Chloroquine or hydroxychloroquine are the oral prescription drugs that have been used for the treatment of malaria as well as for certain inflammatory conditions, and especially when you talk about chloroquine has been used for malaria treatment and chemo prophylaxis and hydroxychloroquine is used for the treatment of rheumatoid arthritis systemic lupus erythematosus (SLE). So, both of the drugs have in vitro activity against SARS CoV-2 and the novel corona virus circulating now. So, with the hydroxychloroquine having a relatively higher potency against COVID-19 patients when compared to that of the chloroquine, but when we see both of the drugs chloroquine and hydroxychloroquine have been reported to inhibit SARS CoV-2 and have potent antiviral activity (Colson *et al*., 2020). The use of chloroquine, especially included in treatment guidelines from the China National Health Commission and was reportedly associated with the reduced progression of the disease and decreased the duration of symptoms. However, the primary data supporting these claims have not been published. Other published clinical data on either of these agents are pretty limited. In an open-label study among 36 patients with COVID-19, the use of hydroxychloroquine was associated with a higher rate of undetectable source code 2 RNA on nasopharyngeal specimens at day six compared with no specific treatment. So, in this particular clinical study, the use of azithromycin in combination with the hydroxychloroquine appeared to have a much more additional beneficial effects on these patients, but there are methodological concerns about the control groups for the study and the biological basis using azithromycin in the setting is unclear as of date (Mehra *et al*., 2020).

Currently, no data available from randomized clinical trials to inform clinical guidance on the use, dosing, or duration of hydroxychloroquine for the prophylaxis of the treatment of novel corona virus infection. Although the optimal dosing and the duration of the hydroxychloroquine for the treatment of COVID-19 are unknown (Mehra *et al*., 2020).

PREVIOUS STUDIES

Several studies investigated the effect of various pharmacological treatments for COVID-19. In a study conducted by Almazrou *et al* (2020), the study aimed at comparing the effectiveness of Hydroxychloroquine based treatments and standard treatments on COVID-19 patients. The study was a retrospective, hospital-based cohort study that included a sample of 161 COVID-19 patients. The patients were categorized into two groups; group one who were treated using hydroxychloroquine and group two who were treated using the antiviral and antibacterial drugs mentioned in the standard protocol issued by the Saudi Ministry of health. The results of the study showed that the length of stay among patients treated with hydroxychloroquine was shorter compared to those treated with standard antiviral and antibacterial drugs. In addition, the first group patients were in less need for admission to ICU. However, there was no significant difference between the patients outcome between the two groups.

Beigel *et al* (2020) evaluated the use of Remdesivir for the treatment of COVID-19. The researcher conducted a double-blind randomized, placebo controlled trial that involved 1062 COVID-19 patients. The results of the study indicated that the mean recovery time for COVID-19 patients who received Remdesivir treatment was 10 days, whereas it was 15 days among the placebo group. at day 15, COVID-19 patients who received Remdesivir treatment were more likely to get clinical improvement compared to the placebo group. In addition, there was lower mortality rate among Remdesivir group (6.7%) compared to placebo group (11.9%) at day 15. Finally, significant and serious adverse events occurred among 24.6% of Remdesivir patients, whereas 31.6% of placebo group patients suffered from adverse events.

Moreover, Melatonin was investigated by Zhang *et al* (2020) as a potential adjuvant treatment for COVID-19. Melatonin, as an anti-inflammatory and anti-oxidative agent is protective against ALI/ARDS caused by the viral infection. The study reported that using melatonin is a strong agent that limits the virus-related diseases and would be likely useful in COVID-19 patients.

Cai *et al* (2019) examined the effect of Favipiravir versus Lopinavir for the treatment of COVID-19. The results of the study showed that COVID-19 patients who were treated using Favipiravir had a shorter viral clearance time (4 days). In addition, they had a significant improvement in the chest CT scan compared to the Lopinavir group. Further, the study found that fewer adverse events were observed among Favipiravir group compared to the Lopinavir group.

Chen *et al* (2020) carried out a prospective, randomized, controlled open-labelled multicenter trial that examined the effectiveness of Favipiravir versus Arbidol as potential treatments for COVID-19 patients. A total of 240 COVID-19 patients who went under randomization. The participants were assigned equally into two groups; Favipiravir group and Arbidol group. The study results showed that there was no significant difference between the two groups with regard to the recovery time. In addition, the study showed that Favipiravir led to shorter latencies to relief for both hypoxia and cough. Finally, the study reported that there was an elevation of the serum uric acid as an adverse event among the participants who received Favipiravir drug.

In a different study that was carried out by Arshad *et al* (2020), the purpose was to evaluate the role of hydroxychloroquine therapy either alone or with azithromycin in hospitalized COVID-19 patients. The study was a multi-center retrospective observational study. The participants in this study were consecutive patients hospitalized with a COVID-19 related admission between March and May/2020. The results of the study showed that using both regimens; hydroxychloroquine and hydroxychloroquine with azithromycin significantly reduced the mortality rate. However, there was no significant difference between the two protocols.

RESULTS

Everyone in this world is busy dealing with the new infectious disease, new Corona virus, and known as COVID-19. Based on the most recent published data, majority or almost half of the patients developed respiratory failure and 31% developed ARDS, in addition, a high percentage of the patients demanded ventilator support including High Flow Nasal Cannula, oxygen therapy and non-invasive mechanical ventilation (NIV). So, there is a lot of debate on how to best use this ventilator support.

Currently, there are more than a hundred candidates in development including some new platforms technologies like mRNA technology, as well as some unique delivery systems and modifications to vaccine approaches that are more tried-and-true where we have platforms with more extensive records of safety and delivering on vaccines in other contexts, but the novel platforms presents some new opportunities such as being able to get into large-scale production faster, they also create some opportunities for having a multiple shot on goal approach to dealing with the pandemic, they present some special issues as well.

Arguably, four items, amongst many others, were used in COVID-19 cases. Remdesivir was given emergency-use authorization from the FDA based on a study showed that the time to recovery was reduced in that randomized controlled trial. It did not show a mortality benefit, but many people believe that if the study was taken out to its conclusion - in other words, if a thousand people as was planned were enrolled in the study - that would have statistical difference. Nevertheless, it didn't happen. There has been some new regarding that, in that it has been broadened in its scope.

The second one was dexamethasone, and they used it for about 10 days in the study, this came out of the recovery trial in Great Britain, and in this case, there actually was survival benefit, and in this case, it was six milligrams, either orally or intravenously, in these patients. A number of patients were observed to get better very quickly and are able to go home after about four to five days or even a week. It was found that these patients who would benefit from dexamethasone are the patients that are on oxygen, very similar to the initial type of patients that were requiring remdesivir, so for remdesivir, we would give these patients

remdesivir, if they were requiring supplemental oxygen. Same thing in the recovery trial, regarding dexamethasone. So these patients will come in, they would require oxygen, we would start them on dexamethasone, and it would be given for 10 days, because that is exactly the length time that they used in the recovery trial. But there were some patients that didn't get better. In fact, there is a lot of patients that stick around in the intensive care unit for days, even weeks. One of the observed things is that when healthcare providers start these patients on 10 days of dexamethasone, there is an improvement not only in the clinical scenario, but also in a number of the blood tests that are checked. For example, C-reactive protein, which is a marker of inflammation going on in the body, and typically we see that the CRP levels are very elevated initially, and then patients are started on dexamethasone, then they start to come down, showing a response. A very similar picture is seen among patients with ferritin. Ferritin has iron as opposed to CRP, and some people may think that ferritin may actually work into the pathophysiology. There was arguments about that iron seemed to be the reason why patients were getting sick, but in fact it was reported later that ferritin is also an acute phase protein and it is going to go up if there is an inflammation going on. Again, typically these patients have high ferritin levels and when they are started on decadron it goes down. Moreover, LDH, which is an intracellular enzyme and when cells are being broken down and there is inflammation, LDH increases as well. Another one that we keep track of in these patients is a d-dimer. D-dimers are little pieces of protein that is usually the byproduct of coagulation, and so this is a very rough way of determining if there is coagulation occurring in the human body, so we would typically see these levels up, because it is known that there is an increased risks of thrombosis in COVID-19 patients, but we don't yet know whether or not this the be-all and end-all coagulation. In other words, some groups have put forward some evidence that would seem to indicate that the d-dimer isn't capturing anything. That may be the case, but nevertheless, in all of these patients, a pattern of high CRP, high ferritin, and elevated d-dimer levels were observed.

Furthermore, researchers have data about plasma as a drug to treat COVID-19 patients, but it's not placebo-controlled, it's not a controlled trial, and so more work still needs to be done on that, but there was also another emergency use authorization by the FDA to allow the healthcare providers to use plasma in COVID-19 patients. So that has continued and healthcare providers are continuing to use plasma.

DISCUSSION

An important thing to realize that individuals who are hospitalized generally have symptoms for about a week before they are admitted to the hospital and there after their disease progresses actually quite rapidly, so that within a few days individuals may often be admitted to the intensive care unit.

Taking a look into the clinical studies and people who are treated for COVID-19, there are two important things to think about; first is clinical endpoints, can we prevent people from winding up in intensive care unit, can we shorten the hospitalization, obviously can we reduce mortality, but stopping the shedding of virus is also a very important role, and if we had a therapeutic that didn't shorten the course of illness, but stop viral shedding that would be important from a public health perspective, it would probably prevent some individuals from becoming infected. A hundred and forty three clinical trials were registered for COVID-19, which is not a small number of trials for any disease, and this in the very beginning of understanding some of the results from those studies. A short summary article in science magazine talked about the antiviral strategies indicated that there is a lot of interest of antibodies and plasma to prevent the fusion of the virus to the ACE2 receptor, in addition to the interest in chloroquine and hydroxychloroquine, which probably inhibits virus replication through interacting with lysosomes during the endocytosis process. Moreover, remedesivir has been tested and suggested by other researchers as one of the most promising agents to treat this disease. A placebo controlled comparison of Lopinavir/ritonavir with an outcome of time to improvement, ninety individuals who were scored on study with 12 days or less of symptoms and another group a little bit over a hundred who started on therapy a little bit later, both drugs did not shorten the time to clinical improvement though one of the important clinical endpoints were when the important endpoints, clinical endpoints, was not realized in the study.

Looking to understand the ideal approach for clinical trials to COVID-19, what is needed is to stop the virus replication, a lot of people who are really sick shed virus for a long period of time, second thing is to understand how should we be modulating the immune response in people with severe disease and whether or not that will be any benefit at all, and it is critically important is to have treatments for individuals who are less symptomatic at home with disease to try to decrease the spread of the illness in the community.

CONCLUSION

The present study was a literature overview of the recent advances in the pharmaceutical therapy of COVID-19 pandemic. The released data from the clinical trials indicated that the still there is no cut-off evidence of any drug to totally eradicate the viral infection caused by COVID-19. In addition, none of the clinical trials had reported an effective drug that suits the different cases of COVID-19. However, the emergency use approved drugs are used currently to reduce the mortality rate and reduce the complications of COVID-19 infection. Finally, the safety precautions such as wearing masks, social distancing and hand hygiene still the key issues that individuals have to follow to avoid infection until the release of an approved vaccine or drug showing a tested effectiveness against COVID-19.

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