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Review Article

Coronavirus Disease (COVID-19) and the Search for Effective Treatment Options: A Systematic Review

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Abstract

As corona virus disease (Covid-19) reaches a pandemic status within short time, it is a call to order, to the global health system, because, as at the moment, there is no nation or group of nations spared off the disease. This review aimed to assess, the journey so far, with regards to the search for effective treatment options for covid-19. Relevant data were obtained using various search engines, like Google, Ask.com, Bing and yandex among others. In the course of that, it was discovered based on the previous restudies that, many different agents are candidates for treatment of Covid-19. These include antiviral, antibacterial/antiparasitic as well as anti-inflammatory agents. Due to the significance of the disease to public health, World Health Organization (WHO) initiated a large-scale trial called ("Solidarity Trial"), covering many countries and enrolling large number of hospitalized patients at once. This was designed to cut down the normal lengthy period clinical trials and evaluation of drugs takes, by up to 80%. In the course of that, as at 1st July, 2020, a total of 5500 patients were enrolled from 21 out of 36 countries approved to participate. Documented evidence from published works reviewed, also suggest that, Chloroquine/hydroxychloroquine, Remdesivir, Lopinavir-ritonavir and Favipivir; which are primarily; malaria drugs, experimental antiviral drug; HIV drugs combination and immunomodulators respectively, could be used for this fight. However, their function is now further redirected to become (repurposed drugs) to help contain the Covid-19 pandemic, as such their effectiveness is being evaluated in that direction. It could therefore be concluded that, there are some head ways in the search for treatment options, but much more needs to be done to arrive at the desired destination with regards prevention and cure of the Covid-19.

Keywords: *Coronavirus Disease; Treatment Options; Solidarity Trial; Repurposed Drugs*

Introduction

Coronavirus disease (covid-19) is an illness caused by a novel stain of coronavirus (nCoV) not been identified in human before. It belongs to the family of viruses that causes mainly respiratory diseases like Middle East Respiratory Syndrome (MERS-CoV) and Severe Acute Respiratory Syndrome (SARS-CoV). Diseases due to these viruses are zoonotic, meaning that, they are transmitted between animals then later to human, for example, MERS-CoV was believed to be transmitted from dromedary camels to humans and SARS-CoV from civet to cats then to human while the source of SARS-CoV-2 (COVID-19) is yet to be determined but researches are ongoing, although some are linking it to bats.

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes an acute respiratory infection that was believed to be cleared in most cases by competent immune system within 7 days of attack [1]. Systemic inflammatory reactions is the characteristic of

the severe lung pathology associated with acute viral stage, were large number of cytokine moves to the site in severe cases of the disease [2]. The primary target of the SARS-CoV-2 infection is the lower respiratory tract and it is associated with decreased in both CD4 and CD8 T-cell of cell mediated immunity [3,4].

In this disease, patients usually suffers from what is known as acute respiratory distress syndrome for up to 7 to 10 days after disease onset, due to increased viral replication, high proinflammatory cytokines as well as chemokine response and at the same times, there is increased inflammatory cells infiltration [4,5]. But, as against SARS cases in 2003, some patients infected with SARS-CoV-2, do not show severe symptoms of upper respiratory tract infection like sore throat and viremia-associated indicators like (lymphopenia, leukopenia, lactic dehydrogenase and higher liver enzymes) or indications of chest abnormalities seen through imaging [6,7].

Unlike in human coronavirus NL63 (HCoV-NL63) where children were believed to be less susceptible and show milder disease severity than adults [8], the SARS-CoV-2 infection affects children and the old aged individuals more in some cases, when compared to other age ranges and this proved to be of public health concern due to high transmission rate and unpredictability of disease progression all over the world [8].

Centers for Disease Control (CDC) calls for strict prevention and control protocols in order to contain SARS-CoV-2 spread among communities world over, according to [9], patients with SARS-CoV infection had the highest viral load (in posterior oropharyngeal saliva samples) and found that early intervention with potent antiviral agents plays vital role in controlling COVID-19 and reducing its severity, but highlighted that, adequate and standard treatment for COVID-19 is presently on the search.

Also, according to world health organization (WHO), at the moment there are no approved effective drugs/agents for the treatment or prevention of the disease COVID-19, the only alternatives for patients managements, are effective infection prevention and control strategies and supportive care like supplemental oxygen and mechanical ventilatory support, were applicable [1].

The possible treatment options

Activity of many antimicrobial agents, such as: Antiviral, some antibacterial/antiparasitic and anti-inflammatory agents are being evaluated to explore their efficacy in combating the SARS-CoV-2 (data until March, 2020) [10]. Moreover, the World Health Organization (WHO) launched a large scale global trial, named the "Solidarity Trial". This trial includes thousands of patients from many different nations and will be used to evaluate the efficacy of what WHO refers to as, the four most promising therapies on covid-19: Chloroquine and hydroxychloroquine; remdesivir, Lopinavir/Ritonavir (LPV/r) and LPV/r plus interferon-beta; which are primarily: Malaria drugs, an experimental antiviral drug; HIV drug combination and an immunomodulator respectively [11].

"Solidarity" trial for COVID-19 treatment

The solidarity" is an undertaking of the WHO and partners which is an international clinical trial to assist in getting effective treatment for COVID-19, which was launched by the World Health Organization and partners in this year 2020, to compare 4 treatment options against standard of care protocols, to determine their relative effectiveness against coronavirus disease (Covid-19) with aims to rapidly discover whether any of the selected drugs effectively slow down the disease, decrease its progression or improves survival of patient. However, WHO cautions against recommending or administering these unproven treatments to COVID-19 patients and discourages self-medication with them [1].

Participation in solidarity

Based on records, till the 1st July, 2020, about 5500 patients were enrolled in 21 different countries out of the 39 countries with approvals to begin recruiting. In all, more than 100 countries have joined or expressed willingness to join the trial, and WHO is actively supporting them.

Solidarity trial update

According to WHO release on 4, July, 2020, hydroxychloroquine and lopinavir/ritonavir treatment wing of the trial is discontinued, this was because it has accepted recommendation by Solidarity Trial's International Steering Committee to discontinue the trial with hydroxychloroquine and lopinavir/ritonavir arms of the trial, due to evidence obtained for hydroxychloroquine vs standard-of-care and lopinavir/ritonavir vs standard-of-care from solidarity trial interim results and review of evidence from all trials presented at the 1st to 2nd July, WHO Summit on COVID-19 research and innovation.

But this decision applies only to the conduct of the solidarity trial in hospitalized patients and does not affect the possible evaluation in other studies of hydroxychloroquine or lopinavir/ritonavir in non-hospitalized patients or as pre and/or post-exposure prophylaxis for COVID-19 [1].

But why the solidarity trial?

The pressing needs to contain COVID-19, exacts pressure on global health systems which led WHO to consider the need for speed and scale in the trial. While randomized clinical trials normally take years to design and conduct, the solidarity trial will reduce the time taken by at least 80%.

Enrolling patients in one single randomized trial will help facilitate the rapid worldwide comparison of unproven treatments. This will overcome the risk of multiple small trials not generating the strong evidence needed to determine the relative effectiveness of potential treatments.

Antiviral drugs

There is still no antiviral drug that has been approved to treat this human coronavirus. Because a specific, highly potent antiviral drug for SARS-CoV-2 will under normal condition take years to develop and evaluate in clinical studies, for now the main focus for COVID-19 treatment is the repurposing of drugs that have already been approved for other diseases conditions.

Because, those drugs have established safety profiles and their production strategies is known, examples include unapproved drugs that showed antiviral activity in animal models for SARS-CoV-1 and/or middle east respiratory syndrome coronavirus (MERS-CoV).

Currently, clinical trials have already been conducted or are ongoing to evaluate the efficacy of several repurposed/experimental drugs for the treatment of COVID-19. As of 7th March, 2020, the most evaluated antiviral medications were lopinavir/ritonavir (LPV/r) (n¼15), chloroquine (n¼11), arbidol (n¼9), hydroxychloroquine (n¼7), favipiravir (n¼7) and remdesivir (n¼5) Most of these agents have demonstrated antiviral activity in cell culture against coronaviruses [12].

Chloroquine and hydroxychloroquine

The antiviral activity of chloroquine was already identified in the late 1960s [13,14]. Base on records, chloroquine and hydroxychloroquine inhibits many different viruses from different families in cell culture, including coronaviruses (SARS-CoV-1 and MERS-CoV) [15]. Of recent, in vitro antiviral activity against SARS-CoV-2 has also been demonstrated [16].

In the same vein, many clinical trials were conducted in over 10 hospitals in China, to assess the efficacy of chloroquine on patients with COVID-19, also, news briefings' on 'results of over 100 patients revealed that chloroquine phosphate was found more active than control treatment, improve lung imaging findings, and promotes a virus negative conversion, as well as shorten the disease progression. But, no data released from the clinical trials as at the time to support the announcement, making it difficult to firmly conclude on that [17].

Data from France also revealed that, 26 COVID-19 patients were treated for six (6) days using hydroxychloroquine (200 mg, 3 times/day), Six (6) of the patients also received azithromycin while sixteen (16) patients were used as control group, nasopharyngeal swabs were used to measure SARS-CoV-2, RNA daily, during the treatment. The results revealed clearance of SARS-CoV-2 RNA in 57% of chloroquine-treated patients as against 12.5% of untreated patients. Synergistic effect was also seen between azithromycin and hydroxychloroquine, because patients treated using the combination showed viral RNA clearance by day 6 post- inclusion. However, before chloroquine can be considered safe and effective as a treatment for COVID-19, more studies are needed [18].

Remdesivir

The experimental drug Remdesivir (GS-5734) was under development for the treatment of Ebola virus-infected patients, it is a nucleotide prodrug with ability to inhibit viral RNA replication [19]. When assessed in cell culture, remdesivir showed broad-spectrum antiviral activity against several other RNA viruses, including arenaviruses [19] and coronaviruses [20]. Previous records also showed that remdesivir efficiently inhibited SARS-CoV-1 and MERS-CoV in cell culture, including human airway epithelial cells. It also demonstrated antiviral activity against them in animal model. When tested against MERS mouse model, the remdesivir was found to reduced lung viral load and severe lung pathology [21], it is also been shown now that, remdesivir is active against SARS-CoV-2 in cells, which is a good development [16].

The remdesivir was used in one COVID-19 patient case report, in which a patient presented with mild symptoms including cough and low-grade intermittent fevers, without evidence of pneumonia, but later, progressed to pneumonia, as such intravenous remdesivir was initiated and on illness day 12, the clinical condition of the patient improved. Although this is encouraging, but been effective on one patient is not enough for it to be approve. At the same time remdesivir is being evaluated in COVID-19 patients in five clinical studies worldwide: Two studies in China, and a study in the United States, Singapore and South Korea, but results of these trials are not yet available [22].

Lopinavir-ritonavir

Originally, Lopinavir is an HIV protease inhibitor which when combined with ritonavir increases its half-life via the known cytochrome P450 inhibition. Antiviral activity of LPV/r against SARS-CoV-1 has been reported in cell culture, but conflicting results were reported for MERS-CoV [14,23].

In a MERS-CoV mouse model, prophylactic use of LPV/r in combination with interferon-beta slightly reduced the viral load in the lungs, with no effect on other disease parameters [21] while therapeutic treatment of the same combination was found to improve the pulmonary function, but fail to reduce virus replication or reduce severe lung pathology, however, in SARS-CoV-1-infected patients, treatment results with LPV/r were inconclusive [24].

In one open-label controlled trial, on hospitalized matured patients with severe COVID-19, out of the total patients; 99 were treated with LPV/r, and 100 of the patients received the standard care treatment, but no difference was observed in terms of clinical improvement and mortality between two different groups [5].

Favipiravir

Favipiravir was another agent also evaluated on COVID-19 patients in China. The agent, Favipiravir (T-705) is an antiviral drug that was approved in Japan in 2014 for the treatment of influenza virus pandemic, being a prodrug, it is converted intracellularly to ribofuranosyl 50-triphosphate metabolite (favipiravir-RTP) capable of inhibiting wide range of other RNA viruses [25].

It is believed that favipiravir-RTP could be misincorporated in a growing viral RNA chain, or binds to conserved polymerase domains, thereby preventing viral RNA replication. Based on evaluation mainly in Japan, in clinical trials for influenza virus infections, Favipiravir

was found well tolerated, with only mild to moderate diarrhoea reported, but is important to note that, favipiravir is contraindicated in pregnant and lactating mothers, because of its association with teratogenicity and embryonic deaths as found in cases in animal studies [25].

As part of efficacy evaluation, Favipiravir was found to have moderate antiviral activity against SARS-CoV-2 when monitored in cell culture (EC50 value of 62 mM) [4].

Due to urgent search for treatment option, in one open-label, non-randomised controlled study, clinical trial on favipiravir for use as an anti-coronavirus agent was vigorously pursued in China, despite weak scientific bases, in which laboratory confirmed cases of COVID-19 patients were treated with oral favipiravir: Day1, treated with 1600 mg twice; days 2 to14 treated with 600 mg twice daily, plus interferon-alpha through aerosol halation (5 million U twice daily) [26].

Conclusion

Although optimistic, from the current available data, it is evident that, there is still a long way to go, in getting highly potent and effective antimicrobial agent that can effectively prevent or cure coronavirus disease (covid-19).

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