POTENTIAL THERAPIES FOR TREATMENT OF COVID-19

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ABSTRACT

Since discovery of the novel coronavirus (SARS-CoV-2) in December of 2019, this viral pneumonia originated in Wuhan, China quickly spread around the world. This new disease, called COVID-19 can cause Acute Respiratory Distress Syndrome (ARDS) due to an uncontrolled inflammatory response like sepsis, that leads to multiple organ failure and even death. Several pharmacotherapeutics alternatives are being tested over the world, looking for most diverse drugs that might be able to fight the infection. The objective of this paper is to review the main pharmacotherapeutics techniques development, as remdesivir, chloroquine/hydroxychloroquine, lopinavir plus ritonavir, interferon-β, ivermectin, anticoagulants, convalescent plasma and vaccine, currently undergoing clinical trials in order to evaluate its effectiveness and safety to combat the COVID-19, presenting their characteristics, possible adverse effects and main scientific findings of its potential action. In conclusion, some therapies presented promising in-vitro results or in the treatment of some patients, nonetheless, multicentric blinded placebo controlled clinical trials are necessary to determine their effectiveness, safety, dosage, and best time point of treatment.

Keywords: antiviral, coronavirus, convalescent plasma, drugs, SARS-CoV-2

INTRODUCTION

In December 2019, an outbreak of viral pneumonia caused by a novel highly pathogenic coronavirus started in Wuhan, China and quickly spread to the rest of the world. This new disease was named COVID-19 (Coronavirus Disease 2019) by the World Health Organization (WHO) as a severe acute respiratory syndrome caused by a coronavirus-2 (SARS-CoV-2). This is the third emergence of a highly pathogenic coronavirus into the human population after the severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002 and the Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012 (LI et al., 2020). It has been demonstrated that the genetic sequence of the COVID-19 has more than 80% identity to SARS-CoV and 50% to the MERS-CoV (REN et al., 2020). Thus, based on genetic sequence identity and phylogenetic reports, SARS-CoV-2 is sufficiently different from SARS-CoV and it can be considered as a new beta-coronavirus that infects humans (ROTHAN and BYRAREDDY, 2020).

The coronaviruses contain a relatively large single-stranded, positive-sense RNA genome and the viral coat is composed by structural proteins including the spike (S), envelope

62

(E) and membrane (M), and the nucleocapsid (N) protein that packages the viral genome (TU et al., 2020). Coronavirus S protein has been reported as a significant determinant of virus entry into host cells. The primary target cells of SARS-CoV infection are respiratory epithelial cells. The spike glycoprotein in SARS-CoV and SARS-CoV-2 binds to the same functional host cellular receptor, Angiotensin-Converting Enzyme-2 (ACE-2) (GRONEBERG et al., 2005; ZHOU et al., 2020).

According to Kuba et al. (2005), the binding of the viral S protein to ACE2 induces a negative feedback loop that ultimately results in down-regulation of ACE2. The decrease of ACE2 subsequently directs its substrate angiotensin I towards its related enzyme ACE. Increased ACE activity results in elevated levels of angiotensin II. Once angiotensin II binds to its receptor, AGTR1A, pulmonary vascular permeability is increased.

Among the symptoms reported, fever is the most typical, however, patients may present fatigue, dry cough, dyspnea etc., with or without nasal congestion. In severe condition may have shortness of breath, moist rales in lungs, weakened breath sounds, dullness in percussion. Computed Tomography (CT) images reveals bilateral pulmonary parenchymal ground-glass and consolidative pulmonary opacities, sometimes with a rounded morphology and a peripheral lung distribution (JIN et al., 2020; LI et al., 2020).

Respiratory dysfunction caused by virus infection, lead to patients with severe COVID-19 to reach the criteria for sepsis diagnosis of the third international consensus definitions (Sepsis-3; SINGER et al., 2016). According to Huang et al. (2020) the main cause of death in patients affected by COVID-19 is the Acute Respiratory Distress Syndrome (ARDS) caused by an uncontrolled systemic inflammatory response resulting from large amounts of pro-inflammatory cytokines and chemokines release, called as cytokine storm. This cytokine storm will trigger a violent tissue attack by the immune system, developing ARDS, multiple organ failure and even death, similar to SARS-CoV and MERS-CoV infections development (GRONEBERG et al., 2005; LI et al., 2020).

Furthermore, COVID-19 may predispose to both venous and arterial thromboembolic disease due to excessive inflammation, hypoxia, immobilization, and Disseminated Intravascular Coagulation (DIC) (THACHIL et al., 2020; TANG et al., 2020). In fact, a high incidence of thrombotic complications has been reported in critical ill patients caused by COVID-19 infection (KLOK et al., 2020).

Currently, does not exist specific treatment for COVID-19, however, several clinical trials are takin place to test potential antiviral therapies, aiming to develop or repurpose drugs that help reduce morbidity and/or mortality of this disease (MAHASE, 2020). With these precepts, the objective of this article is to review the main therapeutic techniques being tested to treat the COVID-19.

DEVELOPMENT

The therapies, depending on their target, can be divided into two categories: one is acting directly on the coronavirus, either by inhibiting crucial viral enzyme responsible for genome replication or by blocking viral entry to human cells; and second is designed to modulate the immune system, either by boosting the innate response or by inhibiting the inflammatory processes that cause lung injury (TU et al., 2020). The WHO has launched the solidarity trial to investigate four potential treatments: remdesivir, chloroquine/hydroxychloroquine; lopinavir plus ritonavir; and lopinavir plus ritonavir associated with interferon-β. Besides antiviral treatment, ivermectin, anticoagulant and convalescent plasma therapy are also being considered and studied for treatment of severe patients.

Remdesivir

Remdesivir works to inhibit viral replication and is being investigated through several clinical trials as a potential COVID-19 treatment (MAHASE, 2020). Remdesivir is an adenosine analogue, which incorporates into nascent viral RNA chains and results in pre-mature termination (WARREN et al., 2016). It has been recognized as a promising antiviral drug against a wide array of RNA viruses (including SARS/MERS-CoV) infection in cultured cells, mice, and nonhuman primates (SHEAHAN et al., 2017). Wang et al. (2020) demonstrated in-vitro that remdesivir functioned at a stage post virus entry and achieved concentration that suggests it will work in nonhuman primates and, according to preliminary data, also inhibited virus infection efficiently in a human cell line.

On January 2020, the first case of COVID-19 in the United States has been treated with intravenous remdesivir on 7 days after hospitalization (illness day 11) and no adverse events were observed in association with the infusion (HOLSHUE et al., 2020). According to Grein et al. (2020), 60% of the patients with COVID-19 who received remdesivir reported adverse events during follow-up and 8% discontinued remdesivir treatment. The most common adverse events include increased hepatic enzymes, diarrhea, rash, renal impairment, and hypotension, which were more common in patients receiving invasive ventilation. However, the safety and side-effect profile of remdesivir in patients with COVID-19 require proper assessment in placebo-controlled trials.

Some randomized, placebo-controlled, double-blind, multicenter, phase III clinical trial has been described to be launched in China in order to evaluate the efficacy and safety of this drug in patients with COVID-19, expecting to be concluded by the end of April 2020 (DONG et al., 2020).

Chloroquine/hydroxychloroquine

Chloroquine and hydroxychloroquine (a less toxic metabolite of chloroquine) are a widely used anti-malarial and autoimmune disease drug, has been reported as a potential broad-spectrum antiviral drug in 2006 (SAVARINO et al., 2020). Both drugs are considered to be immunomodulators rather than immunosuppressants, are widely distributed in the whole body, including lung, after oral administration (ZHOU et al., 2020; WANG et al., 2020) and known to block virus infection by increasing endosomal pH required for virus/cell fusion, as well as interfering with the glycosylation of cellular receptors of SARS-CoV, being effective in preventing the spread of SARS-CoV in cells culture (VINCENT et al., 2005).

An in-vitro study demonstrated that chloroquine functioned at both entry and at post-entry stages of the SARS-CoV-2 infection in Vero-E6-cells. Besides its antiviral activity, chloroquine has an immune-modulating activity, suggesting that may synergistically enhance its in-vivo antiviral effect (WANG, 2020). The immunomodulatory characteristics of chloroquine and hydroxychloroquine is considered an advantage, since they do not bring risks of infectious complications (ZHOU et al., 2020).

The most common adverse effects of these drugs are gastrointestinal alterations, such vomiting and diarrhea and cardiac arrithmia. However, long therm exposure to chloroquine may causes severe side effects, such as retinopathy composed by circular defects (or bull's eye maculopathy), diametric defects in the retina and cardiomyopathy. In elderly patients and in overdosage (required for antiviral effect) are associated with serious toxicities for their limited safety margins. In contrast, hydroxychloroquine has a lower level of tissue accumulation, which explain the fact that long therapy with tis drug were associated with fewer adverse effects than chloroquine (SCHREZENMEIER and DÖRNER, 2020; ZHOU et al., 2020).

Furthermore, hydroxychloroquine is strongly recommended for pregnant patients with an autoimmune disease as it prevents the development of congenital heart block due to a potential inhibitory effect of type I interferon production, while chloroquine may cause a number of severe side effects on fetal development, thus hydroxychloroquine may confer a

similar antiviral effect at both pre- and post-infection stages, as found with chloroquine, has fewer side effects and is safe in pregnancy (ZHOU et al., 2020).

It is important to emphasize that to date, clinical trials indicate no acute virus infection has been successfully treated by chloroquine/hydroxychloroquine in humans and no benefit has been seen in animal models, highlighting the need of more research to confirm or disapprove the in-vitro efficacy of this drugs before using as a COVID-19 treatment (TOURET and DE LAMBALLERIE, 2020).

Lopinavir plus ritonavir (Kaletra)

Lopinavir and ritonavir combination (Kaletra) is normally used to treat Human Immunodeficiency Virus (HIV). Lopinavir was identified after the 2003 SARS outbreak as a potential treatment (MAHASE, 2020). These drugs inhibit aspartyl protease, an enzyme encoded by the pol gene of the HIV that cleaves the precursor polypeptides in HIV, thus inhibits its replication cycle (TU et al, 2020).

Coronaviruses encode a different enzymatic class of protease, the cysteine protease, theoretical evidence exists that lopinavir plus ritonavir may also inhibit the coronaviral-3CL1pro-protease (CHU et al., 2004; DE WILDE et al., 2014). However, at the clinical trials performed on patients with severe COVID-19, no benefits of lopinavir plus ritonavir beyond standard care were observed, therefore gastrointestinal adverse events were more common in the lopinavir–ritonavir group, including nausea, vomiting, and diarrhea (CAO et al., 2020).

Interferon-β 1a

Is a molecule that forms part of the lung's own defense mechanism to fight with viruses, formulated as an inhaled drug. It has been tested in phase two trials for asthma patients, being demonstrated to improve lung function. In COVID-19, IFN-β production may be suppressed by coronaviruses, so IFN-β 1a could work to prevent or decrease symptoms of severe respiratory illness, such as pneumonia (MAHASE, 2020).

Ivermectin

Ivermectin is an FDA-approved anti-parasitic agent which was also proven to exert antiviral activities toward HIV and dengue virus (TU et al., 2020). To test the antiviral activity of ivermectin towards SARS-CoV-2, Caly et al. (2020) infected cells *in vitro* with SARS-CoV-2 and demonstrate that ivermectin has anti-viral action against the SARS-CoV-2 clinical isolate *in vitro*, with a single dose able to control viral replication within 24–48 h in our system. Ivermectin has an established safety profile for human use and adverse effects depend on infection intensity and on parasitic species (CANGA et al., 2008), and are characterized by pruritus, headache and dizziness and also might be associated with polymorphisms in the mdr-1 gene (CHANDLER, 2018). However, clinical trials are required to determine the adequate dosing and effectiveness to treat COVID-19.

Anticoagulants

Klok et al. (2020) reported the incidence of thrombotic complications in critical ill patients with COVID-19 infections by 31%. This incidence highlights the importance of investigating signs of thrombotic complications. The International Society of Thrombosis and Haemostasis has proposed a new category identifying an earlier phase of sepsis-associated DIC called sepsis-induced coagulopathy (SIC) (IBA et al., 2019) and a guidance has been created to manage the coagulopathy of COVID-19 (THACHIL et al., 2020).

Tang et al. (2020) studied the usefulness of SIC score and other coagulation parameters, in screening out patients who can benefit from anticoagulant through retrospective analysis. According to their results, only the patients meeting SIC criteria or with markedly elevated D-

65

dimer may benefit from anticoagulant therapy mainly with low molecular weight heparin (LMWH), while unselected patients may not benefit from this therapy. Side effects and contraindications includes active bleeding and platelet count less than 25×10^9/L, monitoring is advised in severe renal impairment (THACHIL et al., 2020).

Convalescent plasma

The use of convalescent plasma (CP) or immunoglobulins from patients who recovered from disease have been reported to improve the survival rate of patients with SARS (CHENG et al., 2005), Ebola (WHO, 2014) and was established as a part of the protocol for the treatment of Middle East respiratory syndrome coronavirus (ARABI et al., 2015). The patient usually develops a primary immune response by day 10–14, followed by clearance of the virus (CHENG et al., 2005).

Duan et al. (2020) compared 10 severe COVID-19 patients that, besides antiviral treatment, received CP and 10 patients with the same age, gender and severity of the disease who does not received CP, and found that convalescent plasma group presented three cases discharged and seven cases in much improved status and ready for discharge, as compared to three deaths, six cases in stabilized status and one case in improvement in the control group.

Same study showed that all investigated patients achieved serum SARS-CoV-2 RNA negativity after CP transfusion, accompanied by an increase in oxygen saturation and lymphocyte counts, improvement liver function and C-reactive protein, suggesting that the inflammation and overreaction of the immune system were alleviated by antibodies contained in CP. However, the optimal transfusion time point seems to be an important factor to be considered and investigated, since a better treatment outcome was observed among SARS patients who were given CP before 14 days post onset of illness and a patient who received after 14 days post onset showed much less significant improvement.

In another study also observed a better clinical outcome in SARS patients given CP early in the course of the disease (CHENG et al., 2005), highlighting the importance of the therapy time point.

The risk of this treatment are adverse reactions (hypersensitivity) and infections transmission, including HIV, Hepatitis B and C, however these risks are low as only screened and compatible blood is used for transfusion (WHO, 2014).

Vaccine

The development of vaccine is a long-term strategy to prevent COVID-19 outbreaks in the future and depends on the sequence of SARS-CoV-2 genome (TU et al., 2020). Characterization of the prefusion S structure would provide atomic-level information to guide vaccine design and development. Wrapp et al. (2020) tested three published SARS-CoV Receptor Binding Domain (RBD) specific monoclonal antibodies and found that, despite the relatively high degree of structural homology between the SARS-CoV-2-RBD and the SARS-CoV-RBD, the antibodies do not have appreciable binding to SARS-CoV-2, suggesting that antibody cross-reactivity may be limited between the two RBDs. Therefore, future antibody isolation and therapeutic design efforts will benefit from using SARS-CoV-2 S proteins as probes.

CONCLUSION

This article presented a short review of current potential COVID-19 pharmacotherapeutic treatments. Nevertheless, it is necessary to understand that clinical trials to ensure safety and effectiveness of these therapies including vaccines will require several

months. But there is a light, since therapeutic agents like, remdesivir, chloroquine / hydroxychloroquine; lopinavir, ritonavir, interferon-β, ivermectin, anticoagulants, and convalescent plasma have shown potential to combat some specific stages and complications of the virus, without being preventive or miraculous cures. Meanwhile, social distancing and supportive treatment (including oxygen therapy, fluid management and antibiotics to cover secondary bacterial infection) remains the main strategy against COVID-19.

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68

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