

Pharmacological Strategies to Manage COVID-19

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Abstract

COVID-19 is an infectious disease caused by SARS-CoV-2 that emerged in December 2019 in Wuhan, China. Great efforts have been made to find effective drugs to fight the virus. The aim of the study is to review the possibilities of pharmacological therapy in the management of COVID-19 and the repositioning of drugs, highlighting the main characteristics pointed out, advantages and limitations of the alternatives proposed by the scientific community. The study was descriptive, exploratory, cross-sectional, with a qualitative approach. Therapeutic strategies include antimalarials chloroquine and hydroxychloroquine; antibiotics azithromycin and association with chloroquine; antivirals lopinavir-ritonavir, ribavirin, remdesivir, favipiravir; glucocorticoids; immunoglobulins tocilizumab, sarilumab; convalescent plasma; antiparasitic ivermectin, emetine and anticoagulant heparin. Therapeutic possibilities are underway. However, these possibilities come up against the lack of studies proving their efficiency and effectiveness in large populations, given the recent emergence of the disease caused by SARSCoV-2.

Keywords: SARSCoV-2; COVID-19; Repositioning Drugs; Re

Abbreviations

SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; ARDS: Acute Respiratory Distress Syndrome; CoVs: Coronaviruses; HCoV: Human CoVs; MERS: Middle East Respiratory Syndrome; ACE2: Angiotensin-Converting Enzyme 2; COPD: Chronic Obstructive Pulmonary Disease; RdRp: RNA-Dependent RNA Polymerase; SLC: Cytokine Release Syndrome; TNFi: Tumor Necrosis Factor Inhibitors; GABA: Gamma-Aminobutyric Acid; DVP: Deep Vein Thrombosis; PE: Pulmonary Embolism; PTT: Partially Activated Thromboplastin Time

Introduction

COVID-19 is an infectious disease caused by SARS-CoV-2 coronavirus, first noticed in Wuhan, China, in December 2019 and the World Health Organization (WHO) declared it a pandemic on January 30, 2020. WHO firstly called this virus “the novel coronavirus” (2019-nCoV), and it is now known as SARS-CoV-2 (it stands for Severe Acute Respiratory Syndrome Coronavirus 2) causing acute respiratory distress syndrome (ARDS) to patients. COVID-19 has challenged and exposed governments worldwide and the fragility of their sanitary systems, which struggle to slow down the spread of this disease that moves beyond physical borders [1]. In the beginning, several patients

who presented respiratory diseases caused by COVID-19 in Wuhan had had some contact with seafood and living animals, leading to the assumption that these animals transmitted the virus to humans. However, the increasing number of patients not exposed to the meat market made it evident that the virus is transmitted from human to human.

The first coronavirus isolated cases in humans took place in 1937. The virus got this name because of the spike forms on its surface (protein S), giving it a crown-like appearance when observed through an electron microscope [2]. This virus belongs to the Betacoronavirus group and is characterized by its high pathogenicity. According to the worldometer's [3] platform, COVID-19 has led to more than five million, eight hundred thousand infections, and about 358 thousand deaths worldwide by May 28, 2020 [3]. Scientists are struggling to find effective drugs for fighting this virus, but there is no specific treatment so far.

Coronavirus groups

Coronaviruses (CoVs) are a genus of the Coronaviridae family; they are positive-strand RNA viruses with the largest viral genome of all group of RNA viruses (27 - 32 kb) [4].

The first reports on human CoVs (HCoV) appeared in the mid-1960s. Up to December 2019, humans had been infected by six different types of coronavirus:

- I) Alphacoronavirus 229E and VNL 63: Viruses from the genus of the Coronaviridae family that cause respiratory and gastrointestinal diseases in several mammals. HCoV-NL63 and HCoV-229E circulate all over the world. CoV-NL63 is associated with croup in children and common cold in healthy adults⁴. The human coronavirus NL63 was discovered in 2004 by Dutch virologists after the SARS outbreak. Nowadays, it is present worldwide and is a highly prevalent virus. It "primarily infects the upper respiratory tract, typically causing mild upper respiratory infectious symptoms such as cough, rhinorrhoea and fever. The clinical course of HCoV NL63 infection is more severe in immunocompromised patients" [5].
- II) Betacoronavirus OC43: it is the coronavirus most commonly associated with human infections. However, we still know little about its molecular epidemiology and evolution. There are four HCoV-OC43 genotypes (A to D), with genotype D most likely arising from recombination. The latter is associated with pneumonia in the elderly population [6].
- III) CoV-HKU1: This coronavirus is associated with community-acquired pneumonia. It was firstly found in 2 patients with pneumonia in Hong Kong, China. "This new coronavirus was detected by RT-PCR of the *pol* gene of coronaviruses with use of conserved primers in the nasopharyngeal aspirates of patients" [7].
- IV) SARS-COV: It causes Severe Acute Respiratory Syndrome (SARS) and was first discovered in China in the end of 2002. At that time, there was a worldwide outbreak, with more than 8 thousand cases and 800 deaths. Since there have been no more cases registered, the authorities have considered that the Severe Acute Respiratory Syndrome is eradicated since 2004. Civets have been known as the immediate vectors of this disease because they were sold at living animals' markets as exotic food. However, there is no information about how civets got infected by this virus, but bats are the possible SARS virus host in the nature [8].
- V) MERS-COV: The virus for the Middle East Respiratory Syndrome (MERS). It was first reported in Jordan and Saudi Arabia in 2012 and has not been eradicated. Scientists suspect that dromedaries are the primary source of this disease, but we do not know how it is transmitted to humans. MERS is more common among males and tends to be more severe on the elderly or those with underlying chronic conditions. Studies suggest that infected people do not transmit the virus before presenting symptoms, which may start after five days. The symptoms usually are fever, shivers, muscle pain, and cough [8].

Physiopathology

An infected person can transmit coronavirus, symptomatic or not, through droplets from nose and mouth produced by sneezing and coughing [9]. Most of these droplets land on a surface. People can also get contaminated by breathing the aerosol microdroplets released into the air by infected people [10].

The virus enters the alveolar epithelium by inhalation or direct dissemination, and then protein S attaches to the angiotensin-converting enzyme 2 (ACE2). Such enzyme is largely produced by many body cells, mainly by humans' pneumocytes type 2. These cells are responsible for the surfactant type C production, a substance that reduces the surface tension of water in the pulmonary alveoli. This facilitates gas exchange and contributes to pulmonary compliance. Once inside the pneumocytes, the virus uses the cell structure to replicate. During this process, there is an inflammatory response and cytopathic effect, causing pneumocyte apoptosis or destruction, therefore compromising the pulmonary dynamics. In addition, the virus enters the blood flow and infects other extrapulmonary tissue cells, such as heart, kidney, endothelium and intestine, that also have ACE2 [11]. Angiotensin-converting enzyme 2 in several tissues might explain the multiple organ dysfunction cases on patients [12]. When the virus reaches the central nervous system, it may cause cerebral contusion, seizures, loss of sensitivity, and encephalitis. In kidneys, the infection may cause proteinuria, albuminuria, and acute renal insufficiency, especially of the oliguric type [13].

Viral replication causes an accentuated inflammatory response. Severe COVID-19 patients may develop hypercytokinemia from this inflammation. Cytokine is a substance naturally expelled into our blood to activate responses in our immune system. In cases of hypercytokinemia, there is an unbalanced reaction, causing high fever, mild nausea, and potentially fatal inflammation. Interleukin-6 (IL-6) seems to be the proinflammatory cytokine that causes this inflammatory event [14]. The main cause of death is the respiratory insufficiency caused by acute respiratory distress syndrome [15].

Signs and symptoms

COVID-19 symptoms may range from mild to severe. They typically appear 2 - 14 days after exposure to the virus [13]. The elderly or people with preexisting chronic diseases such as diabetes, pulmonary or cardiac conditions may have a poor prognosis that can lead to death. It also applies to people with weakened immune systems. Few children have been reported with this virus.

According to several investigations and medical institutes, the main COVID-19 symptoms are cough, fever (this may not appear on young, elder or immunosuppressed patients), shortness of breath, sputum production, headache, sore throat, swallowing difficulty, conjunctival and nasal congestion, discomfort, myalgia, diarrhea, fatigue, dysgeusia, and anosmia [16,17].

COVID-19 complications can include the following: respiratory, such as pneumonia and Severe Acute Respiratory Syndrome; cardiac, such as arrhythmia, acute heart injury and failure, acute myocardial infarction, cardiogenic shock and cardiac arrest; secondary infections such as sepsis, renal insufficiency, and multiple system atrophy; rhabdomyolysis and death [13].

On February 28, WHO-China Joint Mission's report, released by WHO, stated that from the study conducted on 55,924 laboratory-confirmed cases, the average time from symptom onset to clinical recovery for mild cases is around 2 weeks. For severe or critical cases, it takes 3 - 6 weeks. In these cases, it can take 1 week from symptom onset to an advanced condition - including hypoxia. Among cases in which patients have died, the time between symptoms onset and outcome varies from 2 - 8 weeks [17].

The Chinese Journal of Epidemiology [18] states that 80% of the cases are mild. Based on all confirmed, suspected, and asymptomatic COVID-19 cases in China since February 19, it is possible to say that 80.9% of the cases are mild (with symptoms similar to the flu) and can recover at home; 13.8% are severe (which includes pneumonia and dyspnea); 4.7% of the critical cases may have respiratory failure, septic shock, and multiple organ dysfunction; and the virus is fatal in about 2% of the reported cases [17].

The World Health Organization (WHO) reported that the COVID-19 lethality rate varied from 5.8% in Wuhan to 0.7% across China (WHO 2020c) [18]. Most of the lethal cases happened to elderly people or patients with comorbidities, such as heart or chronic pulmonary disease, diabetes mellitus, hypertension, and cancer [18].

The fatality rate and critical case numbers vary among countries. In Italy, for example, 12% of the reported COVID-19 cases and 16% of the hospitalized patients needed ICU with a 5.8% lethality rate in May [18]. During the same period in South Korea, the lethality rate was 0.9%. Both countries have different population characteristics: in Italy, the age average of the infected people was around 64 and in Korea 40. In addition, Korea took early action by not restricting the extensive testing to hospitalized people [18].

The Epidemiological Report by the Ministry of Health in Brazil released from 18 to 21 May 2020 stated that 73,482 (62.5%) of the cases presented cough, 65,029 (55.3%) fever, 35,979 (30.6%) sore throat and 31,309 (26.2%) dyspnea. This report considered the most frequent clinical manifestations and the disease development in e-SUS (the national public health system). Regarding disease development, 16,362 (13.9%) cases recovered, 8,988 (7.6%) were prescribed home care, 1,316 (1.1%) were hospitalized, and 2,147 (1.8%) died [19].

Prophylaxis

Despite the ongoing studies in Brazil and all over the world, there is no vaccine or effective prophylactic medication for patients with COVID-19 yet. The Brazilian Ministry of Health and the World Health Organization recommend collective and individual actions in order to prevent COVID-19 transmission: washing hands and wrists frequently with water and neutral soap; using 70% Alcohol Hand Sanitizer Gel; performing respiratory hygiene and cough etiquette; avoiding touching eyes, nose, and mouth before washing hands and washing these areas after touching them; keeping a distance of at least 2m from any person that is coughing or sneezing; avoiding intimate touching such as hugs, kisses and handshakes; frequently disinfecting cell phones and kids' toys; not sharing personal objects such as cutlery, towels, plates, and cups; keeping environments clean and airy; avoiding crowds, streets, stadiums, theaters, malls, concerts, cinemas, and churches; having a healthy diet; and avoiding eating raw or undercooked meat and handling it carefully following food safety principles [10].

Brazilian cities also adopted protective measures such as compulsory face mask covering for asymptomatic people in public places. WHO recommends people to wear masks if they are taking care of persons with suspected COVID-19 infection and if they are coughing and sneezing [10].

Additionally, some Brazilian federal states have adopted social distancing and isolation, quarantine and lockdown to slow down the risk of COVID-19 transmission.

Diagnostic criteria

Patients with fever, flu symptoms, and severe acute respiratory syndrome who live or have been in a COVID-19 community transmission territory are more likely to be diagnosis for this disease.

COVID-19 infection can be confirmed by laboratory and clinical-epidemiological criteria. Laboratory criteria include RT-PCR molecular biology testing to detect the presence of SARS-CoV2 virus in the body and rapid or classic serological testing to detect antibodies. These tests show positive to IgG and/or IgM antibodies seven days after the onset of symptoms.

For clinical-epidemiological criteria confirmation, the patient must have flu symptoms or severe acute respiratory syndrome and close contact with a confirmed COVID-19 individual seven days prior to the onset of symptoms [9].

A frequently used method as a complementary exam to diagnose COVID-19 is chest computerized tomography (CT). Imaging findings of viral pneumonia can precede a positive result on RT-PCR for SARS-CoV-2 in some asymptomatic patients. However, patients with a regular chest CT can also have a RT-PCR positive result [9].

Epidemiology

On May 31, 2020, Worldometers' [3] website reported the global number of 6,197,450 COVID-19 confirmed cases. It also reported 371,624 individuals who had a fatal outcome and 2,760,885 recovered cases [3].

The Brazilian Ministry of Health reported 50,985 new coronavirus cases across the country and 28,872 deaths (5.8%) caused by the disease. From this number, 205,371 people recovered (41.3%) and 259,424 were being monitored (52.5%). On that day, the Federal Government's official systems reported 30,102 new cases and 956 new deaths.

Although many Brazilian municipalities have not yet reported confirmed COVID-19 cases or deaths, the virus has spread across the entire country. São Paulo state is still the epicenter of the disease with cases and 7,532 deaths. The federal states with the fewest number of reported cases are the following: Mato Grosso do Sul, with 1,418 cases and 19 deaths; Mato Grosso, with 2,361 cases and 57 deaths and Tocantins, with 3,981 cases and 71 deaths.

This article is a literature review concerning possible pharmacologic therapies and drug repositioning to handle COVID-19. We also analyze the main characteristics, advantages and limitations of the alternatives proposed by the scientific community. The researched keywords are the following: coronavirus, COVID-19, COVID-19 pharmacology, COVID-19 epidemiology.

Methodology

This is a transversal, exploratory, and descriptive study with a qualitative approach. It is descriptive because the researchers describe reality with no attempt to manipulate it. However, this study is also of an evaluative kind in order to facilitate understanding the subject at hand.

When we established the research theme, we carried out an exploratory study in order to approach to currently recommended COVID-19 treatment-related questions.

A transversal study means that the observations are based only on one period in order to withhold the information here proposed.

The data were collected from electronic databases, books, and scientific journals. The descriptors investigated were limited to coronavirus, COVID-19, COVID-19 pharmacology, COVID-19 epidemiology. The period established for our data collection were publications from January to May 2020. This research resulted in 57 files, including 36 articles. The subsequent procedure was an analytical reading in order to organize the information on the sources, so it was possible to collect the data for the research. The selection criteria for articles included those that referred to the same topic of this research: COVID-19 pharmacological treatment. The articles collected for the research are published on BVS, Cochrane, SciELO, PubMed and Science Direct databases and official the Ministry of Health and Brazilian universities websites.

Results and Discussion

This study analyses and discusses some articles that address the previously mentioned theme. Some relevant studies about the topic are shown in table 1 and explored later.

Journal	Authors	Title	Summary	Drug Classification
<i>Clinical Infectious Diseases</i>	Yao., et al. 2020	<i>In vitro</i> Antiviral Activity and Projection of Optimized Dosing Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)	The immunomodulatory effect of hydroxychloroquine may also be useful in controlling the cytokine storm that occurs at a late stage in critical condition patients infected with SARS-CoV-2.	Antimalarial
<i>Journal of Critical Care.</i>	Cortegiani., et al. 2020	A systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19	The use of chloroquine in trial records shows that 23 clinical trials are underway in China. Chloroquine appears to be effective in limiting the replication of SARS-CoV-2 <i>in vitro</i> .	Antimalarial
<i>International Journal of Antimicrobial Agents</i>	Gautret., et al. 2020	Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial	Despite the small sample size, hydroxychloroquine is significantly associated with the reduction or disappearance of viral load in patients with COVID-19. Its effect is reinforced by azithromycin.	Antimalarial and antibiotic
<i>Antiviral Research</i>	Choy., et al. 2020	Remdesivir, lopinavir, emetine e homoharringtonina inibem a replicação de SARS-CoV-2 <i>in vitro</i>	Report on the antiviral effect of remdesivir, lopinavir, emetine and homoharringtonine against SARS-CoV-2. Synergy was observed between remdesivir and emetin in reaching a 64.9% inhibition of viral yield.	Antiviral
<i>Science Direct</i>	Fang Liu., et al. 2020	Patients of COVID-19 may benefit from sustained lopinavir-combined regimen and the increase of eosinophil may predict the outcome of COVID-19 progression	The increase in eosinophils may be an indicator of the recovery from COVID-19. COVID-19 patients may benefit from prolonged use of lopinavir.	Antiviral
<i>The Lancet</i>	Norri., et al. 2020	Remdesivir for COVID-19: challenges of underpowered studies	There is no significant effect with intravenous remdesivir in severe COVID-19 patients that confirms the benefit of at least the minimally important clinical difference.	Antiviral
<i>Pharmaceuticals</i>	Martin., et al. 2020	Emetine, Ipecac, Ipecac Alkaloids and Analogues as Potential Antiviral Agents for Coronaviruses	Possible efficacy of emetine as a coronavirus inhibitor based on its action on MERS-CoV and SARS-CoV.	Antiviral
<i>National Center for Biotechnology Information</i>	Youseke., et al. 2020	Favipiravir (T-705), a broad spectrum inhibitor of viral RNA polymerase	Favipiravir (T-705; 6-fluoro-3-hydroxy-2-pyrazinecarboxamide) is an antiviral agent that selectively and potently inhibits RNA-dependent RNA polymerase (RdRp) from RNA viruses.	Antiviral

<i>Life Science</i>	Elfiky, et al. 2020	Anti-HCV, nucleotide inhibitors, repurposing against COVID-19	Ribavirin is a drug derived from nucleotides that competes with the physiological nucleotide for the active RdRp site, a central component of the replication/transcription mechanism of the coronavirus. Nucleotide inhibitors bind to Rdv COVID-19 and SARS-HCoV-Rd, showing strong evidence of inhibition of emerging viral RdRps.	Antiviral
<i>JAMA</i>	Wu., et al. 2020	Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China	A retrospective cohort study of 201 COVID-19 patients with pneumonia. Treatment with methylprednisolone decreased the risk of death among patients with SARS.	Glucocorticoid
<i>PNAS</i>	Duan., et al. 2020	Effectiveness of convalescent plasma therapy in severe COVID-19 patients	Convalescent plasma therapy, maximum supportive care and antiviral agents have been well-tolerated and could potentially improve clinical outcomes through neutralizing viremia in severe COVID-19 patients.	Convalescent Plasma
<i>Journal of Medical Virology</i>	Di Giambedetto., et al. 2020	Use of off-label Tocilizumab in patients of SARS-CoV-2	Tocilizumab (humanized antibody - Ig1 that binds to IL-6 receptors) efficacy in the treatment of 3 COVID-19 patients: relief of respiratory symptoms, resolution of fever, and reduction in CRP were the first effects after the administration of tocilizumab, without adverse events.	Monoclonal Antibody
<i>BioRxiv</i>	Chunyan Wang., et al. 2020	A human monoclonal antibody blocking SARS-CoV-2 infection	The emergence of the new human coronavirus SARS-CoV-2 in Wuhan, China, caused a worldwide epidemic of respiratory disease (COVID-19). Currently, there is a lack of vaccines and therapies aimed at treating this disease. A human monoclonal antibody that neutralizes SARS-CoV-2 (and SARS-CoV) has been reported. This cross-neutralizing antibody targets a community epitope on these viruses and offers potentials for the prevention and treatment of COVID-19.	Monoclonal Antibody
<i>Antiviral Research</i>	Caly, et al. 2020	The FDA-approved Drug Ivermectin inhibits the replication of SARS-CoV-2 <i>in vitro</i>	Ivermectin has broad-spectrum antiviral activity and is a SARS-CoV-2 inhibitor. In the study with addition to Vero-hSLAM cells 2 hours after infection with SARS-CoV-2 capable of reducing 5000 times in viral RNA after 48h.	Antiparasitic
<i>Wiley Online Library</i>	Tang., et al. 2020	Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy	Heparin in patients with severe symptoms of the disease has been recommended by consensus among some experts to decrease the risk of disseminated intravascular coagulation.	Anticoagulant

Table 1: Articles listed by bibliographic reference, a summary of the study, and studied drug classification.

There is no specific treatment or vaccine for patients with COVID-19 yet [9]. However, supportive measures must be adopted. It is a treatment for symptomatic patients in which oxygen therapy has been the main therapeutic intervention for severely infected patients. Mechanical ventilation for hypoxemic respiratory failure to oxygen therapy may be necessary. Likewise, hemodynamic support is essential in the case of septic shock [14].

The doctor may request a chest x-ray, complete blood count, and laboratory tests for confirmed or suspected COVID-19 patients who do not need to be hospitalized, and the health service opts for home care. It will depend on the patients' clinical condition. These patients must have appropriate orientation for controlling infections, preventing transmissions, and reading signs of possible complications. A quick, easy channel must be provided for communication in case of any doubt or report. Signs of worsening should lead the patient to immediate hospitalization [9].

Pharmacologic treatment strategies for covid-19

Among the therapeutic strategies here presented, there are some antivirals (remdesivir, lopinavir/ritonavir), antimalarials (chloroquine and hydroxychloroquine), antiparasitic (ivermectin and nitazoxanide) and iL-6 inhibitors (tocilizumab). However, there is still no scientific evidence for their effectiveness.

Systemic glucocorticoids do not seem to be the recommended treatment for viral pneumonia or acute respiratory distress syndrome. Despite some recommendations, nonselective or inaccurate antibiotic administration must be avoided [14].

The Ministry of Health published the informative note 5/2020-DAF/SCTIE/MS on March 27, 2020 which allows and suggests using chloroquine or hydroxychloroquine as adjunct therapy for treating severe COVID-19 cases [9].

Antimalarials

Chloroquine and hydroxychloroquine

Chloroquine is traditionally used to prevent and treat malaria, rheumatoid arthritis, and some other autoimmune diseases. The use of chloroquine and its derivatives (such as Hydroxychloroquine and chloroquine diphosphate) have been effective in fighting the virus replication. Chloroquine has direct antiviral effects and inhibits pH-dependent viral replication. Additionally, chloroquine has immunomodulatory effects, suppressing the production and release of tumor necrosis factor α and IL-6. These effects mediate the inflammatory several viral diseases complications [20].

Some possible mechanisms were proposed in order to understand its action on the virus. Currently, several research centers performing clinical trials have published articles about such mechanisms on prestigious scientific journals. Three of them have greater acceptance in the scientific and academic field [20].

The first mechanism is the ECA2 receptor conformational change. The virus targets this receptor when it enters the cells. The drug diffuses passively across the cell membrane and lysosomes, where it is protonated and cannot leave. Thus, it changes the glycosylation mechanisms, modifying the binding site and avoiding from linking to the virus protein S [20]. The second mechanism is the ability to increase endosomal pH, decisive for the virus-cell fusion. The alkalization (pH > 7,0) inside the endosome restricts the enveloped virus from bursting, therefore not detaching the viral RNA from the cytoplasm. It prevents the virus replication, reduces the viral charge, and blocks the ACE2 glycosylation [20]. The third mechanism refers to the inhibition and reduction of proinflammatory cytokines such as IL-1, IL-1 β , IL-6 and tumor necrosis factor α (TNF- α) [20].

The clinical trials on the effects of chloroquine and hydroxychloroquine for severe acute respiratory syndrome management have been showing positive results, such as improvement of pulmonary inflammation condition and other symptoms [20]. This result comes from

the analysis of proinflammatory cytokine levels, which have been reduced due to the use of chloroquine and hydroxychloroquine. The third mechanism has greater acceptance among the researchers in the field [20].

Chloroquine and hydroxychloroquine have a strict safety profile: a 30 mg/kg dose is potentially lethal. Their adverse effect is acute toxicity, which may include cardiovascular effects such as hypertension, vasodilation, arrhythmia, QT prolongation, myocardial infarction and cardiac arrest. Neurological side effects such as seizures, mental confusion and coma are also possible. Not to mention the slightly potential hemolysis. Its extended use can cause retinopathy leading to blindness [17].

Antibiotics

Azithromycin

Azithromycin is used as an adjunct therapy for treating bacterial infections. It is also used for treating respiratory viral infections and other pathologies, such as bronchitis, cystic fibrosis, Chronic obstructive pulmonary disease (COPD) and ARDS due to its possible immunomodulatory and anti-inflammatory effects. Azithromycin is a macrolide antibiotic that acts by permanently binding itself to the 50S ribosomal subunit to inhibit translocation steps of protein synthesis. This drug is often used for treating *H. influenzae* and *Moraxella catarrhalis* respiratory infections; *Chlamydia trachomatis* urethritis; and when associated to other drugs, it is used to handle *Mycobacterium avium*, cause of pulmonary systemic diseases in immunocompromised patients. Its adverse effects include gastritis, jaundice, cholestasis, and ototoxicity [21].

Chloroquine-azithromycin combination

A group of Chinese researchers conducted a laboratory study in which they added chloroquine to cells infected by the virus and concluded that this drug is highly efficient for reducing viral replication. This happens especially because of its high tissue perfusion. For this reason, the study recommends using 500 mg of chloroquine twice a day from 5 to 10 days, according to the condition of the COVID-19 patient [21].

A survey released on March 17, 2020, by Gautret [21] shows that this study suggests that hydroxychloroquine and azithromycin have a synergistic effect. That is, hydroxychloroquine effects are reinforced by azithromycin. Henceforth, this combination can act as an antiviral therapy to treat COVID-19 and prevent bacterial superinfection [21]. Azithromycin and hydroxychloroquine are both associated to QT prolongation, and the association of these two drugs can increase this adverse effect, and for that reason, patients must be monitored [21].

Many questions raised concerns on the efficiency and risks of using chloroquine and hydroxychloroquine, despite the recommendation for using these drugs for treating COVID-19 patients in different countries.

A recent article published in The *Lancet* [22] journal pointed out that the use of chloroquine and hydroxychloroquine did not have the desired effect in spite of previous publications. This study stated that it is not possible to confirm that treatment with chloroquine and hydroxychloroquine is fruitful, associated, or not, to macrolides based on COVID-19 clinical studies. Previous investigations came from small studies or inconclusive randomized clinical trials. Considering the urgency to check the evidences regarding the use of chloroquine and hydroxychloroquine to treat COVID-19 patients, this study includes a large number of patients from different geographic areas and understands that there is a lack of substantial evidence about the benefits of these treatments on patients. Considerations suggest the lack of therapeutic benefits but also the potential risks of using hydroxychloroquine or chloroquine associations with to macrolides or not. "Each of these drug regimens was associated with decreased in-hospital survival and an increased frequency of ventricular arrhythmias when used for treatment of COVID-19" [22].

Antivirals

In order to understand the viral replication process, we need to understand the antiviral drug action mechanism. Viral replication consists of several stages: (1) viral attachment to the host cell surface receptors; (2) viral penetration through the host cell membrane; (3) uncoating of viral nucleic acid; (4) early protein synthesis, such as nucleic acid polymerases; (5) new synthesis of RNA or DNA; (6) integration into the nuclear genome; (7) late protein synthesis and processing; (8) packaging and assembly of viral particles and (9) release from the cell. The antiviral agents can potentially act against any of those steps [23].

Lopinavir-ritonavir

The antiviral combination Lopinavir-Ritonavir is usually used for HIV treatment but has also brought good results against respiratory diseases. Lopinavir is an antiretroviral protease inhibitor combined with Ritonavir to increase its plasma half-life by inhibiting cytochrome P450. Its primary mechanism is the inhibition of the protease enzyme, aiming to control viral multiplication inside the host cells and improve the immune system action.

The protease blockage forms an immature and non-infectious virus, incapable of penetrating another cell and replicating itself. This would prevent COVID-19 patients from having a high viral load, which is a poor-prognosis and slow recovery factor. The reduction of viral replication is also linked to the disappearance of symptoms [24]. We must emphasize, however, that the use of this drug is directly linked to the appearance of adverse gastrointestinal effects in patients, such as nausea, vomiting, diarrhea, stomachache, loss of appetite, anorexia, anemia, acute gastritis, and lower gastrointestinal bleeding [25]. Lymphopenia is another common effect.

This drug is contraindicated for patients with known hypersensitivity to lopinavir/ritonavir. It must not be administered concomitantly with other drugs that have the same elimination mechanism, since high drug concentration in blood is associated with severe adverse reactions [24].

Ribavirin

Ribavirin is a synthetic analog of guanosine and an antiviral compound used to treat various viral infections, such as respiratory syncytial virus, hepatitis C virus, herpes virus and some hemorrhagic viral fevers. Ribavirin is an RNA synthesis inhibitor by viral RNA-dependent RNA polymerase (RdRp), competing with the physiological nucleotide for the RdRp active site - a crucial enzyme in the life cycle of viruses, including coronaviruses. RdRp targets different RNA viruses, including hepatitis C virus, Zika virus, and coronaviruses. Ribavirin can bind itself to RdR COVID-19 and SARS HCoV RdR with good binding energy [26].

Ribavirin is not limited to polymerases interference in its antiviral activity, i.e. the structure of this drug also interferes in the RNA capping, which depends on natural guanosine to prevent RNA degradation. In order to destabilize even more the viral RNA, Ribavirin inhibits the natural generation of guanosine by directly hindering the inosine monophosphate dehydrogenase. This is crucial to produce the guanine precursor in guanosine [27].

This drug is used as a virostatic to treat hepatitis, inhibiting the replication of the hepatitis C virus and allowing the natural development of an immune response. It is indicated for all forms of viral hepatitis and is used in combination with alpha-interferon to treat chronic hepatitis C [28].

The drug is promptly transported into cells and then converted by cellular enzymes to 5-mono-, di- and triphosphate derivatives. They are responsible for inhibiting certain viral enzymes involved in the synthesis of viral nucleic acid.

Studies using ribavirin plus lopinavir-ritonavir in patients with SARS have reduced ARDS and mortality. There was also a significant decrease in ARDS and mortality in patients with SARS-CoV who received corticosteroids with ribavirin, lopinavir-ritonavir [29].

The possible adverse effects of this medication include the following: anemia, anorexia, depression, insomnia, headache, dizziness, decreased concentration, breathing difficulty, cough, diarrhea, nausea, abdominal pain, hair loss, dermatitis, itching, dry skin, muscle and joint pain, fever, chills, pain, tiredness and irritability.

This drug or any of its excipients are contraindicated for Ribavirin -hypersensitive patients, pregnant and lactating women, individuals with severe heart disease backgrounds, including uncontrolled heart disease in the previous six months, people with severe liver dysfunction or decompensated cirrhosis, hemoglobinopathies, and patients with severe renal failure [28].

Remdesivir

Remdesivir is a prodrug with promising antiviral activity. Analog to nucleotide, it disrupts viral replication affects viral RNA polymerase, preventing viral dissemination and reducing the production of viral RNA.

Originally evaluated in clinical trials to prevent the Ebola outbreak in 2014, remdesivir showed its capacity of inhibiting coronavirus replication, including SARS-CoV-2, through subsequent evaluation by numerous virology laboratories [30].

Remdesivir was originally developed by Gilead Sciences. Even though it did not pass the phase 3 clinical trial to treat Ebola, it showed a moderately promising improvement in the mortality rate of this deadly disease [31].

After adding remdesivir, the polymerase enzyme stops adding more RNA subunits, interrupting the genome replication. These mechanisms are linked to the ability that remdesivir must metabolize in an active form known as GS-441524, which is an adenosine nucleotide analog. GS-441524 interferes with the action of viral RdRp and prevents revision by viral exoribonuclease (ExoN), decreasing the production of viral RNA [32].

Intravenous administration of 10 mg/kg dose of remdesivir resulted in concomitant persistent levels of its active form in the blood (10 μ M) and conferred 100% protection against Ebola virus infection. Data showed that EC 90 value of remdesivir against SARS-CoV-2 in Vero E6 cells was 1,76 μ M. This outcome suggested that its working concentration will be likely achieved in non-human primate models. Preliminary data also showed that remdesivir efficiently inhibited a viral infection in a human cell line sensitive to 2019-nCov (human liver cancer Huh-7 cells) [33].

Remdesivir has been clinically tested against MERS-CoV and has shown significant effectiveness. For this reason, a phase 3 study of remdesivir is currently underway in China and the USA [31].

Favipiravir

Favipiravir (T-705; 6-fluoro-3-hydroxy-2-pyrazinecarboxamide) is an antiviral agent that inhibits RdRp of RNA viruses selectively and powerfully. Favipiravir was discovered by Toyama Chemical Co., Ltd during the chemical library triage for antiviral activity against the influenza virus. Favipiravir undergoes intracellular phosphoribosylation to be an active form: favipiravir-RTP (favipiravir-RTP (favipiravir ribofuranosil- 5'-triphosphate), which is recognized as a substrate by RdRp and inhibits the activity of RNA polymerase. Since the catalytic domain of RdRp is conserved among various types of RNA viruses, this mechanism of action supports a broader spectrum of its antiviral activities. Favipiravir is effective against a wide variety of influenza virus types and subtypes, including strains resistant to existing anti-influenza drugs. It is noteworthy that favipiravir shows antiviral activities against other types of RNA viruses that cause fatal hemorrhagic

fever, such as arenaviruses, bunyaviruses and filoviruses. These unique antiviral profiles will make favipiravir a potentially promising drug for categorically incurable RNA infections [34].

However, in order to reduce viral infection, favipiravir requires a high concentration of less effective nucleoside analogs.

Two trials, in Wuhan and Shenzhen, confirmed the effectiveness of the drug against the infection. Dr. Zhang Xinmin, director of the China National Center for the Development of Biotechnology, released the result under the Ministry of Science and Technology.

According to Zhang, the drug was recommended to medical treatment teams and should be included to diagnose and treat COVID-19 patients [35].

The drug is still a concern of safety since hyperuricemia, teratogenicity and QT prolongation are elements that have not yet been adequately studied. Favipiravir may be safe and tolerable in short-term use, but the scientists need more evidence to assess the long-term effects of treatment. Given the limitations of the evidence and unresolved safety concerns, its widespread use of favipiravir against the COVID-19 pandemic needs to be cautious [36].

Glucocorticoids

Glucocorticoids, such as methylprednisolone, are crucial agents in many disorder treatments, including inflammatory and hematological disorders. The synthetic presentations of these drugs show great anti-inflammatory and immunosuppressive activity, hence being the steroids of interest for COVID-19 treatment.

Glucocorticoids dramatically reduce inflammation symptoms, resulting in pronounced effects on the peripheral leukocytes distribution, function, and serum concentration. Additional effects include the suppression of inflammatory cytokines, chemokines and other mediators. The inflammation process is characterized by leukocyte extravasation and infiltration into the affected tissue regardless of the cause. These events happen due to a complex series of interactions of leukocyte adhesion molecules with molecules found in endothelial cells, which are inhibited by glucocorticoids. After the administration of a short-acting single dose of glucocorticoids, the concentration of neutrophils increases in the circulation while the number of lymphocytes (T and B cells), monocytes, eosinophils, and basophils reduces [23].

Glucocorticoids reduce the synthesis of prostaglandins, leukotrienes and the platelet-activating factor that results from the phospholipase A2 activation, thus influencing the inflammatory response. Lastly, glucocorticoids act in inflammatory cells by decreasing the expression of the cyclooxygenase-2 enzyme in its inducible form, therefore reducing the enzyme amount available for prostaglandin production.

The benefits of glucocorticoids vary considerably. The use of these drugs must be carefully weighed against their widespread effects in the body, such as acute pancreatitis, a rare but severe adverse effect of glucocorticoids in high doses [37].

According to Yuen, glucocorticoids have been widely used as experiments in the treatment of SARS. They are still the choice of some doctors to treat COVID-19 patients because they can stop the cytokine cascade and prevent pulmonary fibrosis. However, the investigation shows that its use should be restricted to patients whose SARS-CoV-2 has already been eliminated by the immune response. Otherwise, the replication of SARS-CoV-2 will increase, which will lead to an exacerbation of symptoms, along with the substantial spread of the virus throughout the body and increased risk for nosocomial transmission and secondary infection [38].

Immunoglobulins

Tocilizumab

Tocilizumab is a humanized monoclonal antibody that acts as an IL-6 receptor antagonist. This immunoglobulin has been registered for at least ten years under the trade name of RoActemra®. Studies have established its effectiveness in treating adult patients with rheumatoid arthritis [39].

After SARS-CoV-2 infection, the innate immune system, macrophages and other innate immune cells release many cytokines and chemokines, in particular, IL-6 [40].

IL-6 is described as a crucial component of the “cytokine storm” and plays a central role in acute inflammation. This immunoglobulin is a multifunctional cytokine that is important for human metabolism, autoimmune cell differentiation and the treatment of diseases.

In the early stage of infectious inflammation, IL-6 is produced by monocytes and macrophages and can promote the expansion and activation of the T cell population and the differentiation of B cells, regulate the acute phase response and affect the following hormonal properties: vascular dysfunction, lipid metabolism, insulin resistance, mitochondrial activity, neuroendocrine system, and neuropsychological behavior.

Tocilizumab specifically binds itself to soluble IL-6 receptors located on the membrane of inflammatory cells (inhibiting the binding of IL-6 to these receptors). Tocilizumab can potentially block classical and alternative signals from the complement system and consequently inhibit Cytokine Release Syndrome (SLC).

According to Di Giambenedetto [41], tocilizumab proved to be effective in treating critically ill patients with SLC, acting in the prevention or treatment of this syndrome observed in patients who progress to cardiovascular collapse, multiple organ dysfunction, and death.

Clinical studies suggest that there are minor and major cytokine storms in critically ill patients, and this condition is a significant cause of death. The treatment of the cytokine storm with tocilizumab that blocks the IL-6 signal transduction pathway has become an alternative to treat critically ill COVID-19 patients [40].

Recent investigations have shown a reasonable efficacy of tocilizumab in patients infected with COVID-19. In January 2020, a small clinical trial took place in China in which 21 COVID-19 positive patients were divided by their symptoms: severe (shortness of breath, respiratory rate greater than 30 BPM; oxygen saturation below 93% in rest; $\text{PaO}_2/\text{FiO}_2 \leq 300$ mmHg) or critical (respiratory failure requiring mechanical ventilation; shock; and ICU admission with failure of other organs). After a few days of treatment, the results were interruption of fever in 100% of the patients; 75% of the patients had their need for oxygen support reduced and 90.5% of the patients had an evolution in relation to lung injuries on CT scan. Laboratory tests showed that the proportion of peripheral blood lymphocytes and C-reactive protein returned to normal.

Despite these promising results from the use of tocilizumab in COVID-19 patients, Zhang (2020) [40] states that from a pharmacoeconomic point of view, this drug should only be used in critically ill patients and with significantly elevated IL-6.

Tocilizumab is currently used in the direct treatment of rheumatoid arthritis, systemic juvenile idiopathic arthritis, Castleman’s disease, Crohn’s disease, etc. This drug is also used to reduce the side effects of other treatments. It is an FDA approved drug to reduce the SLC caused by the CAR-T immunotherapy for relapsed or refractory B-cell acute lymphoblastic leukemia.

A study of 21 severe COVID-19 patients ranging from 25 to 88 years (mean age 56.8 ± 16.5 years) demonstrated that there were no complications associated with tocilizumab use and no history of worsening health status or death. The risk of secondary infection is also not very high [40].

We are still not aware if tocilizumab increases the risk of cardiovascular disease. A study with 3,080 rheumatoid arthritis patients over 50 years old and with more than one risk factor for cardiovascular disease used tocilizumab and etanercept. The study concluded that etanercept presented a higher cardiovascular risk than the latter [42].

Nevertheless, studies comparing the action of tocilizumab with tumor necrosis factor inhibitors (TNFi) pointed out that there was no significant difference in the risk of cardiovascular events associated with the use of this medication. However, considering that all these studies presented 95% non-significant CI (containing 1), it is possible to determine that so far, there is no evidence that the use of tocilizumab increases cardiovascular events [40,41].

Sarilumab

Sarilumab is a fully human-sourced monoclonal antibody that inhibits the interleukin IL-6 pathway by binding and blocking the IL-6 receptor and is suggested to treat severe COVID-19 patients with a confirmed viral load. However, the potential benefit of sarilumab in COVID-19 patients is the suppression of the cytokine storm, which may be a more beneficial and lasting contributor to lung damage than the viral infection itself [43].

Sarilumab is used to treat moderate to severe rheumatoid arthritis. In these patients, the medication blocks the IL-6-mediated signaling that contributes to the inflammation of rheumatoid arthritis, which is the same mechanism of action as that observed in studies with COVID-19 patients [43].

One of the COVID-19 characteristics is the local and systemic increase in neutrophils that act to eliminate viral infections, but also cause collateral damage to the pulmonary epithelium [44]. A neutrophil count combined with IL-6 inhibition can help mitigate the coronavirus-induced effects.

Sarilumab can potentially reduce the severity of COVID-19 pulmonary complications since it inhibits soluble forms linked to IL-6, suppressing proinflammatory signaling through pulmonary epithelial and immune cells [45]. In a study conducted with 21 COVID-19 patients, they presented a rapid decrease in fever and 75% of them reduced the need for supplemental oxygen a few days after receiving another IL-6 receptor antibody (tocilizumab) [43].

The adverse effects and contraindications observed in COVID-19 patients were skin redness; liver problems; and throat, nose and bladder infections. There is still no consensus on the use of this medication to treat COVID-19. Larger sampling experiments with this medication are necessary to guarantee greater precision in the analysis of therapeutic results [46].

Convalescent plasma

Chinese authorities have reported success in treating COVID-19 patients with plasma transfusion from recovered COVID-19 patients. These patients have developed antibodies in their plasma. Plasma transfusion and blood purification therapies have already been effectively used in the treatment of diphtheria, measles, swine flu, SARS, and MERS [47,48]. Treatment of the systemic response might be the most sought aspect in care, while there is still no definitive treatment for SARS-CoV-2.

Convalescent plasma therapy removes inflammatory cytokines, stabilizes endothelial membranes and redefines the hypercoagulable state, offering exclusive benefits in multiple levels [47].

In one of the studies, clinical symptoms improved rapidly within three days of therapy. The radiological examination showed varying degrees and absorption of lung lesions in seven days. Patients' pulmonary function improved, and those with high ventilatory dependence started weaning from mechanical ventilation. There was also an increase in the levels of neutralizing antibodies and the disappearance of

the detectable SARS-CoV-2 virus RNA [48].

No serious adverse effects were described in the study, and red facial rashes were the only collateral effect. Despite that, the following potential risks of this therapy must be considered: allergies, transfusion-associated circulatory overload and acute lung injury, antibody-dependent improvement, and greater tendencies for coagulation [49].

Lastly, convalescent plasma therapy shows a potential therapeutic effect and a low-risk treatment for severe COVID-19 patients. However, more randomized clinical trials are necessary to attest its efficiency, benefits and safety.

Antiparasitic

Ivermectin

Ivermectin acts against a wide range of helminths and arthropods. It is indicated to treat filariasis, ascariasis, onchocerciasis, scabies, and pediculosis. Studies carried out on *Caenorhabditis elegans* (an extensively studied soil-transmitted helminth in eukaryotic biology used as a model for simple organisms) suggest that the mechanism of action of Ivermectin involves potentiation and/or direct activation of chloride channels regulated by glutamate in nematode plasma membranes. In the helminth, the action results in hyperpolarization of neuromuscular cells and paralysis [50]. Ivermectin is believed to affect the inhibitory transmission of gamma-aminobutyric acid (GABA), potentiating its release from presynaptic terminations, directly activating its receptors and potentiating their binding to the receptor. These effects increase GABA-mediated signal transmission in peripheral nerves, resulting in hyperpolarization.

As ivermectin does not cross the blood-brain barrier, it tends to be well tolerated, even though human GABA receptors are found mainly in the CNS. Ivermectin can cause headaches, ataxia, and coma when the blood-brain barrier becomes permeable, as it happens in patients with meningitis.

Studies have shown that ivermectin has antiviral activity against a wide range of viruses *in vitro* and *in vivo* [51-54].

These studies suggested that nuclear transport inhibitory activity of ivermectin can be effective against SARS-CoV-2 [55]. For the *in vitro* study, ivermectin was added to SARS-CoV-2 infected cells. The cells and the supernatant material were collected at 24, 48, and 72 hours and viral RNA replication was analyzed. Viral clearance was 93% in 24 hours and 99.98% in 48 hours [55].

The results demonstrate that ivermectin has antiviral action in an *in vitro* SARS-CoV-2 clinical isolate, with a single dose capable of inhibiting viral replication in 24 to 48 hours [55].

Emetine

Emetine is an anti-protozoal drug with antiviral activity. It is used as an amebicide against *Entamoeba histolytica* and as an antileukemic to fight tumors. This drug might be effective against COVID-19 since it presented the lowest EC_{50} levels in antiviral therapies for other coronaviruses, like SARS and MERS. The concentration of EC_{50} emetine is achievable in blood, but it can be almost 300 times higher in the lungs. When comparing relative EC_{50} of emetine in coronaviruses to *Entamoeba histolytica*, emetine can be much more effective as an anti-coronavirus agent than against amebiasis [56].

Emetine-based therapy is also used in HIV infections. In COVID-19, emetine acts as a protein synthesis inhibitor, blocking ribosomes action in the RNA messenger irreversibly in the S phase DNA replication and the reverse transcriptase.

Despite its benefits, patients may go through situations of cardiotoxicity, hypotension, nausea, and vomiting [56].

Anticoagulant-Heparin

Heparin is a natural blood anticoagulant consensually recommended by some specialists to reduce lung damage in severe COVID-19 patients. It is a way to reduce the risk of disseminated intravascular coagulation that can cause venous thromboembolism [57].

Heparin can be used in high or low-dose therapeutic regimens. It is indicated in low doses to prevent DVT (deep vein thrombosis) in patients at risk of thrombosis, for cases such as postoperative care of abdominal and orthopedic surgeries; patients with neoplasms or sepsis; patients at a prolonged rest and others. High doses of heparin are used therapeutically to prevent a second thromboembolic episode in DVT, patients with DVT/PE (pulmonary embolism), thromboses or arterial embolisms or even in patients undergoing procedures with a thrombotic risk, such as arterial catheterizations, angioplasties, hemodialysis and cardiovascular surgery with cardiopulmonary bypass [58].

Heparin is a heterogeneous mixture of a natural polysaccharide extracted from animal viscera (mainly bovine and porcine) and has a molecular weight ranging from 3,000 to 30,000 daltons. Its main anticoagulant effect comes from the interaction with antithrombin III. Through a change in the conformation of antithrombin III, there is an acceleration in its ability to inactivate the coagulation enzymes: thrombin and factors Xa and IXa [58].

is the most frequent complication of heparin use. The occurrence of hemorrhagic phenomena with clinical significance varies from 3 to 5%. It does not appear to be related to levels of a PTT (partially activated thromboplastin time), but to individual risk factors. The main form of preventing hemorrhagic phenomena observed was therapy interruption.

Thrombocytopenia is the most frequent non-hemorrhagic complication due to heparin use. The mildest and most common event related to heparin and thrombocytopenia is related to platelet aggregation caused by some products of conventional heparin. In such cases, patients rarely need to stop their treatment. Thrombotic and/or hemorrhagic phenomena may also be associated with this condition. Low molecular weight heparin is less frequently related to this type of complication [58].

The drug has other rarely occurring adverse effects, such as hypersensitivity, skin necrosis, and osteoporosis in long-term use [58].

Conclusion

There are ongoing therapeutic possibilities that still needs more studies to prove their efficiency and effectiveness in large populations with the onset of the novel coronavirus disease. The achievement of a specific pharmacological strategy for the global demand is still a challenge.

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Conflict of Interest

The authors declare no competing interests.

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