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RESEARCH ARTICLE

ANALYSIS OF SCIENTIFIC EVIDENCE FOR PHARMACOLOGICAL MANAGEMENT OF COVID-19: THERAPEUTIC APPROACHES DESCRIPTION AND DISCUSSION

Lana Francischetto[1], Lara Rafaela Rodrigues de Oliveira[1], Isis Micaelly de Oliveira Morais[1], Melissa Meireles Coelho de Oliveira[1], Alana Mesquita Brezinski[1], Nicholas Alfred Joseph Mayers[2] and Marli do Carmo Cupertino[1,3*]

[1]Escola de Medicina, Faculdade Dinâmica do Vale do Piranga. Ponte Nova. Minas Gerais, Brasil
[2]Departamento de Medicina Veterinária. Universidade Federal de Viçosa. Viçosa. Minas Gerais, Brasil
[3] Departamento de Biologia Geral. Universidade Federal de Viçosa. Viçosa. Minas Gerais, Brasil

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ABSTRACT

The current COVID-19 pandemic is unprecedented. In the last four months, since the onset of the disease on December 31, 2019, more than 200,000 deaths and 3 million cases have been confirmed in over 200 countries worldwide. There are still no recognized specific pharmacological therapies and/or vaccines to regulate the virus. So, we aim to analyze and compile data on the main scientific evidence of treatment for COVID-19, and critical discussion of the use of drugs still in the experimental phase A search was performed using the descriptor "COVID-19 treatment", in the PubMed database, searching for original articles published between January & April 2020, which presented reports/case series, *in vitro*, *in vivo* or *in silico* studies, and clinical trials. A total of 234 articles were retrieved, precluding reviews, duplicate articles and other exclusion factors, 30 articles remained. According to the studies, no specific pharmacological and vaccine therapies have been developed to appropriately counteract SARS-CoV-2, with the majority yielding results from *in silico*, *in vitro* or *in vivo* studies, with a small range of case reports or case series. Amongst the hundreds of drugs that are being tested, pharmacological research on the Azithromycin, Ivermectin, Methylprednisolone, Anticoagulants, Remdesivir, Chloroquine/Hydroxychloroquine and the combination Ribavirin, Lopinavir/Ritonavir & Interferon beta-1b were assayed. Although there are some auspicious pharmacological therapies and, in some cases, an emergency release of such by regulatory agencies, there is still a desideratum for extensive scientific testing with randomized clinical trials to definitively prove the effectiveness of these drugs in combating SARS-CoV-2 in the human body.

INTRODUCTION

The Coronavirus Disease-2019 (COVID-19) is a respiratory tract infection caused by a newly discovered coronavirus called SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2), whose genetic sequencing suggests that it is a coronavirus of the genus Betacoronavirus (β-CoV) (Team NCPERE, 2020). Although most people affected by COVID-19 are asymptomatic or manifest only mild symptomatology, approximately 14% develop acute conditions requiring hospitalization and oxygen support and about 5% require admission to intensive care units (ICU). Under exceptional circumstances, the disease triggers SARS, which may be associated with sepsis/septic shock, failure of several organs, including acute kidney injury and cardiac injury; accentuating those more susceptible being senior citizens, diabetics and/or individuals with cardiac & respiratory comorbidities (Xiaobo *et al*., 2020; Cupertino, *et al.* 2020). In the last four months, since the onset of the disease on December 31, 2019, more than 200,000 deaths and 3 million cases have been confirmed in over 200 countries worldwide (WHO, 2020). The current COVID-19 pandemic is unprecedented, nevertheless, the global response to the disease emanates from the cumulative knowledge acquired from the other disease outbreaks in recent decades such as Ebola, SARS-CoV and the Middle East respiratory syndrome (MERS-CoV), in addition to data from countries that were severely afflicted by SARS-CoV-2, including China. As a measure to confront the disease, the World Health Organization (WHO) declared the pandemic to be a Public Health Emergency of International Interest, instigating a scientific race to search for methods that facilitate diagnoses, vaccines and therapies for this new coronavirus, through the coordination between scientists and global health professionals. Endorsed by the WHO, these professionals are establishing an unprecedented program to assess the available information on the new virus. They deliberate on solutions for

Corresponding author: **Marli do Carmo Cupertino,**
1Escola de Medicina, Faculdade Dinâmica do Vale do Piranga. Ponte Nova. Minas Gerais, Brasil.
2Departamento de Biologia Geral. Universidade Federal de Viçosa. Viçosa. Minas Gerais, Brasil.

critical unresolved research questions, to facilitate and sustain priority investigations (vaccination; pharmaceutical treatments) while strengthening information-sharing channels between countries and prepare for potential future outbreaks of the disease (WHO, 2020). There are still no recognized specific pharmacological therapies and/or vaccines to regulate SARS-Cov-2 and its dissemination, neither optimized support for critically ill patients (WHO, 2020). However, as with the majority of viral diseases, treatment is based on clinical support measures, and the administration of drugs to orient symptomatic control (Feijoo *et al*., 2020). At present, several drugs have been widely studied, demonstrating promising results in some of the experimental studies, mainly in vitro (Caly *et al*., 2020 & Cortegiani *et al*., 2020). This study seeks to elucidate the main scientific proof on the pharmacological therapies utilized to manipulate COVID-19 so far and substantiate the efficacy of each one of them.

METHODOLOGY

To execute this study, the PubMed database was searched for original articles, published between January & April 2020. The search strategy was based on three components: (i) pharmacological therapy for COVID-19, and (ii) clinical trials, case reports and case series, *in silico, in vitro and in vivo* studies. The search filters were developed in concordance with the thesaurus platform - MeSH terms (Medical Subject Headings). The following descriptor was utilized "covid 19 treatment". Neither language nor chronologic restrictions were applied when searching for the articles. The initial screening was carried out considering the title and abstract of all articles found. Contrasting the authors, title, year and journal of publication eliminated duplicated studies. After the first selection, all potentially relevant studies were downloaded in their entirety to have their eligibility evaluated.

Exclusion and Inclusion Criteria: The exclusion of studies relied solely on the following well-defined criteria: (i) studies concerning COVID-19 not associated with pharmacological treatments, (ii) drug studies that did not include data on COVID-19, (iii) studies from secondary or incomplete texts (i.e. editorials, remarks/comments, letters to the editor, dissertations, theses, book chapters, publications in annals and articles unavailable in full-text). The reference lists of relevant articles were selected as potentially admissible documents. The inclusion criteria was premised on original articles that presented study results on the use of distinct drugs in the treatment of COVID-19, whether it be a description of clinical trials, case reports & series, and studies *in silico, in vitro or in vivo.*

Data extraction: Qualitative data was collated from all of the included articles. The extraction of the data was classified as follows: (i) Therapeutic indications; (ii) Chemical composition; and (iii) Effects (therapeutic and general adverse effects). Institutional documents, such as manuals and guides, produced by the Ministry of Health, the National Health Surveillance Agency and the WHO, were employed to scrutinize the data.

RESULTS AND DISCUSSION

There were 30 original articles chosen to compose the present study.

In the scientific literature, in general, most of the published studies show research results in silico, *in vitro* or *in vivo*, with a small range of case reports or case series. There are no reports of results from randomized controlled trials. Faced with a scenario of limited therapeutic approaches, scientists have sought pharmacological redirection in which, various drugs administered for other etiologic agents are examined with adjusted dosages, and/or new substances are investigated, with unknown medicinal aptitude against the disease. Supportive therapy is necessary in severe cases of the disease, mainly due to frank respiratory failure and hypotension (Ministéro da Saúde, 2020). In these situations, the patients' admission to the ICU is mandatory for their appropriate monitoring and treatment. In the cases of individuals with hypotension, the administration of vasoactive drugs (Norepinephrine; Epinephrine; Dobutamine) and volume expansion can be performed to maintain good tissue perfusion (Azevedo *et al*., 2018; Ministério da Saúde, 2020). Additionally, oxygen therapy should be offered to those with a significant drop in saturation, and Orotracheal Intubation (IOT) may be necessary in acute situations. When opting for IOT, a mechanical ventilator must be installed under distinct parameters for the patient (Azevedo *et al*., 2018). In some circumstances, mechanical ventilation is insufficient to guarantee the ideal oxygenation of the patient, so as a counterbalance, the patient is positioned and left in prone position, to relieve the weight retained on the lungs. This maneuver favors alveolar hemostasis, consequently, improving hypoxemia (Dalmedico *et al*., 2017; Paiva & Beppu, 2005).

The following are some candidate drugs being administered and/or researched in the pharmacological therapy of COVID-19:

Azithromycin: Azithromycin is an antimicrobial in the macrolide class, utilized to treat several bacterial infections, especially those prone to the respiratory tract; in these cases, it can act prophylactically contra eventual co-infections by germs *(e.g. Streptococcus pneumoniae & Haemophilus influenza)* (Gautret *et al*., 2020). The drug has also presented *in vitro* activity against other pathogens, such as the Zika and Ebola viruses (Tavares, 2014). Similarly, its therapeutic application against COVID-19 has indicated its potential benefit. Its mechanism of action is through irreversible binding to the 50S subunit of the ribosomes of bacteria, inhibiting steps in protein biosynthesis. However, the exact action of this drug in relation to SARS-CoV-2 is still unknown. It been concluded that there possibly exists synergy between Azithromycin and Hydroxychloroquine when used simultaneously, given that the latter has its aptitude enhanced (Gautret *et al*., 2020). Some adverse reactions from the use of Azithromycin include gastric discomfort, increased gastrointestinal peristalsis, diarrhea, ototoxicity and cholestasis (Tavares, 2014).

Ivermectin: Ivermectin is a broad spectrum antiparasitic. In recent years, it has served as counter against several viruses, including HIV-1, West Nile virus (WNV), Venezuelan equine encephalitis virus (VEE) and influenza. Highlights that the drug works by inhibiting the integration of fundamental proteins for the *in vitro* replication of different viruses (Caly *et al*., 2020). Approved by the Food and Drug Administration (FDA), Ivermectin has merited further examination, after studies show that it is an inhibitor of the viral replication *in vitro* of SARS-CoV-2.

In Australia, tests cells were infected and isolated with the virus and then administered with the antiparasitic and after 24 hours, there was a significant decrease of viral RNA in the supernatant (93%) and viral RNA (98%). During the following 48 hours, there was an apparent increase in the reduction of the viral RNA (~5000 times), representing an effective loss of the viral material. It can be deduced that the drug binds and destabilizes the importin-α/β1 (IMPa/b1) heterodimer preventing its coupling with the viral protein and impeding the entry of the nucleus of the cell, which results in effective loss of virtually all of the viral genetic material (Caly *et al*., 2020). Furthermore, there was also an observed synergistic action between Ivermectin and Hydroxychloroquine, both for treatment and chemoprophylaxis (Patrì & Fabbrocini, 2020). The study concluded that both drugs have inhibitory activity against SARS-CoV-2 and, when administered simultaneously, evince a potentiated effect. Adverse reactions from the use of Ivermectin are generally mild. A few gastrointestinal symptoms stand out, such as the occurrence of abdominal pain, nausea, vomiting, diarrhea and/or even constipation. Additionally, other symptoms such as drowsiness, dizziness and transient tremors have been reported (Basano *et al*., 2011).

Remdesivir: Remdesivir is an antiviral medication, analogous to adenosine, of recognized significance when considering its therapeutic action against several RNA-viruses, including Ebola, SARS-CoV and MERS-CoV. The drug acts by binding to viral RNA chais and hindering premature replication (Wang et., al 2020). In a study, 61 COVID-19 patients were treated with the drug and their responses evaluated during hospitalization (Grein *et al*., 2020). Of that total, remaining 53, there were documented improvements in 36 patients (68%) after 18 days of observation. During this period, 25 patients were discharged (47%) from the hospital and 7 patients died (13%). The rest of the patients remained hospitalized. In view of the evident antiviral activity and probable therapeutic proficiency, this medication has been regarded as a promising treatment alternative against COVID-19 worldwide. Moreover, there are several positive reports from across the globe where Remdesivir was implemented for remedial therapy in diagnosed patients. Based on research results, in May 2020, the FDA approved the emergency use of the drug to treat hospitalized COVID-19 patients (Al-tawfiq *et al*., 2020).

Methylprednisolone: Methylprednisolone is a synthetic corticosteroid with immunosuppressive, anti-allergic and anti-inflammatory activity. It is the option of choice for hypertensive patients because it is five times more potent than Hydrocortisone, but with less sodium and water retention. A study conducted in China, collected data from 225 hospitalized patients, of which 37 were diagnosed with severe COVID-19 disease. When administered with this medication a 0.89% mortality rate was discerned (Li, *et al*. 2020). In Brazil, according to the Ministry of Health, there is one documented case with promising results from Methylprednisolone administration. A healthy 60-year-old man who was hospitalized due to a serious altered state of consciousness, progressive irritability, confusion and asthenia, beyond that, fever, cough and cognitive fluctuations. At the hospital, the diagnosis of SARS-CoV-2 was confirmed. Therapy with Lopinavir/Ritonavir and Hydroxychloroquine was initiated. The symptoms persisted after 3 days, so intravenous Methylprednisolone (1 g / day) was administered. In the following days, the patient experienced a significant recovery (Ministério da Saúde, 2020). Ibuprofen, a non-steroidal anti-inflammatory (NSAID), was not well accepted due to the lack of substantial evidence in the treatment of COVID-19. Understanding pathogenesis can help postulate possible reasons: the angiotensin-converting enzyme 2 (ACE2) is important for viral entry into the pneumocytes. Imbalances in ACE2 caused by ACE inhibitors or Ibuprofen can facilitate the onset of severe disease (Mirsa *et al*., 2020).

Anticoagulants: Anticoagulants are a class of drugs used to treat dysfunctions in homeostasis and are essential in preventing thromboembolic events. The use of these drugs in the prophylactic treatment of patients with COVID-19 began to be tested in several countries after some research. Experimental results have shown that abnormal coagulation parameters are associated with poor prognosis in patients with the new coronavirus pneumonia. Furthermore, there is extensive intravascular coagulation prevalent amongst the documented deaths of such patients (Tang *et al*., 2020). The role of coagulopathy in pneumonia caused by SARS-CoV-2 still needs to be clarified; however, some autopsy findings have shown the existence of occlusions in small pulmonary vessels and other organs, possibly due to an intense release of the cytokines associated with the endothelial impairment that leads to activation of the coagulation cascade (Zhang *et al*., 2020). A study carried out by a team of scientists at the University of Science and Technology in Wuhan, China, compared the mortality rate of patients during a period of 28 days, with the utilization of Heparin. They found that mortality amongst patients who used the drug was lower, which suggests that, anticoagulant treatment mainly with Low Molecular Weight Heparin may be consociated with an improvement in the clinical outlook of critically ill patients with COVID-19 (Zhang *et al*.,2020).

Chloroquine / Hydroxychloroquine: Chloroquine and Hydroxychloroquine are drugs that have scientifically proven anti-inflammatory, immunomodulatory, anti-infectious, antithrombotic and metabolic effects. They are commonly endorsed for the treatment of various infectious, rheumatological and immunological diseases (Anvisa, 2020). Chloroquine is an aminoquinoline derivative, first developed in the 1940s for the treatment of Malaria, having received approval by the FDA on October 31, 1949. Hydroxychloroquine is a racemic mixture that consists of an enantiomer R-S, approved by the FDA on April 18, 1955 (Cortegiani *et al*., 2020; Patrì & Fabbrocini, 2020). The molecular difference of these two drugs is mainly due to the presence of a hydroxyl (-OH), which occurs only in Hydroxychloroquine, characterizing the name. Moreover, the use of Hydroxychloroquine apparently produces fewer side effects when compared to Chloroquine (Hughes, 2018). The *in vitro* antiviral activity of these drugs was identified since the late 1960s (Inglot, 1969; Miller & Lenard, 1981; Shimizu *et al*., 1972) and the growth of several viruses can be inhibited in cell culture by both respectively (Keyaerts, *et al*., 2004). In addition, these medications are capable of inhibiting SARS-CoV-2 *in vitro* as well, however, Hydroxychloroquine is seemingly more potent (Colson *et al*., 2020; Patrì & Fabbrocini, 2020). The mechanism of action of Chloroquine is by its passive diffusion through the cell membranes and lysosomes, where it is protonated, and constrained.

Consequently, the endosomal pH increases and prevents the glycosylation of ACE2, the receptor that SARS-CoV-2 targets for cell entry. Accordingly, one of its activities is the alkalization of the phagolysosome, which hinders the stages of viral replication dependent on low pH, including fusion and desquamation. Other mechanisms of antiviral activity are still inadequately explained (Patrì & Fabbrocini, 2020).

Nevertheless, Chloroquine is evidently effective in preventing the dissemination of SARS-CoV-2 in cell culture, with favorable inhibition of viral distribution observed when cells were treated with the drug before or after infection. An indirect immunofluorescence assay represents a simple and fast method for screening SARS-CoV-2 antiviral compounds. Therefore, it would be possible to implement this procedure and the drug in prophylaxis and as a curative treatment. If clinical data corroborates these biological results, this new infectious respiratory disease would become one of the most feasible and economical to treat and prevent (Oliveira & Silveira, 2020). Regarding Hydroxychloroquine, its exact mechanism of action is still unknown. Notwithstanding, it also notably accumulates in human lysosomes and increases the pH of the organelle, which inhibits the processing of antigens, prevents the alpha (α1, α2) and beta (β1,β2) chains of the class II major histocompatibility complex (MHC) from dimerizing, inhibits the presentation of cell antigens and reduces the inflammatory response. Moreover, it can also reduce the release of cytokines such as Interleukin-1 (IL-1) and tumor necrosis factor (TNF) (Patrì & Fabbrocini, 2020). These drugs are used in different pathologies as shown in table 1.

Table 1. Posology of Hydroxychloroquine in the treatment of Malaria, Systemic lupus erythematosus (SLE) and Rheumatoid arthritis (RA) in adults (Adapted from the 3rd Edition of the Ministry of Health's Epidemiological Surveillance Guide).

Malaria	SLE	RA
800 mg in a single dose at the time of exigency. Take another 400 mg after 6 to 8 hours. For the next 2 days, take 400 mg daily in a single dose. Continue treatment taking 400 mg every 7 days for 4 weeks.	400 mg in a single dose or twice daily.	400 to 600 mg daily in a single dose, continuously. Reassess after 4 to 12 weeks and, if successful, reduce the dose to 200 to 400 mg.

Source: Epidemiological Surveillance Guide. 3rd Edition. Ministry of Health.
(Ministério da Saúde, 2019).

Table 2. Therapeutic recommendations according to the clinical situation of patients with COVID-19

Clinical situation	Recommendation	Considerations
Hospitalized patients with severe forms of COVID-19	Chloroquine diphosphate: 3 cp. From 150mg 2 x / day on the 1st day (900mg of loading dose) followed by 3 comp. 150mg 1x / day on the 2nd, 3rd, 4th, 5th days (450mg/ day) Hydroxychloroquine: 1 cp. 400mg 2x / day on the 1st day (800mg loading dose), followed by 1 comp. 400mg 1x / day on the 2nd, 3rd, 4th and 5th days (400mg / day)	Check the ECG before the start, risk of prolongation of the QT interval. The risk is greater in patients using other QT prolonging agents. Maintain ECG monitoring for subsequent days
Critical cases of COVID-19		

cp: tablet; ECG: Electrocardiogram; QT: interval between Q-wave and T-wave, observable on the ECG. Adapted: ANVISA, 2020.

There is considerable evidence that corroborates the benefits of Chloroquine usage, however it is only a preclinical legitimation, randomized clinical trials will yield more assuredness; medical ethics is fundamental, following the rules of biosafety in this context. Based on the test results and preclinical studies carried out with the use of this medication, The Brazilian Health Regulatory Agency (Agência Nacional de Vigilância Sanitária; ANVISA) on March 27, 2020 authorized the research of Chloroquine and Hydroxychloroquine administration for the treatment of COVID-19 patients considering the exacerbation of the disease in the country, according to table 2 (Anvisa, 2020). The positive feedback exhibited from the local physicians, enabled this decision nevertheless it can be altered at any time. A study involving 36 patients from Southeastern France substantiated the utilization of Hydroxychloroquine with the antibiotic Azithromycin as beneficial in the treatment of SARS-CoV-2 (Gautret *et al*., 2020). However, it is premature to affirm its concrete efficacy and therefore new tests need to be conducted to validate its application. The most common adverse reactions from Chloroquine and Hydroxychloroquine include headache, visual turbidity, gastrointestinal discomforts (abdominal pain, nausea, vomiting and diarrhea), cramps and itchy skin rash. Additionally, there are cases in which acute Chloroquine toxicity occurs, with cardiovascular symptoms such as arrhythmias, hypotension and even cardiorespiratory arrest (Lacava, 2010 & Ponchet *et al*., 2005).

Ribavirin, Lopinavir/Ritonavir & Interferon beta-1b.

Another researched pharmacological therapy against COVID-19 is the combination of Ribavirin, Lopinavir/Ritonavir (LPV/r) with Interferon beta-1b (IFN-β1b), due to its positive *in vitro* activity (Hung *et al*, 2020). Lopinavir and Ritonavir are antiretroviral drugs, sometimes formulated in combination, and used to treat the human immunodeficiency virus (HIV) (Dorward & Gbinigie, 2020). Ribavirin is a medication used in conjunction with Interferon alpha (IFN-α) in the treatment of several viral diseases, especially Hepatitis C (Kim *et al*, 2015). These drugs are considered potential candidates for tackling the disease (Dorward & Gbinigie, 2020). The therapeutic study of these drugs was in accordance with the following posology, LPV 400 mg with Ritonavir 100 mg every 12 hours for 14 days, Ribavirin 400 mg every 12 hours for 14 days and subcutaneous injection of 1 to 3 doses of IFN-β1b 8,000,000 IU every other day. When the patient is under IOT, this mixture w/o IFN-β1b must be administered via a nasogastric tube (Hung, 2020). The association of subcutaneous injections of IFN-β1b proved to be superior to treatment without IFNs (Hung, *et al*., 2020; Dorward & Gbinigie, 2020). LPV/r acts by inhibiting protease, a protein essential for viral replication, notably in HIV. According to *in vitro* studies, LPV is also able to inhibit the *in vitro* replication of the MERS-CoV infection (Kim, *et al*, 2015 e Dorward & Gbinigie, 2020). Ribavirin inhibits the replication of several viruses, nonetheless, it has a synergistic action when used in combination with LPV/r (KIM *et al*, 2015). At present, the documented side effects of the drug cocktail (LPV/r and ribavirin) are mostly limited to gastrointestinal disorders, mainly diarrhea. Other adverse reactions reported on a smaller scale were hepatitis, pancreatitis and dyslipidemia. The use of IFNs, in general, produce pro-inflammatory effects (Dorward & Gbinigie, 2020).

Conclusion

The specific form of pharmacological treatment required for SARS-CoV-2 has not yet been defined, requiring tedious and meticulous scientific investigations with randomized clinical trials to identify the ideal dosage and administration scheme for the cited potentially beneficial drugs to combat the disease. There are several auspicious pharmacological therapies, however, it should emphasized that the results ofsuch are only preliminary. Notably, there have also been redundant contentious issues on basic principles of scientific research between common sense and scientific practice, which in the grand scheme is superfluous. It should be underlined that the more potent drugs of *in vitro* trials may have little or no effect in clinical trials, as occurred with Remdesivir for the treatment of the Ebola virus in the past. It is also noted that the pharmacokinetics and pharmacodynamics, follow different cell culture patterns and cause different side effects, in the human organism, which in certain cases make the administration ofthe drug impractical. In a scenario, where time is worth human decisions and judgments, liberty from trends and irrationalities is essential to determine the sequence of the research methodologies and subsequently facilitate the appropriate pharmacological treatment for COVID-19. It is important to state that encouraging results are preludes to pharmacological validation, which includes *in silico, in vitro and in vivo* tests, such as those identified in this article. Such research is fundamental for the felicitous selection of drugs and therapeutic treatment to be administered, and consequently the preservation ofhuman life.

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