

Perspectivas das terapias da COVID-19: conflitos e consenso

Perspectives on COVID-19 therapies: conflicts and consensus

Perspectivas de las terapias COVID-19: conflictos y consenso

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Resumo

A cronologia das infecções por COVID-19 mostra que os primeiros casos foram notificados em dezembro de 2019. Vários pacientes foram internados em hospitais com uma doença respiratória de etiologia desconhecida em Wuhan, província de Hubei, China. Os pacientes apresentaram sintomas como tosse, febre persistente, dor de garganta e pneumonia. A situação da infecção respiratória piorou rapidamente e teve uma disseminação muito rápida. Logo após, foi relatado que o agente causador da doença havia sido confirmado como o novo Coronavírus (SARS-CoV-2), pertencente à subfamília Orthocoronavirinae, da família Coronaviridae, na ordem Nidovirales. Em 7 de janeiro de 2020, a doença foi nomeada como Doença de Coronavírus 2019 (COVID-19) pela Organização Mundial da Saúde (OMS). Cloroquina (CQ), Hidroxicloroquina (HCQ), Remdesivir, Heparina, Plasma Convalescente, Corticosteróide, Anticoagulantes, Lopinavir, Ritonavir, Ivermectina e Nitazoxanida são alguns dos medicamentos no mercado que estão sendo testados para combater o COVID-19. O objetivo desta revisão de literatura é analisar estudos sobre o potencial de cura desses medicamentos para o COVID-19. Alguns pesquisadores relatam sobre a eficácia desses medicamentos, a taxa de sucesso em doenças virais e seu potencial de ação por diferentes mecanismos. Assim, dadas as pesquisas analisadas neste estudo, ficou evidente para a maioria dos autores que esses medicamentos são tratamentos promissores para o COVID-19, enquanto a vacina não é fabricada e disponível.

Palavras-chave: Coronavírus; Drogas; Pandemia.

Abstract

The chronology of COVID-19 infections shows us that the first cases were reported in December 2019. A number of patients were admitted to hospitals with a respiratory disease of an unknown etiology in Wuhan, Hubei Province, China. The patients presented symptoms such as coughing, persistent fever, sore throat and pneumonia. The respiratory infection situation got worse rapidly and had a very fast spread. Soon after, it was reported that the causing agent of the disease had been confirmed as the novel Coronavirus (SARS-CoV-2), which belongs to the subfamily *Orthocoronavirinae*, of the family *Coronaviridae* in the order *Nidovirales*. On January 7, 2020, the disease was named as Coronavirus Disease 2019 (COVID-19) by the World Health Organization (WHO). Chloroquine (CQ), Hydroxychloroquine (HCQ), Remdesivir, Heparin, Convalescent Plasma, Corticosteroid, Anticoagulants, Lopinavir, Ritonavir, Ivermectin and Nitazoxanide are some of the drugs on the market that are being tested to combat COVID-19. The purpose of this literature review is to analyze studies regarding the healing potential of these drugs for COVID-19. Some researchers about the effectiveness of these medications, the success rate on viral diseases and its action potential by different mechanisms. Thus, given the researches analyzed in this study, it was evident for most authors that these drugs are promising treatments for COVID-19, while the vaccine is not manufactured and available.

Keywords: Coronavirus; Drugs; Pandemics.

Resumen

La cronología de las infecciones por COVID-19 muestra que los primeros casos se informaron en diciembre de 2019. Varios pacientes ingresaron en hospitales con una enfermedad respiratoria de etiología desconocida en Wuhan, provincia de Hubei, China. Los pacientes tenían síntomas como tos, fiebre persistente, dolor de garganta y neumonía. La situación de infección respiratoria empeoró rápidamente y se extendió muy rápidamente. Poco después, se informó que el agente causal de la enfermedad había sido confirmado como el nuevo Coronavirus (SARS-CoV-2), perteneciente a la subfamilia *Orthocoronavirinae*, de la familia *Coronaviridae*, en el orden *Nidovirales*. El 7 de enero de 2020, la Organización Mundial de la Salud (OMS) denominó a la enfermedad Coronavirus 2019 (COVID-19). Cloroquina (CQ), hidroxicloroquina (HCQ), remdesivir, heparina, plasma convaleciente, corticosteroides, anticoagulantes, lopinavir, ritonavir, ivermectina y nitazoxanida son algunos de los medicamentos en el mercado que se están probando para combatir el COVID-19. El propósito de esta revisión de la literatura es analizar estudios sobre el potencial curativo de

estos medicamentos para COVID-19. Algunos investigadores sobre la eficacia de estos medicamentos, la tasa de éxito en enfermedades virales y su potencial de acción a través de diferentes mecanismos. Por lo tanto, dada la investigación analizada en este estudio, fue evidente para la mayoría de los autores que estos medicamentos son tratamientos prometedores para COVID-19, mientras que la vacuna no se fabrica y no está disponible.

Palabras clave: Coronavirus; Drogas; Pandemia.

1. Introduction

In the province of Wuhan, in China, on December 31, 2019, patients were diagnosed with a respiratory disease without defined etiology. These patients presented symptoms such as coughing, persistent fever, sore throat, diarrhea and dyspnea that soon triggered pneumonia (Bai Y, Yao L, Wei T, Tian F, Jih DY, Chen L, 2020; H. Lu et al., 2020). It was reported that contamination had come from a local market that sells live meats, ranging from fish to snakes and bats (Ji et al., 2020; H. Lu et al., 2020).

The respiratory infection situation worsened rapidly, there was a very rapid spread, and computerized tomography tests showed diffuse bilateral alterations (Shi et al., 2020). Serological tests were performed by the Chinese Center for Disease Control and Prevention, such as C-Reactive Protein with real-time fluorescence (CRP) on blood samples and saliva collected via swab (Zhu et al., 2020). These tests had the aim to sequence the genes and find out what type of viral infection it was. Soon after, it was announced that the Coronavirus (CoV) was the etiological agent. The SARS-CoV-2 belongs to the subfamily *Orthocoronavirinae*, in the family *Coronaviridae* and the order *Nidovirales*, and has a single strand RNA as its genome (Zhang et al., 2020). The RNA of the SARS-CoV virus and SARS-CoV-2 showed high similarity with the RNA genes of the Ebola virus (Shen et al., 2019). Thus, studies on antivirals were intensified to test their effectiveness against COVID-19 and their level of toxicity for patients.

Due to being a viral and a respiratory tract disease the most likely form of spread is through aerosols and salivary droplets emitted through speech and coughing (Y. Chen et al., 2020; Zhiyong & Liuyan, 2020). Thus, an outbreak of COVID-19 generated a worldwide pandemic. Travelers and tourists disseminated the virus on several continents due to the lack of knowledge about the potential for transmission of the virus during the period of incubation (Lai et al., 2020; Song et al., 2019).

Respiratory infections are usually cured without major problems, but COVID-19 has mainly affected elderly people with systemic diseases such as diabetes, high blood pressure and pre-existing lung problems (Wu & McGoogan, 2020). COVID-19 still does not have a defined treatment, therapies are being based on some drugs to manage the infection and the patients symptoms (Sohrabi et al., 2020). Among the antivirals tested in the combat of COVID-19 are Ribavirin, Penciclovir, Nafamostat, Favipiravir, and two others broad-spectrum also have been tested severe conditions in patients such as Chloroquine (CQ) e Remdesivir (Mauthe et al., 2018).

CQ is an amine acidotropic form of quinine that was synthesized in Germany by Bayer in 1934 (Parhizgar, 2017; Winzeler, 2008). Quinine is a compound found in the bark of Cinchona trees native to Peru (Spiro, 1986). It is a medication used to treat Malaria, Amoeba (worms) and autoimmune diseases (Gao et al., 2020; Lee et al., 2011; Liu et al., 2020; White et al., 2014; Zhu et al., 2020). Remdesivir and CQ are classified as broad spectrum antivirals, so these medications can be very effective against the SARS family viruses (Lai et al., 2020).

Due to the indiscriminate use of CQ for many years and toxicity risks, the availability of the drug on the market was restricted (Liu et al., 2020). Chloroquine is a cheap and safe drug that has been used for more than 70 years (Gao et al., 2020). In 1946, a hydroxyl group was introduced into CQ and the resulting drug was demonstrated to be 40% less toxic than CQ in animals. COVID-19 commonly progresses to coagulopathy such as disseminated intravascular coagulation (DIC) which appeared in most deaths (Tang et al., 2020). The application of Heparin in the treatment of COVID-19 was recommended by expert consensus due to the risk of DIC and venous thromboembolism, but its effectiveness is not yet entirely validated (Tang et al., 2020).

Furthermore, medications such as Hydroxychloroquine (HCQ), anticoagulants such as Heparin, the use of convalescent plasma, antibody, corticosteroid and Ivermectin are being tested as potential therapeutics against COVID-19. However, there is no reliable evidence for the treatment of COVID-19, which still requires research and more clinical trials.

Although several clinical studies are also underway, possible therapies have been tested *in vitro*. Ivermectin, a Food and Drug Administration (FDA) approved antiparasitic, previously shown to have broad-spectrum antiviral activity, is an inhibitor of the SARS-CoV-2 *in vitro*, capable to effect ~ 5,000-fold reduction in viral RNA in 48 h (Caly et al., 2020). Another oral antiparasitic emerging in this scenario is Nitazoxanide. It was developed to be administered systemically and is being reused as a new broad-spectrum agent with a new mechanism of action for the treatment of influenza (Rossignol, 2014). Thus, several

medications need further investigation to become a viable therapeutic alternative in the near future bringing possible benefits in humans.

Even after using antiviral drugs, there is still a high viral load in the patient. It is known that viral loads are highly correlated with the severity and progression of the disease (Shen et al., 2017). Therefore, the convalescent plasma or immunoglobulins were used as a last resort to improve the survival rates of patients with SARS, whose condition continued to deteriorate (L. Chen et al., 2020). In addition to antiviral treatment, the use of a specific antibody that could neutralize the virus can speed up its elimination and prevent that SARS-CoV-2 enters into target cells, serving as the main mechanism for restricting and eliminating viruses (Rossignol, 2016; Shen et al., 2019; C. Wang et al., 2020).

In the face of the facts exposed above and the current urgency for scientific knowledge that assists evidence-based clinical practice, this study aims to conduct a literature review on alternatives for COVID-19 treatment.

2. Methods

This literature review was based on articles in the PubMed scientific platform and medRxiv. Articles from the last few years that presented correlation with the present study were selected. The publication period (2003 to 2020) and specific descriptors were used as inclusion criteria: COVID-19, SARS-CoV-2, SARS, Drugs, Pandemics, Hydroxychloroquine; Chloroquine; Ivermectin; Convalescent Plasma; Antiparasitic drugs; Anticoagulant; Corticosteroids; Antivirals; Antibody. As exclusion criteria, articles not related to the topic were discarded.

3. Results and Discussion

Laboratory and clinical studies published with promising repurposed drugs for COVID-19 can be seen in Table 1.

Table 1. Simplified information and description on the results of drug related therapies with potential for treating COVID-19.

| AUTHOR | YEAR | CONCLUSION |
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| SAVARINO et al. (Savarino et al., 2003) | 2003 | – CQ has limited toxicity and it is viable for the treatment of SARS-CoV. |
| SOO YO et al. (Soo YO, Cheng Y, Wong R, 2004) | 2004 | –Therapy associated to convalescent plasma in patients with SARS proved to be more favorable when compared to patients who used drugs like Ribavirin steroids in high dosages. |
| CHENG Y et al. (Cheng et al., 2005) | 2005 | – In spite of limitations, studies suggest that the use of convalescent plasma in the initial treatment of patients with SARS virus could be beneficial. |
| BIOT et al. (Biot et al., 2006) | 2006 | – CQ has been shown to inhibit SARS-CoV replication <i>in vitro</i> , but its clinical action is still unknown. – CQ compounds were tested against the replication of the virus in Vero cells, which are modified cells, with altered genetic and morphological characteristics. These cells are used for quality control and vaccines. These tests showed selectivity and confirmed the anti-SARS-CoV activity. |
| ROSSIGNOL (Rossignol, 2014) | 2014 | – Originally developed as an antiprotozoal agent, Nitazoxanide was later identified as a broad-spectrum antiviral drug and was used for the treatment of Influenza. Nitazoxanide is bioavailable and orally safe, with extensive experience involving more than 75 million adults and children. |
| BACHARIER et al. (Bacharier et al., 2015) | 2015 | – The use of Azithromycin during severe respiratory diseases reduced the infection compared to a placebo group. |
| MADRID et al. (Madrid et al., 2015) | 2015 | – The reuse of existing drugs facilitates the process of finding a cure in major pandemics. – In view of all the tested drugs, CQ showed an average survival rate of 80% when administered in a 90 mg/dose, 02 times a day, in an <i>in vitro</i> study. – CQ was the most promising drug in the initial activity, its pharmacological properties were reasonable against viral reproduction and it can play a role on immunological activity <i>in vivo</i> . |
| MARMOR (Marmor et al., 2016) | 2016 | – The risk of toxicity of HCQ depends on the dosage and duration of use: up to 05 years risk of 1%, 10 years less than 2%; rises to 20% over 20 years. |
| REBALLACK et al. (Retallack et al., 2016) | 2016 | – The antibiotic Azithromycin reduced the viral proliferation of Zika virus. – This provides a basis for evaluating therapeutic strategies to combat serious epidemics. |
| ROSSIGNOL (Rossignol, 2016) | 2016 | – Literature data suggests a potential role for Nitazoxanide in the treatment of MERS-CoV. It includes <i>in vitro</i> activity against MERS-CoV and other coronaviruses, inhibition of pro-inflammatory cytokines and of IL-6 production in mice, reducing the duration of flu symptoms in humans and a favorable safety profile demonstrated in clinical trials and in widespread use. |

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| SHEN et al. (Shen et al., 2017) | 2017 | <ul style="list-style-type: none"> – Recently, the generation and characterization of a chimeric monoclonal antibody, C12G6, has been described, which neutralizes representative viral samples of influenza B. In particular, C12G6 exhibits a wide hemagglutination inhibiting activity against influenza viruses. – C12G6 is a promising candidate for the development of prophylactics or therapeutics against influenza B infection and may inform the design of a truly universal influenza vaccine. |
| BOSSEBOEUF et al. (Bosseboeuf et al., 2018) | 2018 | <ul style="list-style-type: none"> – The <i>in vitro</i> activity of Azithromycin against Zika virus may be the first safe compound shown to prevent and treat viral infections. |
| MAUTHE et al. (Mauthe et al., 2018) | 2018 | <ul style="list-style-type: none"> – The authors defined that HCQ is not very reliable for cells in late stages and its use requires caution. |
| SHEN et al. (Shen et al., 2019) | 2019 | <ul style="list-style-type: none"> – BnAbs antibodies have been evaluated as promising agentes in the fight against influenza and other infectious diseases. It is highly desirable to find a new approach to identify and/or engineer bnAbs with even greater potency and breadth of recognition to counteract the rapidly evolving threat from Influenza and other virus infections. |
| BIAN et al. (Huijie Bian, Zhao-Hui Zheng, 2020) | 2020 | <ul style="list-style-type: none"> – Meplazumab efficiently improved the recovery of patients with SARSCoV-2 pneumonia with a favorable safety profile. The results support to carry out a large-scale investigation of Meplazumab as a treatment for COVID-19 pneumonia. – No adverse effect was found in Meplazumab-treated patients. – Meplazumab treatment significantly improved the discharge and case severity in the critical and severe patients vs control; the time to being virus negative in treatment was reduced relative to the control group. |
| BORBA et al. (Borba et al., 2020) | 2020 | <ul style="list-style-type: none"> – Suggests that a higher CQ dosage should not be recommended for critically ill patients with COVID-19 because of its potential safety hazards, especially when taken concurrently with Azithromycin and Oseltamivir. |
| CAO et al. (Cao et al., 2020) | 2020 | <ul style="list-style-type: none"> – In hospitalized adult patients with severe COVID-19, no benefit was observed with Lopinavir–Ritonavir treatment beyond standard care. |
| CALY et al. (Caly et al., 2020) | 2020 | <ul style="list-style-type: none"> – Ivermectin, which is a medication for parasite treatment, has been shown to be effective for the SARS-CoV virus <i>in vitro</i> and has enormous potential to decrease viral replication in a single application to <i>Vero</i> cells. |
| CHEN et al. (H. Chen et al., 2020) | 2020 | <ul style="list-style-type: none"> – After 4 to 12-day treatment with danoprevir boosted by Ritonavir, all patients (n=11) discharged from the hospital based on normal body temperature for at least 3 days; there was substantial improvements in respiratory symptoms. – The CT lung imaging revealed absorption and recovery of acute exudative lesions. |

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| CHEN et al. (L. Chen et al., 2020) | 2020 | <ul style="list-style-type: none"> – To date, no specific treatment has been proven to be effective for SARS-CoV-2 infection. – Convalescent Plasma or immunoglobulins have been used as a last resort to improve the survival rate of patients with SARS whose condition continued to deteriorate despite treatment with pulsed Methylprednisolone. – Evidence shows that convalescent plasma from patients who have recovered from viral infections can be used as a treatment without the occurrence of severe adverse events. |
| CHEN et al. (N. Chen et al., 2020) | 2020 | <ul style="list-style-type: none"> – A study with 99 patients, without defined protocol, used the following medications: Oseltamivir, Ganciclovir, Lopinavir and Ritonavir, Cephalosporin, Quinolones, Carbapenems, Tigecycline/egacycline against methicillin-resistant <i>Staphylococcus aureus</i>, Linezolid, and Antifungal drugs. – Patients were also treated with Methylprednisolone sodium succinate, Methylprednisolone, and Dexamethasone. – It was recommended to use immunoglobulin to decrease the infection rate. |
| COLSON et al. (Colson et al., 2020) | 2020 | <ul style="list-style-type: none"> – HCQ has the same mechanism of action as CQ and is very suitable for longer prescriptions. – Thus, an attack dose should be administered and followed with maintenance doses. |
| CORTEGIANI et al. (Cortegiani et al., 2020) | 2020 | <ul style="list-style-type: none"> – There is sense in the HCQ pre-clinical evidence for COVID-19. – HCQ use should be monitored. |
| DEVAUX et al. (Devaux et al., 2020) | 2020 | <ul style="list-style-type: none"> – CQ has been shown to be able to inhibit replication <i>in vitro</i> of several coronaviruses. – Chloroquine could act indirectly through reducing the production of proinflammatory cytokines and/or by activating anti-SARS-CoV-2 CD8+ T-cells. |
| GAO et al. (Gao et al., 2020) | 2020 | <ul style="list-style-type: none"> – On urgent clinical demand, Chloroquine phosphate is recommended to treat COVID-19. – The effect of CQ was apparently superior to the control treatment in inhibiting the exacerbation of pneumonia, improving the findings in pulmonary imaging, promoting a negative conversion of the virus, and reducing the course of the disease. |
| GAUTRET et al. (Gautret et al., 2020) | 2020 | <ul style="list-style-type: none"> – HCQ treatment is significantly associated with the reduction/disappearance of the viral load in patients with COVID-19 and Azithromycin reinforces its effect. |
| GRITTI et al. (Gritti et al., 2020) | 2020 | <ul style="list-style-type: none"> – The results suggest a potential role of Siltuximab in treating patients with ARDS secondary to SARS-CoV-2 infection. |
| HUANG et al. (Huang et al., 2020) | 2020 | <ul style="list-style-type: none"> – Remdesvir, even with all its antiviral potential was not considered effective against the SARS virus. – A controlled study of 41 patients was started to test the ability of Lopinavir associated with Ritonavir. |
| LAI et al. (Lai et al., 2020) | 2020 | <ul style="list-style-type: none"> – Among the various medications tested against COVID-19, Remdesvir and CQ were shown to be more effective <i>in vitro</i> research up to the moment. – Corticosteroids have not been recommended for use in cases of COVID-19, as they can increase the RNA load of SARS-CoV. |
| LANE et al. (C.E.Lane et al., 2020) | 2020 | <ul style="list-style-type: none"> – Researchers found no excess risk of severe adverse events was when 30- day hydroxychloroquine and sulfasalazine use were compared. However, when azithromycin was added to hydroxychloroquine, researchers reported an increased risk of 30-day cardiovascular mortality. – Short-Term hydroxychloroquine treatment was safe, but when azithromycin is added, it can induce heart failure and cardiovascular mortality. – Researchers urged caution in the use of this combination in COVID-19. |
| LI et al. (Li et al., 2020) | 2020 | <ul style="list-style-type: none"> – Lopinavir/Ritonavir or Arbidol monotherapy presents little benefit for improving the clinical outcome of hospitalized patients with mild/moderate COVID-19 beyond symptomatic and supportive care, causing instead more events that are adverse. |

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| LIU et al. (Liu et al., 2020) | 2020 | <ul style="list-style-type: none"> – HCQ is a safe and successful anti-inflammatory agent that has been used extensively in autoimmune diseases and can significantly decrease the production of cytokines and, in particular, pro-inflammatory factors. – HCQ can efficiently inhibit SARS-CoV-2 infection <i>in vitro</i>. – CQ appears to be the drug of choice for large-scale use due to its availability, proven safety record, and a relatively low cost – Remdesivir is a nucleoside analog prodrug developed by <i>Gilead Sciences</i> (USA). |
| LU et al. (X. Lu et al., 2020) | 2020 | <ul style="list-style-type: none"> – Corticosteroid therapy must be commenced with caution after full consideration of indications and contraindications, and routine corticosteroid use should be avoided during the process of anti-infection. |
| PATEL et al. (Patel, Amit and Desai, Sapan, 2020) | 2020 | <ul style="list-style-type: none"> – A survival benefit was reported for Ivermectin (mortality rate 18.6% vs 7.7%; length of hospital stay 10.9 +/- 6.1 days vs 15.7 +/- 8.1 days and ICU stay was 6.0 +/- 3.9 days vs 8.2 +/- 6.2 days). |
| SHEN et al. (Shen et al., 2020) | 2020 | <ul style="list-style-type: none"> – Complementary therapies with the use of Convalescent Plasma were carried out in 05 patients in a severe state of infection due to COVID-19, being effective with the use of neutralized antibodies. – This alternative therapy requires more studies to better present the benefits due to the quantitative limitation of the sample analyzed. |
| SOHRABI et al. (Sohrabi et al., 2020) | 2020 | <ul style="list-style-type: none"> – The National Health Commission of the People's Republic of China recommends the use of Lopinavir and Ritonavir, as it has been shown to reduce the mortality rate. – Broad spectrum antibiotics are indicated. – Oseltamivir is being used in China for suspected cases, as it inhibits neuraminidase. – Glucocorticoids have been used in patients with severe immunological disorders. – A Methylprednisolone should be administered in children 1-2mg/Kg daily for at least maximum 05 days. |
| TANG et al. (Tang et al., 2020) | 2020 | <ul style="list-style-type: none"> – Ninety-nine patients who received supporting medication associated with Heparin prophylactically showed satisfactory results against COVID-19. – Patients with d-dimers for coagulopathy who received Heparin medication had a lower mortality rate than those who did not. So, studies need to analyze the viability of the medication on a large scale. |
| THACHIL et al. (Thachil, 2020) | 2020 | <ul style="list-style-type: none"> – Ivermectin proved its effectiveness against several viruses, including SARS-CoV and reduced the mortality rate of patients with COVID-19. – The level of toxicity of Ivermectin was considered to be very low and safe, so its dosage can be increased and the administration of the dose <i>in vivo</i> will be more effective. |
| TOURET & LAMBALLERIE (Touret & de Lamballerie, 2020) | 2020 | <ul style="list-style-type: none"> – CQ should be used with caution in the treatment of COVID-19. |
| WANG et al. (C. Wang et al., 2020) | 2020 | <ul style="list-style-type: none"> – The neutralizing human monoclonal antibodies offer the ability to prevent and treat COVID-19 and other emerging diseases in the subgroup. |
| WANG et al. (M. Wang et al., 2020) | 2020 | <ul style="list-style-type: none"> – CQ and Remdesivir are highly effective in controlling COVID-19. |
| XU et al. (Xu et al., 2020) | 2020 | <ul style="list-style-type: none"> – Clinical data showed that the symptoms, hypoxigenmia, and CT opacity changes were improved immediately after the treatment with tocilizumab in most of the patients, suggesting that tocilizumab could be an efficient therapeutic for the treatment of COVID-19. |
| YAO et al. (Yao et al., 2020) | 2020 | <ul style="list-style-type: none"> – HCQ proved to be more potent against SARS and COVID-19 inhibition <i>in vitro</i> compared to CQ, presenting less interaction. |

COVID-19 is a pandemic without specific therapeutic treatment, and presents substantial mortality rates. Therefore, it is important to find new treatments and have an understanding of the therapeutic alternatives, as well as of the techniques proposed so far. An efficient approach to find proper medication is to test whether existing antivirals are effective in treating new viral infections. This could speed up the identification of a more efficient treatment for critically ill patients, as there is an urgent need for effective treatment to treat symptomatic patients and also to decrease the time during which the patient carries the virus, in order to limit the spread (Liu et al., 2020). The reuse of drugs is very important to fight the battle against rapid expansion infectious diseases such as HIV, influenza, hepatitis C virus, Ebola virus, dengue and many other deadly diseases (Sakurai et al., 2015), including for COVID-19.

Chloroquine and Hydroxychloroquine

CQ is a drug widely used in the treatment of malaria, lupus, amoeba (worms) and in autoimmune diseases (Rynes, 1997). It is considered a broad spectrum antiviral (Savarino et al., 2006; Yan et al., 2013) and it is a low cost drug. This is a weak base and it known to interfere with acid vesicles that lead to the dysfunction of various enzymes. It acts by interfering with the increase in pH in the organelles of the endosomal compartments that are important for the fusion of membranes and for the glycosylation of the SARS-CoV virus cell receptors (Lai et al., 2020; Vincent et al., 2005; Zhang et al., 2020). It is an inflammatory agent that has been widely used and can significantly decrease the production of cytokines and pro-inflammatory factors.

Epidemiology Working Group for NCIP Epidemic Response (Epidemiology Working Group for NCIP Epidemic Response, 2020) claims there is a consensus among some researchers about the effectiveness of CQ, the success rate over viral diseases and its power of action. It is known to act by different mechanisms, which may interfere with viral replication and inhibition of gene expression. This drug was shown to be effective against H5N1, against vertical transmission of the Zika virus and against the Human Immunodeficiency Virus (HIV).

One of the benefits of CQ is expressed by its ability of autophagic modulation (Mauthe et al., 2018). It is suggested that this inhibition is beneficial in the face of inflammatory processes. CQ was tested in ten hospitals in Wuhan on more than 100 patients, who showed significant improvement in decreasing the infection process (Gao et al., 2020). It

was found that radiographs taken after the treatment also showed satisfactory results, as there was a reduction in pneumonia and a decrease in the period of morbidity. Both Chinese and French researchers have obtained positive and promising results from the use of CQ to treat COVID-19 (Cortegiani et al., 2020). They reported that the risks versus the benefits are viable. Based on these results, on February 15, 2020, the researchers attested that CQ medication could be indicated to treat patients affected by COVID-19 (Colson et al., 2020; Devaux et al., 2020).

On the other hand, no significant relevance was found for the use of CQ in the treatment of COVID-19 or other viral diseases, defining the results of using CQ as a form of treatment as inconclusive (Touret & de Lamballerie, 2020). Patients using CQ (irrespective of dosage) failed to present evidence of substantial viral clearance by day 4, even with the concomitant use of azithromycin and in any case, the use of CQ in older patients, especially those with heart disease, should be conducted with caution (Borba et al., 2020). Chloroquine and hydroxychloroquine are associated with concerns of cardiovascular toxicity, particularly because of their known relationship with electrical instability, characterised by QT interval prolongation (the time taken for ventricular depolarisation and repolarisation). Drugs prolonging QTc interval could lead to severe arrhythmias (Borba et al., 2020). Furthermore, 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.

HCQ is a CQ analogue that also has anti-SARS-CoV-2 activity *in vitro* (Liu et al., 2020). During prolonged use it is safer and allows higher daily doses with less drug interactions, being considered more potent (Marmor et al., 2016; Savarino et al., 2003). Also, according some authors to a significant difference was observed between patients treated with HCQ and controls from the third day of use (Gautret et al., 2020; Yao et al., 2020). In combination with its anti-inflammatory function, it is believed that the drug has a good potential to fight the disease in patients with COVID-19 (Liu et al., 2020; Wu & McGoogan, 2020).

A synergistic effect of the combination of HCQ and Azithromycin was suggested (Gautret et al., 2020). This last one has been shown to be active *in vitro* against Zika and Ebola viruses (Bosseboeuf et al., 2018; Madrid et al., 2015; Retallack et al., 2016) and to prevent serious respiratory tract infections when administered to patients with viral infection (Touret & de Lamballerie, 2020). It is believed that this combination can act as an antiviral therapy against SARS-CoV-2 and prevent bacterial superinfections. Combined use is suggested, but the risk should be assessed individually, and further studies on this

combination are needed. This drug combination, HCQ and Azitromycin, should be used especially at the early stage of the COVID-19 infection before the patients develop respiratory distress syndrome with associated cytokine storm and become less treatable by any antiviral treatment according to some authors (Andreani et al., 2020; Gautret et al., 2020).

One *in vitro* study has demonstrated that the combination of HCQ and azithromycin (AZ) inhibits SARS-CoV-2 (Andreani et al., 2020). Despite a lack of evidence on efficacy, HCQ and HCQ + AZM (azithromycin) have become the most popular treatment/s for COVID-19. HCQ appears to be largely safe in both direct and comparative analysis for short term use, but when used in combination with azithromycin this therapy carries double the risk of cardiovascular death in patients with rheumatoid arthritis (C.E.Lane et al., 2020). Wherever of the world, the current evidence around efficacy of HCQ + AZM in the treatment of COVID-19 is quite limited and controversial (Million et al., 2020). Thus, the global community awaits the results of ongoing randomized controlled trials which assess the effects of chloroquine and hydroxychloroquine on COVID-19 clinical outcomes (Funck-brentano & Salem, 2020).

Remdesivir

Other medication, Remdesivir is an adenosine analog that is incorporated into viral RNA chains (Warren et al., 2016). It has recently been considered to have promising potential against a wide variety of RNA virus infections, including SARS/MERS-CoV. Remdesivir was originally developed by Gilead Sciences to treat Ebola virus, but was later abandoned due to disappointing results in a large randomized clinical trial (Mulangu et al., 2019). Its *in vivo* efficacies still require further confirmation and their potential use for treatment of infection by other coronaviruses and emerging coronaviruses in the future is unclear (Xia et al., 2020).

More recently, published the first randomised, double-blind, placebo controlled clinical trial assessing the effect of intravenous remdesivir in adults admitted to the hospital with severe COVID-19 (Y. Wang et al., 2020). Clinical improvement was not significantly different between groups, but was numerically lower in the Remdesivir group than the control group, particularly in those treated within 10 days of symptom onset.

Convalescent Plasma

Alternative therapies such as the use of convalescent plasma collected from recovered patients has been tested in critical COVID-19 patients (Shen et al., 2020). One possible explanation for the effectiveness of convalescent plasma therapy is that its antibodies can suppress viremia (L. Chen et al., 2020). Neutralized antibodies have been used empirically in other viral outbreaks such as avian influenza (H5N1), Influenza A (H1N1) effectively and presented satisfactory results (Hung et al., 2011; Mustafa et al., 2018; Treatment et al., 2006). The donor plasma contained IgG and IgM antibodies to SARS-CoV-2 that neutralized the virus *in vitro* (Shen et al., 2020). Although these patients continued to receive antiviral treatment mainly with Lopinavir / Ritonavir and Interferon, the use of convalescent plasma may have contributed to their recovery. The clinical status of all the patients improved approximately 1 week after transfusion, as evidenced by the normalization of body temperature, in addition to improvements in the scores of the Sequential Assessment of Organic Failure and in the PAO_2 / FIO_2 ratio (Shen et al., 2020). The results were satisfactory for alternative use of convalescent plasma in the treatment of COVID-19. It was found those days after the transfusion of neutralized antibodies, the patients had a lower viral load through CRP exams and improvement in the lung aspects in the computed tomography exams. It was also observed that patients after an average of 09 days of alternative treatment with convalescent plasma no longer needed a mechanical respirator (Shen et al., 2020). In addition, several studies have shown shorter hospital stays and lower mortality in patients treated with convalescent plasma than those who were not (Cheng et al., 2005; Soo YO, Cheng Y, Wong R, 2004).

Lopinavir/ritonavir

A randomized trial study found that a Lopinavir–Ritonavir treatment did not significantly accelerate clinical improvement, reduced mortality, or diminished viral RNA detectability in the throat of patients with serious COVID-19 (Cao et al., 2020). Lopinavir–Ritonavir treatment did not reduce duration of viral RNA detectability as compared with standard supportive care alone. SARS-CoV-2 RNA was still detected in 40.7% of the patients in the Lopinavir–Ritonavir group at end of the trial.

Similar results with Lopinavir/ritonavir or arbidol monotherapy are stated (Li et al., 2020). It demonstrated to have little benefit for improving the clinical outcome of hospitalized patients with mild/moderate COVID-19 beyond symptomatic and supportive care, causing instead events that are more adverse. Thirty-four patients were assigned to receive Lopinavir/ritonavir (LPV/r), 35 to arbidol, and 17 to no antiviral medication as control. The results showed that LPV/r and arbidol did not shorten the time of positive-to-negative conversion of COVID-19 nucleic acid in respiratory specimens (9.0 vs. 9.1 vs. 9.3 days), nor did they improve the symptoms of COVID-19 or pneumonia on lung CT imaging at 7 days and 14 days. Still, a retrospective analysis showed that viral load was negative in 75% of patients with COVID-19 treated with arbidol and lopinavir–ritonavir versus 35% of patients treated with lopinavir–ritonavir alone at day 7 post-treatment (Deng et al., 2020).

Meplazumab/Tocilizumab

Other alternative tested is Meplazumab. It is a monoclonal antibody but now there is insufficient evidence to draw a conclusion on benefits and harms. That effectiveness is being evaluated in various randomized clinical trials. However, according Bian et al. (Huijie Bian, Zhao-Hui Zheng, 2020) compared to control group, meplazumab treatment significantly improved the discharged and case severity in critical and severe patients. Also in the same drug category, Siltuximab was tested that after treatment with this medication, serum C reactive protein levels reduced to within the normal range by day 5 and remained stable in all 16 patients with available data throughout the follow-up period (Gritti et al., 2020). In addition, 33% (7/21) of patients experienced an improvement in their condition with a reduced need for ventilation (i.e. patients were removed from continuous positive airway pressure and non-invasive ventilation), 43% (9/21) of patients experienced a stabilizing of their condition, and 24% (5/21) of patients experienced a worsening of their condition, requiring intubation. Unfortunately, one patient developed a cerebrovascular event.

Tocilizumab, as a recombinant humanized antihuman Interleukin-6 (IL-6) receptor monoclonal antibody (Nishimoto, 2007), can bind to the IL-6 receptor with high affinity, thus preventing IL-6 itself from binding to its receptor, rendering it incapable of immune damage to target cells, and alleviating the inflammatory responses (Xu et al., 2020). Interleukin-6 (IL-6) is a pleiotropic cytokine that regulates immune responses and inflammatory reactions (Nishimoto, 2007). With COVID-19, a large number of T lymphocytes and mononuclear macrophages are activated, producing cytokines such as interleukin-6 (IL-6), which bind to

the IL-6 receptor on the target cells, causing the cytokine storm and severe inflammatory responses in lungs and other tissues and organs. After the treatment with tocilizumab in addition to the improvement of body temperature, the respiratory function was improved to some degree in most of the patients and chest tightness was relieved (Xu et al., 2020). Most patients lowered their oxygen intake flow, and the oxygen saturation remained stable and two patients were taken off the ventilator within 5 days. Early treatment can effectively control the deterioration of symptoms (Xu et al., 2020).

Anticoagulants

Patients with severe infections of COVID-19 have respiratory dysfunction and a decrease in platelets (Tang et al., 2020). This condition, associated with hormonal medications favors the risk of intravascular coagulopathies and venous thromboembolism. It is known that coagulopathy in infection with the coronavirus is associated with high mortality, with high D-dimers, being a particularly important marker for coagulopathy (Tang et al., 2020). Therefore, researchers suggested the need to include drug therapy with Heparin in COVID-19 treatments. The anticoagulant and anti-inflammatory action of this medication minimizes the risk of sepsis and regulates pro-inflammatory cytokines. Ninety nine patients with thrombocytopenia and D-dimer markers for elevated coagulopathy underwent prophylactic treatment with Heparin for 7 days and showed a 20% reduction in mortality by the analysis of the SIC score (sepsis induced coagulopathy) and D-dimers markers for coagulopathy. It is assumed that Heparin treatment may therefore be useful in mitigating lung injury (Thachil, 2020).

Corticosteroid Therapy

Also important is the addition of an adjuvant corticosteroid therapy to standard antiviral treatment of patients with coronavirus disease (COVID-19), common in clinical practice. However, evidence is scarce regarding the efficacy of adjuvant corticosteroids in patients who are critically ill. Corticosteroids dosage was associated with elevated mortality risk, suggesting prudent dosage of corticosteroid should be promoted when necessary (X. Lu et al., 2020). Additionally, abuse of corticosteroids is highly opposed and this study provided evidence that low-dose corticosteroids within effective limits may be recommended for critically ill patients with COVID-19 under certain circumstances.

Ivermectin

Ivermectin is a broad-spectrum medication with antiparasitic action, used to combat worms, scabies, lice and mites. FDA-approved for a number of parasitic infections (Buonfrate et al., 2019; Canga et al., 2008). The level of toxicity of Ivermectin was considered safe and very low. (Caly et al., 2020). Vero cells were infected with the SARS-CoV virus and received a single dose of Ivermectin. After 02 hours it was shown to be able to affect the host's cellular protein and control viral replication with an approximate 93% success rate. It is suggested that if the patient is submitted to Ivermectin therapy at the beginning of viral contamination, this medication has the potential to limit viral load and thus prevent the risks of human-to-human transmission, but *in vivo* tests are needed to prove it. Ivermectin seems to be safe and well tolerated with no serious drug-related adverse events (Sanz-Navarro et al., 2017).

An observational propensity-matched case-controlled study in 1,408 patients (704 that received ivermectin and 704 that did not) demonstrated an association of ivermectin use with lower in-hospital mortality 1.4% versus 8.5% (Ivermectin *versus* not ivermectin. Thus, ivermectin is associated with a potential survival benefit in COVID-19 and this should be investigated urgently in randomized controlled trials (Patel, Amit and Desai, Sapan, 2020).

Nitazoxanide

Nitazoxanide is a broad-spectrum antiviral agent in clinical development for the treatment of influenza and other viral respiratory infections, which exhibits *in vitro* activity against the Middle East respiratory syndrome coronavirus (MERS-CoV) and other coronaviruses. These drug inhibits viral expression in N protein which also suppresses the production of proinflammatory cytokines in peripheral blood mononuclear cells and suppresses the production of interleukin (Rossignol, 2016). Originally developed as an antiprotozoal agent, Nitazoxanide immediate release dosage formulations are licensed in the United States for the treatment of intestinal infections caused by *Cryptosporidium parvum* and throughout Latin America, India, Bangladesh and Egypt as a broad antiparasitic spectrum. A new oral prolonged-release medication was developed to administer the drug systemically and Nitazoxanide is being reused for use in the treatment of viral respiratory infections. The circulating active components of Nitazoxanide and Tizoxanide inhibits viral replication of the coronavirus and a wide range of other RNA and DNA viruses in cell culture assays, including

respiratory syncytial virus, influenza, parainfluenza, coronavirus, rotavirus, norovirus, hepatitis B, hepatitis C, dengue, yellow fever, Japanese encephalitis and human immunodeficiency virus (Rossignol, 2014). Nitazoxanide has also been studied in monotherapy and in combination with Oseltamivir (Rossignol et al., 2009).

These findings are promising and open the possibility of an international strategy for decision making to combat this emerging viral infection in real time, even if other strategies and research include the development of vaccines or if these drugs have mechanisms such as chemoprophylaxis. There have been more than 300 clinical trials going on, several antiviral and immunomodulating agents are in various stages of evaluation for COVID-19 (Şimşek Yavuz & Ünal, 2020).

Future randomized controlled trials may help to confirm or exclude the possibility of a specific beneficial treatment. Combining medications with other antiviral agents, as has been done in others cases, might improve clinical outcomes. It is important therefore that prescribers must pay attention on updated researches evidences. Scientific information has been in a very fast track in order to find if the therapies proposed so far are efficient or if it is not worth anymore and could even be harmful to patients.

4. Conclusion

Based on the researches in this literature review, it was evident that most authors are promising therapies against COVID-19 during the pandemic period. The absence of large tests certainly contributes to the hesitation in using these therapeutic alternatives safely and on a worldwide scale. It is known that there are previous studies on the use of these drugs in other viral diseases that have proven to be quite effective. It is also known that randomized clinical trials and more well established cohort studies are needed to define all benefits and risks. However, there is a consensus among researchers regarding the importance of their use at this time of emergency while there is no adequate vaccine, in order to combat the pandemic of COVID-19.

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