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HEALTH SCIENCES

COVID-19: therapeutic approaches description and discussion

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Abstract: COVID-19 emerged in December 2019 in China, and since then, has disrupted global public health and changed economic paradigms. In dealing with the new Coronavirus, SARS-CoV-2, the world has not faced such extreme global fragility since the "Spanish flu" pandemic in 1918. Researchers globally are dedicating efforts to the search for an effective treatment for COVID-19. Drugs already used in a clinical setting for other pathologies have been tested as a new therapeutic approach against SARS-CoV-2, setting off a frenzy over the preliminary data of different studies. This work aims to compile and discuss the data published thus far. Despite the potential effects of some antivirals and antiparasitic against COVID-19, clinical studies must confirm real effectiveness. However, non-pharmacological approaches have proven to be the most efficient strategy to date.

Key words: antivirals, antiparasitic, COVID-19, SARS-CoV-2, therapeutic approaches.

INTRODUCTION

The world is currently facing a pandemic caused by a virus in the *Coronaviridae* family, namely SARS-CoV-2, disrupting global public health and world economies. COVID-19, the disease caused by SARS-CoV-2 (WHO, 2020a), is a viral infection that affects the respiratory system, resulting in respiratory syndrome. COVID-19 is considered the most serious of pandemics since 1918 when the "Spanish flu" (H1N1) (Al Hasan et al. 2020, Zand & Wang 2020) emerged. The search for effective treatment and vaccine is frenzied, mobilizing research groups worldwide. Currently, there are still no drugs or vaccines proven to treat or prevent infection caused by SARS-CoV-2 (CDC 2020). However, numerous studies are currently being conducted (CDC 2020, NIH 2020).

The dramatic story of COVID-19 began at the end of December 2019, when a new species of the virus from the *Coronaviridae* family emerged in the city of Wuhan, China (Al Hasan et al. 2020, WHO 2020b). Initially, the outbreak demonstrated similar characteristics and symptoms to the Severe Acute Respiratory Syndrome-related Coronavirus (SARS). Initially, the World Health Organization (WHO) gave the virus the nomenclature 2019-nCoV, but it was later renamed SARS-CoV-2 by the International Committee on Viruses Taxonomy (Gorbalenya et al. 2020). Since January 21, 2020, WHO reports daily on the spread of the disease (Millán-Oñate et al. 2020, WHO 2020a)

CORONAVIRUS BIOLOGY

Coronaviridae virus family is enveloped, positive-sense single-stranded RNA included in group IV of the Baltimore classification (Gorbalenya et al. 2020, Arakawa & Morita 2019, Reid et al. 2015). The SARS-CoV-2 virus particles are round

or oval, with a diameter of about 60–140 nm. The sequence analysis demonstrates that the novel coronavirus belongs to Betacoronavirus Lineage β, Sarbecovirus, as SARS-CoV and MERS-CoV are included (Zhu et al. 2020a).

After entering the cells, the coronavirus uses host cell protein translation machinery to produce the viral polyprotein that needs to be cleaved into effector proteins. The viral proteases coronaviral principal protease (3CLpro) and papain-like protease (PLpro) are responsible for the cleavage (Báez-Santos et al. 2015). The viral genome also encodes a variety of nonstructural proteins such as RNA-dependent RNA polymerase (RdRp) (Ziebuhr et al. 2000).

The SARS-CoV-2 genome size varies from 29.8 kb to 29.9 kb, and share 96% identical at the whole-genome level to a bat coronavirus, and 79.6% sequence identity to SARS-CoV (Zhou et al. 2020a). Its genome structure followed the specific gene characteristics (Lu et al. 2020). The 5' region corresponds to approximately two-thirds of the genome and holds orf1ab encoding orf1a polyproteins. The 3' consists of genes encoding structural proteins, including surface, envelope, membrane, and nucleocapsid proteins. Besides, the SARS-CoV-2 contains six accessory proteins, encoded by ORF3a, ORF6, ORF7a, ORF7b, and ORF8 genes (Khailany et al. 2020, Li et al. 2005).

In general, viral infections follow a well-established pattern, in which viruses depend on host-cells' biosynthetic machinery to replicate its genome and generate descending virus particles (Romero-Brey & Bartenschlager 2014). Therefore, viruses are mandatory intracellular parasites (Paul & Bartenschlager 2013, Romero-Brey & Bartenschlager 2016). Inside the cytoplasm, at the onset of infection, the host-cell rises to produce viral proteins instead of protein synthesis, which is interrupted by the viral proteases. This step is essential in starting the process of viral-translating genetic material (Modrow et al. 2013). These viral lifecycle steps provide potential targets for drug therapy.

The virus infection commonly occurs between the interaction of viral surface molecules and the host-cell membrane. A host cell receptor mediates the SARS-CoV-2 entry into cells, as this hypothesis has already been tested for SARS-CoV (Xu et al. 2020, Zhou et al. 2020a). Initially, SARS-CoV was thought to enter host cells through membrane fusion (Ng et al. 2003, Qinfen et al. 2004). However, subsequent studies have shown that the SARS-CoV entry process is by receptor-mediated membrane endocytosis, and that pH also plays a role (Simmons et al. 2005, Wang et al. 2008).

Observations have shown the SARS-CoV infects ciliated bronchial epithelial cells and type-II pneumocytes through Angiotensin-Converting Enzyme 2 (ACE2) as a receptor (Qian et al. 2013). Also, data supports that SARS-CoV uses its Spike glycoprotein (S) to bind its receptor and mediate membrane fusion and virus entry. The trimeric S protein is about 180 kDa and contains two subunits, S1 and S2, mediating attachment and membrane fusion, respectively. Nonetheless, SARS-CoV-2 spike (S) proteins share about 76% and 97% of amino acid identities with SARS-CoV and MERS, respectively (Zhou et al. 2020a). It has been shown the SARS-CoV-2 envelope spike (S) protein mediates receptor binding and membrane fusion, and it is crucial for determining host tropism and transmission capability (Lu et al. 2020).

The S protein of SARS-CoV-2 seems to be more adapted for binding to the human receptor ACE2 (Andersen et al. 2020). Another host cell receptor, the type 2 transmembrane serine protease, TMPRSS2, participates in the infection process facilitating cell entry via the S protein (Hoffmann et al. 2020a). Inside the host cell, viral polyproteins are synthesized that

encode for the replicase-transcriptase complex. The virus then synthesizes RNA via its RNA-dependent RNA polymerase. Structural proteins are synthesized leading to the completion of assembly and release of viral particles (Sanders et al. 2020).

In addition to the replication process, viruses can induce strong antiviral responses in the host organism, representing a "hostility" between the virus and host to gain control over the resources of the infected cell (Nagy & Pogany 2011) and when not neutralized, viruses tend to win the battle. For example, recently, studies have shown the COVID-19 disease severity triggers a "cytokine storm syndromes", a hyperinflammatory syndrome characterized by a fulminant and fatal hypercytokinemia (Mehta et al. 2020). This "cytokine storm syndromes" is characterized by increased interleukin (IL)-2, IL-7, granulocyte-colony stimulating factor, interferon-γ inducible protein 10, monocyte chemoattractant protein 1, macrophage inflammatory protein 1-α, and tumor necrosis factor-α (Huang et al. 2020). This pathophysiological phenotype of COVID-19 is an additional aggravation of infection and development of the disease.

FEASIBLE THERAPEUTIC APPROACHES

From data on other coronaviruses, such as SARS-CoV infection and the viral replication process, as well as drug tests with possible treatment results, start a "gold rush" to look for an available ligand or molecule that may affect SARS-CoV-2.

Thus, this review compiled the principal findings from the recent data. We have grouped the pivotal drugs studied at the moment with a therapeutic alternative to COVID-19. The molecular structures of these drugs are presented in figure 1. In order to make the discussion articulate, we grouped the drugs according to their mechanisms of action, or previously described function.

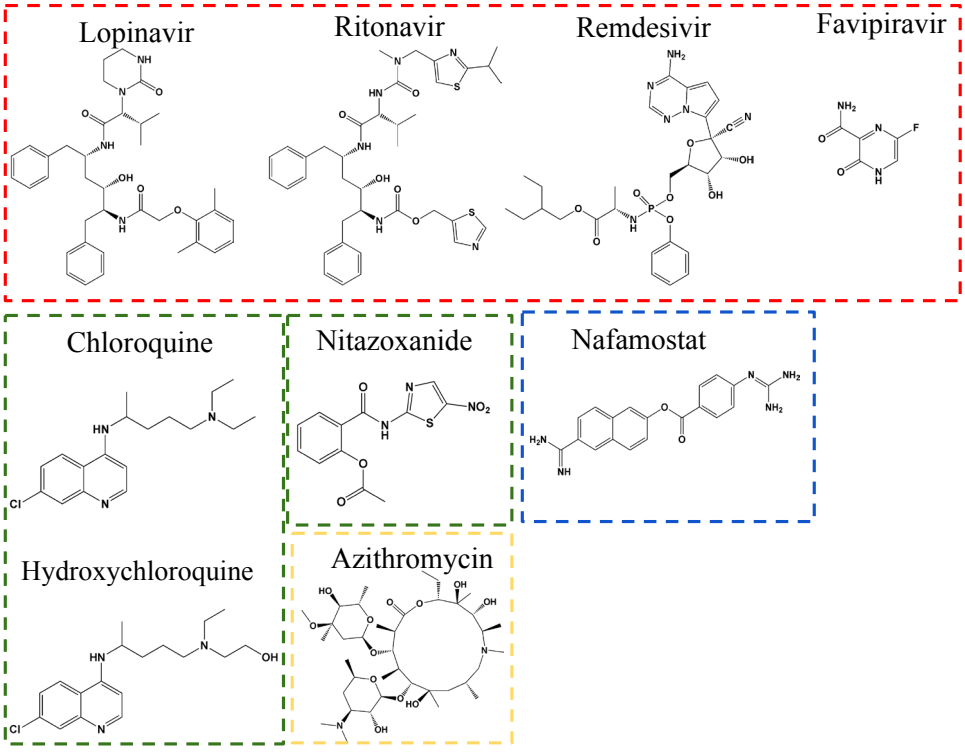

Figure 1. The molecular structure of the primary drugs as a therapeutic approach to COVID-19. Red: *Antivirals*. Green: *Antiparasitic*. Blue: *Serine protease inhibitor*. Yellow: *Macrolide antibiotics*.

ANTIVIRALS

Antivirals belong to the pharmacological class responsible for inhibiting the action of viruses in the body. These drugs are classified according to their action mechanisms (Hardman & Limbird 2005, Ison 2017). Standing out among these mechanisms are the following: the deactivation of virions (virus particles that appear after the viral replication process that are capable of infecting new cells), blocking the virus from binding to the cell receptor and inhibiting processes related to its replication, such as protease, integrase, and/or reverse transcriptase (Ison 2017).

Protease inhibitors

Widely used in the antiretroviral treatment of HIV, these inhibitors interfere with the synthesis of host-cell proteins and consequently interrupt the viral replication process. Ritonavir, Saquinavir, Fosamprenavir, and Lopinavir are examples of protease inhibitors (Mitsuyasu et al. 1998, Tenore & Ferreira 2009, Lv et al. 2015, Midde et al. 2016, Pokorná et al. 2009).

Protease is a key enzyme in coronavirus polyprotein processing, and drugs such as Lopinavir and/ Ritonavir could be an option playing anti-coronavirus activity (Yavuz & Ünal 2020).

Lopinavir, Ritonavir

In 2003, after the appearance of SARS, the combination of Lopinavir and Ritonavir, two antivirals of the protease inhibitor class used in the treatment cocktail of HIV-type 1, demonstrated inhibitory activity against SARS-CoV (Chen et al. 2004, Chu et al. 2004, Wu et al. 2004). The combination of Lopinavir + Ritonavir increases the plasma half-life of drugs through inhibiting cytochrome P450, which results in improved action time (Kirby et al. 2011).

Based on the findings for Lopinavir + Ritonavir against SARS-CoV, a group of researchers conducted a randomized, open, and controlled clinical trial on adult hospitalized patients with a confirmed SARS-CoV-2 infection. The data from this study was recently published in the renowned *The New England Journal of Medicine*. In the study, patients were divided into two groups in a 1:1 ratio. One group received treatment with Lopinavir (400 mg) + Ritonavir (100 mg) twice daily for 14 days in addition to standard treatment. The control group received only standard treatment (Cao et al. 2020).

The most common adverse events observed in the Lopinavir-Ritonavir group were gastrointestinal changes. In contrast, the control group, which received standard treatment, evolved with more serious adverse events such as respiratory failure, acute renal failure, and secondary infection (Cao et al. 2020).

Although the antiviral treatment did not differ significantly from the standard treatment in terms of clinical improvement (risk rate for clinical improvement 1.24, 95% confidence interval [CI], 0.90 to 1.72), the index mortality over 28 days was lower in the group treated with Lopinavir + Ritonavir (19.2% vs. 25.0%, with a 95% confidence interval, 17.3% to 5.7%) (Cao et al. 2020). Another important observation of the study was that a low number of patients in the Lopinavir + Ritonavir group had severe complications (acute renal failure and secondary infection) and less need for non-invasive or invasive mechanical ventilation than the group that received only standard treatment. However, researchers are careful with these findings and suggest additional studies be conducted before affirming that the combination of these antivirals is responsible for improving the clinical picture and changing the course of the disease (Cao et al. 2020).

In another clinical study, a group of Korean doctors with experience in treating patients infected by SARS-CoV-2 suggested that antiviral drugs are not recommended for use in young, healthy patients with mild symptoms and without underlying comorbid conditions (Smith & Prosser 2020). In this study, the researchers recommended that the following treatment be aimed at elderly patients or those with underlying conditions and severe symptoms. The treatment combines the following medications: Lopinavir (400 mg), Ritonavir 100 mg or Chloroquine (500 mg), or Hydroxychloroquine (400 mg) (Gao et al. 2020, *Physicians work out treatment guidelines for coronavirus - Korea Biomedical Review* 2020, Smith & Prosser 2020).

Nucleotide Analogs

This class is applied as broad-spectrum antivirals and may inhibit the RNA polymerase of viruses preventing its replication (Xu et al. 2020a). An animal model study (mice) testing Remdesivir, for example, demonstrated its inhibitory effect on Middle-East respiratory syndrome (*MERS)* (Agostini et al. 2018) and SARS-CoV (Sheahan et al. 2017).

Remdesivir

Remdesivir is an adenosine analog that is incorporated into nascent RNA chains and this step results in RNA premature termination (Warren et al. 2016). Remdesivir is a phosphoramidate prodrug of an adenosine C-nucleoside metabolized into its active form, GS-441524. Remdesivir delays the chain termination and blocking the proofreading function by exoribonuclease (Figure 2), an enzyme responsible for RNA degradation, by removing terminal nucleotides from both ends (5 “or 3”) (Agostini et al. 2018, Siegel et al. 2017).

A broad-spectrum antiviral agent synthesized and developed by Gilead Sciences in 2017 as a treatment for Ebola virus infection (Siegel et al. 2017). Also, Remdesivir has shown promising results for a wide variety of virus infections whose genetic material is RNA (Martinez 2020). It has demonstrated antiviral activity against *SARS* and *MERS* (Wang et al. 2020).

With promising effects previously known against Coronaviruses, a group conducted in vitro tests combining Remdesivir and Chloroquine against SARS-CoV-2. The in-vitro study evaluated the combined activity of these drugs using the Vero E6 cell model (ATC-1586). Tests were performed to measure cytotoxicity and the rate of viral infection (Wang et al. 2020). The data demonstrated that the combination of these drugs potentially blocked SARS-CoV-2 infection at a low micromolar concentration (Wang et al. 2020). Furthermore, the same research group claimed that Remdesivir also effectively inhibited SARS-CoV-2 infection in a human cell line (human liver cancer Huh-7 cells) (Wang et al. 2020).

From these encouraging results, some groups have started clinical studies. Currently, a clinical trial testing the effectiveness of Remdesivir in patients infected with SARS-CoV-2 is being conducted in China (Smith & Prosser 2020). More recently, Remdesivir was evaluated in a compassionate study in hospitalized patients diagnosed with COVID-19. The patients presented an oxygen saturation of 94% or less, breathing in the environment or with the aid of respirators. For 10 days, Remdesivir was administered in the following dosages: 200 mg on the first day and 100 mg on the next 9 days, from January 25 to March 7, 2020 (Grein et al. 2020).

A total of 53 patients, from different regions such as North America (USA and Canada), Europe

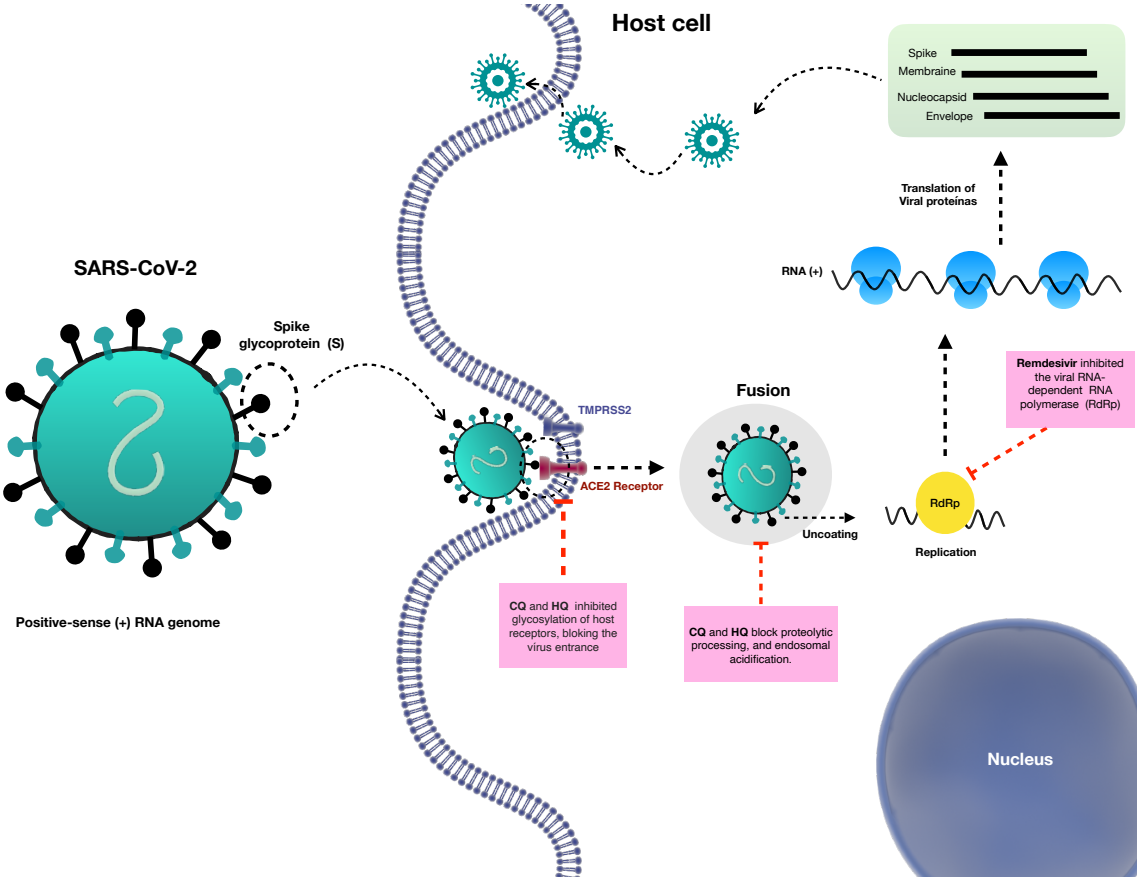

Figure 2. Therapeutic approaches in clinical test for COVID-19. SARS-CoV-2 model of infection and Remdesivir, Chloroquine and Hydroxychloroquine mechanisms elucidated.

and Japan, followed in the study. Interestingly, the data showed that of the 53 hospitalized patients diagnosed with Covid-19 with severe symptoms, treated with compassionate use of Remdesivir, 36 (68%) achieved clinical improvement. However, even with promising results, the authors are cautious and claim that randomized clinical trials are needed, which are currently in progress (Grein et al. 2020).

Favipiravir

Favipiravir (Avigan) has been developed by Fujifilm Toyama Chemical in 2014 in Japan for the treatment of avian influenza or novel influenza resistant to neuraminidase inhibitors. Favipiravir (RNA polymerase inhibitor) is a guanine analog in the same class of the Remdesivir and as its antiviral activity similar this drug could potentially exhibit effects against SARS-CoV-2 (Furuta et al. 2017).

Favipiravir initially acts as a prodrug entering cells through endocytosis, and then after phosphoribosylation and phosphorylation, it is converted into an active favipiravir ribofuranosyl phosphates (Furuta et al. 2013). The antiviral activity is exhibited through selectively targeting the conservative catalytic domain of RNA-dependent RNA polymerase (RdRp), interrupting the nucleotide incorporation process during viral RNA replication (Furuta et al. 2017). Favipiravir demonstrated 100% effectiveness in protecting mice against the Ebola virus, although its EC50 value in Vero E6 cells was high (Oestereich et al. 2014). Favipiravir has been used in the treatment

of infectious diseases caused by RNA viruses such as influenza, Ebola, and norovirus (De Clercq 2019).

OTHER MEDICATIONS

Antimalarial and antiprotozoal

Chloroquine and Hydroxychloroquine

A vigorous discussion about the use of Chloroquine and its derivative Hydroxychloroquine has raised the spirits about practical therapeutic approaches for COVID-19 treatment. Scientific evidence, while impressive, raises many questions. In this fashion, we intend to discuss and present updated data on this topic.

Chloroquine (CQ) and hydroxychloroquine (HCQ) are aminoquinolines with known anti-inflammatory (Ornstein & Sperber 1996) and antimalarial properties (Ben-Zvi et al. 2012, Wellems & Plowe 2001), have recently emerged as "a promise" in the treatment of COVID-19 (Colson et al. 2020, Cortegiani et al. 2020).

Chloroquine was initially used to treat *Plasmodium* sp., a malaria disease agent (Aronson 2016, Homewood et al. 1972, Wellems & Plowe 2001). However, because of its high toxicity and the development of *Plasmodium* resistance to the drug (Krogstad et al. 1987), the need to develop new molecules emerged. Hydroxychloroquine sulfate is a derivative of Chloroquine and was first synthesized in 1946 by the introduction of a hydroxyl group, and proved to be less toxic than Chloroquine (McChesney 1983) (Figure 1). HCQ is widely employed to treat autoimmune diseases such as systemic lupus erythematosus and rheumatoid arthritis (Rainsford et al. 2015). Its availability, proven safety record, and relatively low cost have rendered it a considerable alternative to large-scale treatment.

In humans, the effect of both Chloroquine and Hydroxychloroquine is well described. For example, it is understood that oral absorption is efficient. In animal tests, both drugs share similar standards of pharmacokinetics and bioavailability, with higher concentrations in the liver, spleen, kidney, and lung, peaking between 200–700 times greater than those of plasma (Laaksonen et al. 1974, Popert 1976).

CQ and HCQ are able to modulate some cellular functions involved in immune activation such as inhibition of MHC class II expression, CD154 expression by T cells, cytokines IL-1, IFNα and TNFα, which can protect against cytokine-mediated, GMP-AMP (cGAMP) synthase (cGAS) activity, lysosomes and autophagosomes changing local pH concentrations (Schrezenmeier & Dörner 2020). Besides, both CQ and HCQ are weak bases known to raise the pH to reinforce the hypothesis to interfere in acidic intracellular organelles such as endosomes/lysosomes, which are essential for membrane fusion (Krogstad & Schlesinger 1987). This mechanism is proposed for both drugs acting as the COVID-19 therapeutic approach.

According to these data, some studies tested CQ and HCQ against SARS-CoV-2 and have demonstrated these drugs can reasonably inhibit some virus steps of infection in a safe dosage (Liu et al. 2020). It was proposed that CQ and HCQ could block viral entry into cells by inhibiting glycosylation of host receptors, proteolytic processing (Figure 2), and endosomal acidification (Savarino et al. 2006, Vincent et al. 2005, Zhou et al. 2020b).

Chloroquine, in vitro, was able to inhibit SARS-CoV-2 with a half-maximal concentration (EC50) in the low micromolar range. Culture tests on Vero E6 cells with 50% and 90% effective

concentrations (EC50 and EC90 values) of 1.13 μM and 6.90 μM, respectively (Wang et al. 2020) were done. Also, reported mechanisms suggest a blockage of the transport of SARS-CoV-2 from endosomes to lysosomes. This step seems to be an important process for the release of the viral genome. Assuming that the maturation of the endosome may be blocked in the intermediate stages of endocytosis, this will result in the failure of the additional transport of virions to the final release site (Liu et al. 2020).

A systematic review of the use of Chloroquine for the treatment of COVID-19 affirmed that a sufficient rationale exists for clinical use. This is in addition to preclinical evidence of efficacy and safety evidence based on the prolonged use of the drug for other diseases. However, the researchers emphasize that safety data and high-quality clinical trial data from clinical use for COVID-19 are urgently needed, which should be monitored or ethically approved for clinical trials (Cortegiani et al. 2020).

Since the promising in vitro data, groups have started clinical studies with CQ and HCQ in COVID-19 positive patients. A recent open-label nonrandomized French study of 36 patients (20 in the hydroxychloroquine group and 16 in the control group) reported improved virologic clearance. Oral hydroxychloroquine sulfate 200 mg was administered three times per day for ten days. The endpoint was virological clearance at day-6 post-inclusion, also secondary outcomes were virological clearance overtime during the study period, clinical follow-up (body temperature, respiratory rate, long of stay at hospital and mortality), and occurrence of side-effects. The authors tested the combination azithromycin + hydroxychloroquine, and they reported that the addition in 6 patients resulted in superior viral clearance (6/6, 100%) compared with hydroxychloroquine monotherapy (8/14, 57%) (Gautret et al. 2020).

A recent observational clinical study (Funded by the National Institutes of Health) published on May 7, in *The New England Journal* (Geleris et al. 2020) followed 1376 patients, during a median follow-up of 22.5 days, 811 (58.9%) received hydroxychloroquine (600 mg twice on day 1, then 400 mg daily for a median of 5 days), 45.8% of the patients were treated within 24 hours after presentation to the emergency department, and 85.9% within 48 hours. The authors affirmed the hydroxychloroquine administration was not associated with either a greatly lowered or an increased risk of the composite endpoint of intubation or death. Also, the authors conclude to be necessary randomized, controlled trials of hydroxychloroquine in patients with COVID-19 (Geleris et al. 2020).

A retrospective multicenter cohort study of patients from a random sample published more recently, rated the use of HCQ alone or with the interaction of Azithromycin in the metropolitan area of the state of New York - USA. In all, 1438 patients diagnosed with COVID-19, middle-aged men, aged 63, received only HCQ or both drugs, had more significant complications than patients who did not receive this therapy. The authors conclude the treatment with hydroxychloroquine, azithromycin, or both, compared with neither treatment, was not significantly associated with differences in in-hospital mortality. However, the authors also list a number of limitations of this observational study, they emphasize the need for clinical trials to provide definitive causal evidence of the effect of hydroxychloroquine and azithromycin on mortality, while also providing an opportunity to more finely control baseline patient severity and the dose and timing of drug administration (Rosenberg et al. 2020).

Additionally, it is necessary to point out that even though Chloroquine and Hydroxychloroquine are relatively well-tolerated

since the long time have been using for malaria treatment, studies warn of the risks. About 10% of the patients using both agents can present rare and severe adverse effects, including QTc prolongation, hypoglycemia, neuropsychiatric effects, and retinopathy (Sanders et al. 2020).

Ultimately, a discussion on the emerging use of Chloroquine or its derivative Hydroxychloroquine is undoubtedly necessary. Scientific evidence to ensure that this treatment proposal is genuinely compelling is currently insufficient.

In Brazil, the National Health Surveillance Agency (ANVISA) first declared that although promising, no conclusive studies prove the effective use of these drugs in the treatment of COVID-19 (ANVISA 2020a). More recently, ANVISA authorized a study that will apply Hydroxychloroquine in the treatment of patients with COVID-19 (ANVISA 2020b).

Brazilian healthy agency, ANVISA, has consent (ANVISA 2020b) involves two studies: a) An open, controlled study of the use of Hydroxychloroquine and Azithromycin to prevent complications in patients infected with COVID-19: a randomized and controlled study (mild to moderate cases). b) Evaluation of the safety and clinical efficacy of Hydroxychloroquine associated with Azithromycin in patients with pneumonia caused by infection with the Sars-CoV-2 virus (critically ill patients).

Antibiotic

Azithromycin

Azithromycin is an antibiotic applied for the treatment of several different types of infections caused by susceptible bacteria (Perter et al. 1992). Azithromycin binds to the 50S subunit of the bacterial ribosome, inhibiting mRNA translation (Bulkley et al. 2010, Tu et al. 2005).

The use of Azithromycin together with other drugs has been successfully applied in the clinic for the treatment of viruses and to prevent severe respiratory tract infections for patients suffering from viral infection (Madrid et al. 2015, Retallack et al. 2016). As discussed before, the positive data for the use of its azithromycin along with hydroxychloroquine, in a COVID-19 clinical trial have been proposed (Gautret et al. 2020). In an open-label non-randomized study in France hydroxychloroquine + azithromycin presented with the highest virologic cure rate following 6-day treatment (Gautret et al. 2020).

However, other studies affirm the data presented to date are insufficient to evaluate possible clinical benefits of azithromycin in patients with COVID-19 and repeated the experiments found patients had significant comorbidities (Molina et al. 2020).

Nitazoxanide

Nitazoxanide (Fig. 1), an antiprotozoal, is an orally active nitrothiazolysalicylamide and antiviral prodrug that is converted rapidly to the active metabolites tizoxanide and nitazoxanide conjugates and unlike metronidazole (Rang et al. 2007, Rossignol 2016). Similarly, nitazoxanide is also known to potentiate interferon-alfa and interferon-beta production and it has been previously shown to exhibit an in vitro activity against MERS-CoV and other coronaviruses (Rossignol 2016).

Nitazoxanide is hypothesized as a likely therapeutic approach and could have antiviral potential against Sars-CoV-2, as it works by interfering with host-regulated pathways in viral replication, amplifying the detection of cytoplasmic RNA and Interferon type 1. Some author suggests that nitazoxanide/azithromycin combination could have a potential that should be properly tested in clinical trials including

randomized controlled trials (Kelleni 2020, Şimşek & Ünal 2020).

Serine protease inhibitor

Nafamostat

Nafamostat, a serine protease inhibitor that works as an anticoagulant, has demonstrated satisfactory results in inhibiting the action of MERS-CoV and has been shown to be effective against SARS-CoV-2 infection, preventing membrane fusion (Wang et al. 2020).

Nafamostat mesylate inhibits TMPRSS2-dependent host cell entry of MERS-CoV (Yamamoto et al. 2016), and TMPRSS2 is responsible for cleaving and activate Sars-Cov-2 S protein. However, the use of this anticoagulant in the treatment for COVID-19 is in a clinical trial, and the exact concentration of the compound to inhibit viral replication is not yet clear. In the deficiency of this information, other serial protease inhibitors were tested to inhibit the entry of Sars-Cov-2 into the cell, such as Naphthostat mesylate, which is already used for human use in Japan and the fact that this drug inhibits the action of TMPRSS2 in the host cell for infections caused by MERS-CoV (Hoffmann et al. 2020b).

Nafamostat has FDA approval (unrelated to infections caused by coronavirus), and has been shown to inhibit the entry of Sars-Cov-2 mediated by protein S into the host cell with greater efficiency than Naphthostat mesylate, thus being considered the best option for the treatment of COVID-19 concerning the other serine protease inhibitors due to its higher safety and antiviral activity (Hoffmann et al. 2020b).

Non-pharmacological approaches

An epidemiological modeling study published at *Imperial College (Impact of non-pharmaceutical interventions (NPIs) to reduce COVID-19 mortality and healthcare demand)* has been transforming the world paradigm regarding understanding adopted measures. The study demonstrates that non-pharmacological approaches can have a much more efficient impact on controlling the spread of COVID-19, thus preventing the collapse of the health system (Ferguson et al. 2020).

The proposed strategies to contain the population are: *mitigation* (which aims to reduce the demand for health care by protecting at-risk groups), and *suppression* (which aims to reverse the growth of the epidemic, reducing the number of cases to low levels, and maintaining this situation indefinitely) (Ferguson et al. 2020). According to this epidemiological modeling, without actions of containment, the number of deaths in the United States, for example, could a total of 2.2 million people.

However, the authors emphasize that it is not certain that suppression will succeed in the long term, and that no public health interventions with such disruptive effects on society have been tried before for such a long period (Ferguson et al. 2020).

CONCLUSIONS

There is some scientific evidence of particular drugs such as antivirals, antiparasitic, and anticoagulants as approaches for treatment Coronavirus infections (Chu et al. 2004, Martinez 2020, Wu et al. 2004). Currently, more than 300 active clinical treatment trials are advancing. Unfortunately, until now, there is no evidence from randomized clinical trials with substantial therapy improves outcomes in COVID-19 patients. No clinical trial data are supporting any prophylactic therapy.

The current COVID-19 pandemic has caused hopelessness in the population, resulting in an

overwhelming spread of panic and economic imbalance in affected regions (Anderson et al. 2020, Atkeson 2020, Ruiz Estrada 2020). Thus, the population yearns for a practical therapeutic approach.

It must be emphasized that more clinical tests still need to be performed to ensure the use and effectiveness of the drugs reviewed in this work in the treatment and prevention of COVID-19 (Cao et al. 2020). The world is alarmed and confused; however, science is based on evidence generated through a rigorous methodology, which requires randomized studies for clinical application. Regrettably, these studies require time to be conducted, and results for the general population may differ from those initially evidenced in in-vitro investigations or in specific populations.

Thus, researchers, health professionals, and government representatives must discuss the best way to face this public health crisis. The most reliable way thus far adopted in various countries is preventing the virus from spreading by containing the population and enforcing mitigation. However, the appeal for the use of drugs with probable effectiveness, even with limited studies, is remarkably strong.

An important aspect to consider is that the medications currently proposed have the advantage of already being used as therapeutic options for other diseases. Consequently, these are approved for the treatment of humans, and their effects are well known. However, the results of more refined studies on safe and effective drug options will guarantee patients a truly safe treatment with the possibility of cure and/or prevention. Today, with the data thus far, this cannot be guaranteed.

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