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Review Article

COVID-19: Yet a Treatment to Find

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Abstract

As COVID-19 spreads and increases worldwide since December 2019, the Scientists and the Medical Community are committed to find a treatment or even a vaccine. New therapies are being tested with "old" and well known medicaments but still there are many undesirable effects with each of them depending on your previous health status or age. We summarize a few of them.

Keywords: COVID-19; Vaccine; SARS CoV-2 virus; WHO

Introduction

As COVID-19 cases increases worldwide and there is still no treatment or vaccine for it we summarize a few drugs used to treat it. We start with the controversial Hydroxychloroquine announced in Brazil, the author's home country. Advances in therapy are discovered every day, and we hope a new and safer treatment or vaccine can be found soon.

Since December 2019, Wuhan, China, has experienced an outbreak of the new disease COVID-19, caused by the SARS CoV-2 virus, which affected more than 100 countries in a matter of weeks. This led the World Health Organization (WHO) to declare the outbreak of a pandemic on March 11, 2020 [1]. Therefore, this disease has become a global problem.

It is an infectious disease that can present from asymptomatic patients, with symptoms of flu-like syndrome (cough, sputum and fever), to symptoms of Acute Respiratory Distress Syndrome (ARDS), a serious condition that requires hospitalization [2]. Its severity is not only based on the damage caused by the viral infection, but at the same time, an exacerbated pulmonary inflammatory reaction due to a "cytokine storm". Its mortality rate in the world scenario is approximately 3.7%, a value much higher than that of influenza, less than 1% [3]. In addition to its high lethality, another problem is the high level of contagion, estimated between R 0=1.4 to 2.5 by the WHO [4].

In order to understand the possible pharmacological therapies, it is also necessary to understand the structure and mechanism of infection of the SARS CoV-2 virus. It is an RNA virus, of the *coronaviridae* family. Its tropism to the respiratory tract is due to its main mechanism of infection being through its "spike" protein that binds with great affinity to receptors of Angiotensin-Converting Enzyme 2 (ECA-2), distributed in several organs and in large quantities among pneumocytes type 2 and nasal calyx cells [5]. The angiotensin-converting enzyme 2 is related to several pathophysiological processes, converting angiotensin 1 into angiotensin (1-9) and angiotensin 2 into angiotensin (1-7), that has a regulatory function in blood pressure [6].

The "spike" protein is an essential protein for infection with SARS CoV-2 [7]. Its S1 portion binds to the ECA-2 receptor while its S2 portion undergoes the structural rearrangement necessary for the fusion of the virus and host cell membranes, so the ECA-2 receptor is considered functional for SARS CoV-2 infection [8]. When it binds to the ECA- 2 receptor, the virus needs to activate its "spike" protein to infect the cell through endosomal cysteine proteases cathepsin B and L or *via* Serine Type 2 Transmembrane Protease (TPMRSS2), used as primer of the protein "spike", without the need for the virus to enter the endosome to infect the cell [9].

Taking into account its viral characteristic and cycle of infection, researchers around the world are trying to find pharmacological agents to combat COVID-19, based especially on the drug's mechanism of action. However, the WHO has explicitly stated that, so far, there is no evidence with randomized clinical trials that can recommend an effective and specific therapy for the treatment of COVID19 [10] and the reason for this review is to clarify, the current panorama of the main therapeutic alternatives and what is expected in this regard for the coming months.

Drugs in use to Treat COVID-19

Hydroxychloroquine and Chloroquine

Chloroquine and hydroxychloroquine have been known for decades, being used as an antimalarial and in the treatment of autoimmune diseases. It is a drug that has been used for about 70 years with a well-established clinical safety profile and adverse effects [11]. Recently, they were seen as potential broad-spectrum antiviral drugs for blocking viral infection by increasing the endosomal pH, which is necessary for the fusion of the virus membrane and cell, in addition to acting in the entry and post-entry stages of the virus, which inhibits the infection of cells by SARS CoV-2 *in vitro*. In addition, chloroquine also has an immunomodulatory activity, which can synergistically increase its antiviral effect *in vivo* [12].

It is important to note that both hydroxychloroquine and chloroquine have a low therapeutic index, and a dose of 30 mg/kg of hydroxychloroquine can be fatal. Some precautions are necessary when using these drugs, including drug interactions, electrocardiogram evaluation due to QT prolongation, monitoring of hematological parameters, serum electrolytes, glucose, liver and kidney functions. Furthermore, the addition of azithromycin to hydroxychloroquine may increase the risk of QT prolongation [13].

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A first human study was conducted in China in more than 10 hospitals, in order to test the efficacy and safety of chloroquine and hydroxychloroquine in the treatment of pneumonia associated with COVID-19. More than 100 patients participated in this study that demonstrated that chloroquine phosphate would be superior for the control of treatment in inhibiting the exacerbation of pneumonia and shortening the course of the disease in relation to the population with control treatment. The dose of chloroquine used was 500 mg twice a day. In this letter, the authors inform that no adverse effects were observed in the mentioned patients [14].

In a non-randomized clinical trial conducted in France and published in March 2020, researchers pointed to a significant disappearance of viral load in patients with COVID-19. Patients received 200 mg of hydroxychloroquine sulfate orally, three times a day, for ten days. The trial was carried out with a small sample size of 36 people (considered in the study 20 treated with hydroxychloroquine and 16 control). In most patients using hydroxychloroquine, a shedding of SARS CoV-2 nasopharyngeal viral transport was observed within three to six days, a value much lower than that observed in another study in China, carried out by [15] that showed a decrease of viral transport around twenty days. In addition, a better outcome was observed when associated to azithromycin. Through this study, researchers pointed that hydroxychloroquine had 50% effectiveness in reducing viral load on day 7 and a potency of 85%. This study also showed that the effect of reducing viral load with hydroxychloroquine was significantly greater ($p<0.05$) in symptomatic patients compared to asymptomatic patients with COVID-19 [16]. However, this study presents bias in the methodology. Of the 26 patients who started treatment, six were discharged, 3 died (only 20 patients registered in the study). In addition, it was not a randomized controlled trial and the method used for diagnosis and monitoring of cases was not suitable - it was performed using a nasopharyngeal swab, which has a sensitivity of approximately 66% for PCR of SARS CoV- 2, sensitivity considered low when compared to another method of collecting material such as bronchoalveolar lavage, which has a sensitivity of approximately 95% for SARS CoV-2 [17].

In contrast, another study, also carried out in France, obtained contradictory results when using the same dosage regimen reported by Gautret and colleagues (2020). Eleven patients entered the study, with a mean age of 58.7 years (range 20-77), of which 8 had associated comorbidities. Of these, 10 patients had a fever and received nasal oxygen therapy. On the fifth day, one patient died and two others were transferred to the ICU. One patient had hydroxychloroquine and azithromycin interrupted due to QT prolongation. 5 to 6 days after starting treatment, eight out of ten patients still had their PCR positive for SARS CoV-2. In these results, the sample was very small, therefore, they are not consistent to evidence clinical factors that prove the benefit or harm of chloroquine for COVID-19 [18]. However, a large study was carried out by Mehra and colleagues (2020), with 96,032 patients that tested positive for SARS CoV-2 in 671 hospitals across 6 continents, between December 20th, 2019 to April 14th, 2020. In that study, an attempt was made to eliminate all bias contained in previous studies, such as age, sex, race or ethnicity, body mass index, underlying cardiovascular disease and its risk factors, diabetes, underlying lung disease, smoking, immunosuppressed condition and initial disease severity. Comparisons were also made between the control group and the use of hydroxychloroquine or chloroquine, in association or not with macrolides. A large increase in mortality was observed in the non-control groups, in addition to an increase in the frequency of ventricular arrhythmia, not associated with other risk factors. The data shown here in relation to the benefits are still insufficient and all have some bias, making it impossible to directly and clearly associate any advantage in relation to its use for COVID-19. Regarding the results obtained in the review of the effectiveness of these drugs for the treatment of COVID-19, the current conclusion is that the use of hydroxychloroquine and chloroquine in patients with COVID-19 should not be performed, since the evidence does not demonstrate benefits that justify its use. WHO, on May 25th, 2020, implemented a temporary pause in its tests through Trial Solidarity and will carry out a review of the studies by the Data Safety Monitoring Board, however other studies will continue. These actions were taken due to the great increase in risks of ventricular arrhythmias and mortality, which, as demonstrated in the study with more than ninety thousand patients with COVID-19, are directly associated with the use of these drugs.

Ritonavir and lopinavir

Ritonavir and lopinavir are antiviral drugs used in antiretroviral therapy against HIV and as proteases inhibitors, may act in a stage of the viral replication of SARS CoV-2 [19]. A study published on March 18th, 2020, randomized, controlled and open with 199 patients, was carried out by Cao and colleagues (2020) [20], in order to test the effectiveness of these antiretrovirals for COVID-19. Of these patients, 99 treated with ritonavir-lopinavir (half lopinavir and the other half ritonavir) and 100 patients received standard control treatment, all with previous low O_2 saturation, less than 94%, due to SARS CoV-2. Only 1 patient needed invasive ventilation at the beginning of the study. Mortality, clinical improvement and percentage of viral RNA were the same for both groups, showing no efficacy or benefits for the use of ritonavir-lopinavir. However, they noted that serious adverse events were more associated with control cases. After a review by Dalerba and colleagues [21] published in the same journal on May 5th, 2020, the study was considered statistically insufficient to demonstrate this negative result for treatment with ritonavir-lopinavir, suggesting a lower overall mortality (19% ritonavir-lopinavir and 25% standard treatment) and minor serious adverse effects (20% ritonavir-lopinavir and 32% standard treatment). In addition, it was observed that the population treated with ritonavir-lopinavir had serious illnesses with 22% overall mortality, and 14% of them were unable to continue treatment due to adverse effects, which may have contributed to the results of Cao and colleagues (2020). Thus, the results do not support the conclusion that lopinavir-ritonavir is ineffective. This combination of drugs has a well-known safety profile and *in vitro* data indicate potent activity against SARS CoV-2. Therefore, more data needs to be collected to discover the direct effect of lopinavir-ritonavir on the treatment of COVID-19 [22].

Remdesivir

Remdesivir was originally developed for the treatment of a disease caused by the Ebola virus, but had not yet been approved for clinical use. It is a broad-spectrum antiviral drug that acts by blocking viral RNA polymerase, which inhibits the formation of new viruses in general, and has also been shown to inhibit SARS CoV-2 *in vitro* and MERS-CoV *in vivo* (another virus of the *coronaviridae* family) in animal models, receiving authorization from the US Food and Drug Administration (FDA) for emergency use in patients with severe COVID-19 [23]. In a cohort study conducted between January 25th, 2020 and March 7th, 2020 by Grein and colleagues [24], 61 patients with confirmed SARS CoV-2 infection and oxygen saturation below 94% in ambient air were included. The median age of these patients

was 64 years and 75% were men. Remdesivir (200 mg) therapy was established on the first day and 100 mg on the remaining 9 days (10 days or less), intravenously. In this study, 8 patients were excluded due to lack of post-treatment data or error at the start of dosing, with 53 patients remaining (22 in Europe or Canada, 22 in the United States and 9 in Japan), in which 68% had clinical improvement with the use of remdesivir, while 15% worsened. Of the 30 patients who received invasive mechanical ventilation, 17 (57%) were extubated and 3 of the 4 patients (75%) who received Extracorporeal Membrane Oxygenation (ECMO) stopped receiving it. Seven (13%) patients died using remdesivir, 6 from the group that was using invasive ventilation. A total of 32 patients had adverse effects, with 12 patients having serious adverse effects. The most common adverse events were increased liver enzymes, diarrhea, skin rash, renal failure and hypotension, which are more common in patients over 70 years of age and using invasive ventilation. The researchers considered the treatment with remdesivir to be more promising than the treatment of ritonavir-lopinavir performed by Cao and colleagues (2020). Evaluation of this study is still limited due to the short duration of the follow-up, absence of control patients, small cohort size and other missing data, in addition to the 8 patients removed from the study. Aditional analysis was performed in Taiwan by Chen-Yang and colleagues (2020) based on the study by Grein and colleagues (2020). A control group was included, correcting the error of the original study, which shows that people not treated for remission can also be discharged. In this study, clearer points are also evaluated, such as the possibility of discharge and death and not only criteria for improvement and worsening. The risk status of these patients was classified as low (no use or low oxygen supply), medium (non-invasive ventilator with high oxygen supply) and high risk (ECMO and invasive ventilator). The use of remdesivir for 28 days led to a statistically significant reduction of 29% in relative mortality. With the follow-up time extended to two months, the mean time to discharge for the treated group was estimated at 5.5 days, 16.5 days and 29.5 days for patients with low, medium and high risk status respectively, which is approximately half the average time when compared to the control group. It was also inferred by the researchers the possibility of using remdesivir as a prophylactic for influenza, however there are still no studies that prove this possibility. Chen-Yang and colleagues (2020) believe that this study could serve as a basis for a future large-scale randomized controlled study. Therefore, this study demonstrated the possibility of remdesivir in reducing the sequelae of COVID-19, in addition to accelerating its recovery, and may even decrease the transmission time, reinforcing the results found by Grein and colleagues (2020). On May 12th, 2020, a systematic assessment by Davies and colleagues on the benefits and risks in the treatment of COVID-19 with remdesivir, suggested that there is a favorable benefit in this treatment. Despite this, the review by Davies and colleagues (2020) [25] clarify that it is important to note that remdesivir is currently not scientifically approved for use under any conditions and its safety profile has not been fully characterized, in addition to the fact that there are not yet enough studies to prove its efficacy in the treatment.

Heparin

Heparin mediates its anticoagulant activity when interacting with antithrombin and thus inhibits the activity of thrombin and factor Xa [26]. The importance of anticoagulants in the treatment of COVID-19 arose when observing the presence of pulmonary microthrombi in the dissection of a patient who had severe COVID-19, and then it was suggested that coagulopathy in this infection could be associated with mortality, being observed high D-dimer values. Coagulopathy is believed to occur due to the exacerbated systemic inflammatory response present in this infection, which can cause endothelial dysfunction and increased procoagulant activity, compromising pulmonary gas exchange [27]. Therefore, it is possible that heparin is effective against COVID-19 for reasons that go beyond anticoagulation, such as its anti-inflammatory and antiviral function [28]. Liu and colleagues (2020) [29] in a review, reported evidence that suggests that heparin molecules may interact with the SARS CoV-2 spike protein to prevent viral binding to host cell receptors. In addition, these heparin fragments can interact with chemokines and Damage-Associated Molecular Patterns (DAMPs), thus carrying out an anti-inflammatory function, effects seen as beneficial against COVID-19. In a study that lasted 28 days by Tang and colleagues (2020) [30] with 449 patients with severe COVID-19, 99 patients received heparin (mainly low molecular weight, LMWH) for 7 days or more. The use of heparin in this study was due to the risk of patients' disseminated intravascular coagulation, although its efficacy and safety for these cases have not been validated so far. In the study, the mortality of these patients during hospitalization was assessed, including the risks of coagulophilia due to medication. The authors noted lower mortality in patients using LMWH compared to non-anticoagulated patients and concluded that the use of the drug could be associated with a better prognosis.

On the other hand, Llitjos and colleagues (2020) [31] used a systematic screening strategy for Venous Thromboembolism (VTE) in patients with severe COVID-19 in the Intensive Care Unit (ICU). The study was carried out from March 19th, 2020 to April 11th, 2020, including 26 patients (18 received therapeutic treatment and 8 received prophylactic treatment). The incidence rate of VTE was 69% in these patients. Pulmonary Thromboembolism (PTE) diagnoses were made in 23% of these patients. In addition, unexpectedly, it was found that VTE occurred even in anticoagulated treated patients, emphasizing the thrombogenicity of COVID-19. It is important to highlight that, in addition to being infected with COVID-19, patients already had thromboembolic risks, such as: previous history of hypertension (22 patients), high Body Mass Index (BMI) (median 30.2 kg/m^2), besides the fact that they were hospitalized. In a series of cases published in Brazil and conducted by Negri and colleagues (2020) [32] a significant improvement in oxygen exchange and symptoms was noted in response to therapeutic anticoagulation with heparin in patients with COVID-19. The therapeutic dose used varied according to the patient's clinical severity. 27 patients admitted to the Hospital Sírio-Libanês were included. Of these, one was transferred to another hospital on the fourth day and his follow-up data was lost. 22 were discharged around 11 days. Nine patients had to go to the ICU, and after an average of 13 days, 6 were transferred to the infirmary. No deaths or complications were observed due to the use of anticoagulants during this study. In short, there is great support for the use of LMWH in patients with COVID-19. In a letter published in the Journal of Thrombosis and Haemostasis on April 23th, Thachil and colleagues (2020) [33] highlights the need to consider thromboprophylaxis in all patients who require hospitalization for COVID-19 and points out that there is no evidence that the standard prophylactic dose is insufficient, despite some studies suggesting an increase in the dose to prevent VTE. In addition, the authors report on the preference for using LMWH over Unfractionated Heparin (UFH) in patients without acute renal impairment. Kollias and colleagues (2020) [34] suggest, from a review, that anticoagulant therapy may

improve the prognosis for COVID-19, due to the risk of the disease being complicated by coagulopathy. According to Kreuziger and colleagues (2020) [35] the recommendation from the American Society of Hematology is that all adults hospitalized with COVID-19 should receive pharmacological thromboprophylaxis with LMWH and, in patients in whom anticoagulants are contraindicated, the use of mechanical thromboprophylaxis.

Tocilizumab

As described by Mehra and colleagues (2020) one of the major concerns with COVID-19 is characterized by its exacerbated inflammatory response that produces a "cytokine storm". It was also observed that interleukin-6 (IL-6) plays an important role in this inflammation and the blocking of its receptor by tocilizumab (TCZ - an IL-6 receptor blocker) has become an additional possibility for treatment [36]. A retrospective observational study of patients infected with COVID-19 and treated with TCZ was conducted between January 27th to March 5th, 2020 by Luo and colleagues [37], with patients from Tongji Hospital in Wuhan, China. The study was conducted with 15 patients, 12 men and 3 women with a mean age of 73 years (62-80), and ten of them had one or more cerebrovascular or endocrine comorbidities. Two patients had a moderately severe clinical conditions, six in a severe condition and seven in a very severe condition (the clinical criteria for this division was not informed). The dose of TCZ was between 80 mg to 600 mg, five patients received more than one dose. In addition to TCZ, eight patients also received methylpredinisone. All patients had high IL-6 and C-Reactive Protein (CRP). During treatment, a decrease in CRP was observed in all patients over the course of the days, although 7 of them who were in a very serious condition did not reach normal levels (staying ~ 20 times above). Among 4 patients classified as very severe and 1 severe, 2 had worsening of the disease and 3 died. In common, they all had an increase in IL-6 dosage and made use of methylpredinisone therapy and only one dose of TCZ. The other patients had clinical stabilization. The study suggests that a single dose of TCZ may not be enough, although the combination with glucocorticoid may have influenced it. However, they suggest that repeated doses of TCZ may improve the prognosis of the disease, with subsequent doses reduced (due to its long half-life and saturation of IL-6 receptors) and according to the patient's elevation of IL-6. The authors reported that there are limitations in these data for conclusions such as the small sample. Reinforcing the benefits of TCZ, another retrospective study was conducted by Xu and colleagues (2020) [38] with 21 patients diagnosed with severe COVID-19 (18 men and 3 women) in China. The dose used was 4 mg to 8 mg per kilo of the patient's body mass (the recommended dose being 400 mg/kg to a maximum of 800 mg/kg). Of these, eighteen received TCZ once, and three received a second dose due to fever. In addition to TCZ, all patients followed the standard therapy protocol of the time for COVID-19, with lopinavir, methylprednisolone, oxygentherapy and other analgesics. After starting treatment with tocilizumab, most patients had improved respiratory function to some degree with stable oxygen saturation. All patients recovered by the end of the study, with twenty of them in the first two weeks. No serious adverse effects have been reported due to the use of TCZ in any patient. With the data obtained from these 21 patients, Xu and colleagues (2020) indicate that TCZ therapy is effective in reducing COVID-19 mortality and suggest its use in cases with serum IL-6 content greater than 20 pg/ml. On the other hand, Radbel and colleagues (2020) [39] presented a report of two patients who received treatment with TCZ due to the cytokine release syndrome by COVID-19 and still evolved to secondary hemophagocytic lymphohistiocytosis. Despite the sample limit, the authors warn that further studies are needed to report the safety and efficacy of TCZ treatment for these patients with COVID-19. It is important to make it clear that all studies with TCZ have small sample size, which limits conclusions regarding the efficacy and risks with its use, and that, despite its promising results, the drug could act as an adjunct to treatment and not as monotherapy.

Carmostat mesylate and nafamostat

Camostat mesylate and nafamostat are serine protease inhibitors that can act by inhibiting TMPRSS2, a protease that primes the SARS CoV-2 spike protein and facilitates its entry into the cell through the fusion of the viral membrane with that of the cell host [40]. Camostat mesylate is considered a safe drug, used in Japan for acute symptoms of chronic pancreatitis since 1980 [41]. Due to its mechanism of action, the drugs were made available for studies against SARS CoV-2, and their effectiveness in cell cultures was proven to inhibit membrane fusion and cell infection *in vitro* [42]. Another study carried out with mice infected with SARS CoV, with 60% recovery, suggests the potential use of the drug in COVID-19, but reinforces the fact that there are still no clinical studies proving the reduction of viral spread in humans (UNO, 2020) [43]. As there are no clinical trials with humans, its effectiveness as a treatment for COVID-19 is still not relevant. However, these are drugs with known side effects and therapeutic dose, with potential to treat patients with severe COVID-19.

Glucocorticoids

Glucocorticoids are anti-inflammatory drugs that work by suppressing inflammation mechanisms. Due to the pandemic, these drugs were administered empirically in serious complications of COVID-19, with the justification of suppressing the excessive inflammatory activity of the disease [44]. Despite its empirical use, some studies support it, while others have demonstrated evidence against the use of these glucocorticoids. Wang Y et al. conducted a study with 46 patients with a mean age of 54 years (48-64) in the city of Wuhan. Of these, 26, in addition to standard therapy (antivirals, oxygen therapy and others, according to demand), used methylprednisolone at a dose of 1 g/kg to 2 g/kg for 5 to 7 days and 20 used only standard therapy. It was observed that patients who received methylprednisolone had a faster improvement in SpO_2 and a shorter average time of use of supplemental oxygen therapy (8.2 days) compared to those who did not use it (13.5 days), in addition to a reduced pulmonary inflammation. In another study, Zhou et al. [45] concluded that the use of moderate doses of glucocorticoids (160 mg) associated with immunoglobulin (20 mg), in the short term, can be effective to avoid the continuous deterioration caused by severe COVID-19, taking into account that in its study 4 out of 10 patients with this complication recovered and were discharged. On the other hand, a retrospective study conducted in February 2020, followed 138 patients for a month, with 45% of them using glucocorticoids and no effective results were observed [46]. In addition, Zha and colleagues (2020) [47] reviewed medical records of patients hospitalized with COVID-19, between January 24th and February 24th, 2020. There were 31 patients, with a median age of 39 years (32-54), divided into 20 men and 11 women, with few associated comorbidities. Of these, 11 patients used 40 mg methylprednisolone, once or twice a day, for 4-5 days, in addition to standard treatment. It is important to note that these 11 patients had a higher PCR. It was observed that patients who

used glucocorticoids showed worsening of clinical symptoms and also a higher inflammation rate. In addition, there was no decrease in hospitalization length of time, even in patients with milder symptoms with the use of the drug. The bibliography is different and the evidence does not support the use of corticosteroids in the treatment of COVID-19. Chen and colleagues (2020) recommend that, if necessary, the use of glucocorticoids should be at a minimum dose and for the shortest possible time. Russell and colleagues (2020) [48] in a review with 574 patients with COVID-19 treated with glucocorticoids, suggested that there are no reasons for the use of these drugs in the treatment of COVID-19 infection, highlighting a greater chance of being harmed by the drug and that, therefore its effectiveness is controversial. As there is no evidence related to its benefit for complications of COVID-19, WHO also does not advise its use for suspected cases of COVID-19 and viral pneumonia, note published on March 13th, 2020 (WHO, 2020) [49].

Ribavirin

Ribavirin is a guanosine analogue drug that interferes with the replication of RNA and DNA viruses. Through this mechanism, ribavirin can bind to the SARS Cov-2 RNA-dependent RNA polymerase and inhibit the synthesis of new viruses [50]. The suggestion for administration of ribavirin is by intravenous infusion with 500 mg for adults, 2-3 times a day, in combination with Interferon-α (IFN-α) or lopinavir / ritonavir [51]. In a study carried out in Hong Kong hospitals by Hung and colleagues (2020) [52] a triple combination of interferon beta-1b, lopinavir / ritonavir and ribavirin was given to patients included in a randomized clinical trial, between 10th February and 20th March, 2020. A total of 127 patients participated. For the combination group, therapy was performed during the 14-day period with 400 mg of lopinavir, 100 mg of ritonavir and 400 mg of ribavirin every 12 hours, in addition to 8 million international units of interferon-1beta every other day, with 3 doses in total. In the control group, the dosages were the same, without the use of interferon-1beta and ribavirin. Better results were observed in the group that received the combination, both in time of clinical improvement, as in viral shedding and hospital stay. Despite the positive results in this study, it did not involve a placebo group, demonstrating the possibility that the results may be related to interferon-1beta.

Therefore, even though ribavirin has good antiviral activity against SARS CoV-2 *in vitro* tests, and has been used previously in the treatment of SARS and MERS CoV, there are still several challenges in conducting controlled clinical studies in an outbreak environment such as the current one to include its use as part of the therapeutic plan for COVID-19. One of the limitations would be to create retrospective studies with monotherapy for COVID-19. Even so, controlled clinical studies are already underway to allow a prospective assessment of their effectiveness [53].

Drugs that alter ACE-2 levels Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), Renin-Angiotensin Receptor Blocker (BRA), Angiotensin-Converting Enzyme Inhibitor (iACE) and thiazolidinediones

Drugs are used worldwide on several medical occasions, such as analgesics, antipyretics, anti-inflammatory, antihypertensive and for diabetes control. In addition to their functions in their respective classes, they have been recognized as drugs that can increase the expression of ECA-2, suggesting that they could, hypothetically, facilitate infection by SARS CoV-2 [54]. In a retrospective cohort review, carried out by Santos and colleagues (2020) [55] between 20th January and 15th February, 2020, 406 patients with a diagnosis of COVID-19 and with previous exposure to a drug that increases the expression of ECA-2 (BRA, iECA, NSAID or thiazolidinediones) were selected, among them 112 had some cardiovascular disease. Of these 112 patients, 22 used ARB / iECA, and the proportion of severe and mild patients among those who used these drugs was the same as those who did not. The difference of risk in mortality between the two groups was 0.0374 and the relative risk was 1.2587. In this study, the authors reported that there is no evidence of a higher risk or worsening in the prognosis of COVID-19. It is important to maintain a skepticism regarding the cause-consequence when relating only the theoretical mechanisms of action of each drug, since in the organism its action may not be the expected result [56]. The evidence is not yet conclusive. There is no direct evidence to corroborate the increase in mortality in patients using NSAIDs, such as ibuprofen [57]. Information regarding drugs that interact with the renin-angiotensin system is also insufficient to assess increased risk and its abrupt withdrawal may result in hemodynamic instability [58], and the same applies to thiazolidinediones. No current evidence supports any modification for the treatment of patients with the use of ACE inhibitors, BRA or thiazolidinediones, and any change may jeopardize the patient's health status [59-64].

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