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THE USE OF ANTIPARASITIC DRUGS AS A TREATMENT FOR COVID-19: A NARRATIVE REVIEW

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ABSTRACT

Objective: Describe research related to the use of antiparasitic drugs as likely treatment in COVID-19 based on scientific literature. **Methods:** This is a literature review that uses two platforms as a database: Pubmed and BIREME. Were included in this study twelve published articles, from 2019 to September 2020, which referred to or were related to the use of antiparasitic drugs as a therapeutic alternative to COVID-19. **Results:** The antiparasitic drugs ivermectin, hydroxychloroquine (HQC), and nitazoxanide (NTZ) were the main drugs extensively studied as therapeutic alternatives for SARS-CoV-2. Ivermectin exhibited a 5000-fold reduction in SARS-CoV-2 RNA over a 48h period, at a concentration of 5µM. While HQC was able to block the entry of SARS-Cov-2 into Vero cells previously treated with 50µM. In addition, NTZ, presented an average inhibition concentration (EC50) of 2.12 µM. The mechanisms of anti-SARS-CoV-2 actions of all the drugs mentioned are not yet fully elucidated. However, it is known that the antiviral potential may be related to the inhibition of essential viral proteins (ivermectin), blockade of interaction in virus-host (HTZ), and immunosuppressant (NTZ). **Conclusion:** The use of antiparasitic agents for the treatment of SARS-CoV-2 have shown promise. However, it is necessary to further investigate the efficacy of the drugs mentioned in this study, to obtain more satisfactory results, seeking to avoid adverse effects on patients, and ensuring safety for them.

Keywords: Drugs replacements. Antiparasitic. COVID-19.

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INTRODUCTION

SARS-CoV-2 is a virus of the family coronaviridae, first described in 2019, responsible for Coronavirus Disease 2019 (COVID-19), an air-borne disease that has clinical characteristics ranging from fever, dry cough, discomfort, rashes, difficulty in breathing, chest pain and loss of speech or movements (1). These symptoms can be classified as mild, moderate or severe morbidities, and there are asymptomatic cases. Because of this, many studies have been conducted to find forms of therapy and/or prophylaxis (2-4). However, despite efforts, there are still no specific vaccines or drugs to combat this new disease (1). Alternative solutions, drugs used to combat other diseases, were analyzed *in vitro* and a positive return was observed from some antiparasitic agents, such as ivermectin, hydroxychloroquine and nitazoxanide (4). It is worth noting that experiments performed outside the organism may not exhibit the same behavior when performed on it, but it is still possible to improve the tests that demonstrate good results *in vitro* (5). The so-called “drug repositioning” is a simple technique that uses the analogy between drugs for submitting a certain drug to fight a disease for which it was not created, but which has more general characteristics that can encompass the new coronavirus (6). Based on this strategy, tests with antiparasitic drugs were started to combat a parasitic disease, that is, COVID-19.

OBJETIVE

Describe research related to the use of antiparasitic drugs as likely treatment in COVID-19 based on scientific literature.

METHODS

This review was drawn from a survey conducted in two different databases - PubMed and BIREME; using as search strategy a combination of key words in Portuguese, “Ivermectina”, “Hidroxicloroquina”, “Nitazoxanida”, “Antiparasitários” and “COVID-19”; as well as in English “Hydroxychloroquine”,

“Ivermectin”, “Nitazoxanide”, “Antiparasitic” and “COVID-19”.

After carefully reading each abstract articles published from 2019 to September 2020 were selected that referred to, or were related to, the topic covered in this article. Articles that were repeated in the different bases or clearly did not correspond to the purpose of this study were excluded. Altogether, twelve articles that met the study criteria were selected.

RESULTS

After reading and using the inclusion and exclusion criteria, 12 articles were included in this review. Among the compounds used as new therapeutic and/or prophylactic alternatives to COVID-19, the antiparasitic ivermectin, hydroxychloroquine and nitazoxanide obtained promising results *in vitro*. Ivermectin is a safe antiparasitic drug that has a broad spectrum of action on nematodes, ectoparasites and under single-stranded RNA viruses such as Dengue virus, Zika virus and Yellow fever virus (7). Because of this, several researches have observed the potential of ivermectin against SARS-COV-2 (8). In a recent *in vitro* research, cells of the Vero / hSLAM lineage infected by SARS-CoV-2, exhibited a 5000-fold reduction in viral RNA over a period of 48 hours, when exposed to 5 μ M of Ivermectin (9). The mechanism of action of ivermectin under SARS-CoV 2 is not yet elucidated. However, it is believed that ivermectin exhibits effects similar to those observed in studies with the Dengue virus and HIV, whereas ivermectin inhibited the nuclear import of viral and host proteins such as the integrase protein and the importin heterodimer (IMP) α / β 1, essential for virus survival and virulence (10,11). Regarding hydroxychloroquine (HCQ), it is a drug commonly used in malaria, but its action is also beneficial for the treatment of rheumatic diseases due to its anti-inflammatory effect (12). Because it is an effective drug in several diseases, studies have been started regarding its possible antiviral effect on SARS-CoV-2 (12-14). This medication has a mechanism of action

similar to that of chloroquine, responsible for changing the pH of acidic intracellular organelles, such as endosomes and lysosomes, which play a role in membrane fusion (13). A recent study carried out an *in vitro* assay with cells of Vero E6 lineage treated with 50uM HCQ for 1h, followed by exposure to SARS-CoV-2. As a result, it was determined that HCQ had an inhibitory effect on SARS-CoV-2, *in vitro*, preventing the virus from entering the cell in question (14). In France, researchers started a clinical study, in which some patients infected with the COVID-19 virus received a daily dose of 600 mg of HCQ and azithromycin depending on the patient's clinic. From this, it was evidenced that after 6 days there was a considerable decrease in the viral load in these patients (15). Despite studies with the drug, the effectiveness of HCQ treatment in COVID-19 has not been fully demonstrated, since HCQ can have significant side effects at high doses or when associated with some other medication (16). The other drug used in the search for anti-SARS-Cov-2 compounds was nitazoxanide (NTZ), an antiparasitic medication that demonstrates broad-spectrum antiviral activity for the treatment of viruses such as hepatitis B and C, rotavirus and influenza viruses (17). Recently NTZ and its metabolite tizoxanide, has demonstrated potential antiviral effect *in vitro* against SARS-CoV 2, confirmed by a study carried out with Vero E6 cells in one half maximal effective concentration (EC50) of 2.12 μ M (18,19). In addition, NTZ has a bronchodilating effect and a suppressive role in the production of cytokines in peripheral blood mononucleated cells, with emphasis on tumor necrosis factor alpha (TNF α) and interleukins (IL-2, IL-4, IL-5, IL- 6, IL-8 and IL-10), such characteristics may become beneficial in relieving the symptoms of COVID-19 (20).

DISCUSSION

The current coronavirus outbreak is considered a serious public health problem worldwide (21). The main problems visualized are the rapid spread of the disease, induction of morbid

conditions to infected individuals, and effective absence against SARS-CoV-2 (20). Thus, drug reuse campaigns can reduce production costs and the time set for the development of new medicines (20). According to covid-trials.org (22,23), there are about 342 ongoing studies using HQC as an alternative therapy for COVID-19, and 47 associated with ivermectin. It is important to note that no ongoing study using NTZ was found on this platform cited. Among the antiparasitics cited in the present study, a mean lethal concentration ranged from 0.72 μ M, 2 μ M and 2.12 μ M to hydroxychloroquine, ivermectin and NTZ in studies carried out *in vitro*, respectively. Although the results of *in vivo* studies are still scarce, the data published so far have low reliability due to the low number of samples and variables that are not properly analyzed. Concerning the probable mechanisms of anti-SARS action, the broad spectra of the molecules can help directly, by inhibiting essential virus proteins and blocking the virus-host membrane interaction, and/or indirectly, through immunological modulation and anti-inflammatory activity (10-17). Recent studies using doses of ivermectin ten times higher than those approved by the FDA demonstrate that the compound in question does not show good anti-SARS-CoV-2 activity (9). On the other hand, there is an overuse of HCQ in several studies, observing a better prognosis of those hospitalized in severe phase, diagnosed with COVID-19. The indiscriminate use of HCQ can cause harmful effects to humans. Therefore, an association between the compounds can increase the effectiveness and reduce probably associated effects, since the doses are reduced, and the drugs are spared (24). Thus, there is evidence that HCQ and ivermectin may be able to act synergistically. HCQ is believed to have the role of blocking the virus from entering cells, while ivermectin reduces viral replication (21). Another study using HCQ and azithromycin to change the viral load in less time; however, further investigations are required to observe those likely to have controversial effects (15).

Before the above, although there are several studies developed, the literature, in general, is still scarce and divergent as to the use of antiparasitic against the new coronavirus. In addition, clinical tests use in vivo tests with a greater number of and analysis time are examined for a more reliable analysis of the effectiveness of drugs against COVID-19.

CONCLUSION

Studies on the use of antiparasitic drugs for the treatment of SARS-CoV-2 have shown promising, however, further research is needed on the effectiveness of ivermectin, hydroxychloroquine and nitazoxanide, in order to provide more satisfactory results, seeking to avoid adverse effects on patients and ensuring safety for them.

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