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USE OF IVERMECTIN DRUG FOR TREATING COVID-19: REVIEW ARTICLE

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ABSTRACT

Covid-19, formerly known as pneumonia or 2019-nCoV disease, emerged as a global public health crisis. Severe acute respiratory syndrome (SARS) has spawned an increasing number of coronavirus-associated illnesses that have spread from animals to people. As a result of the rising number of sick people, several people started using drugs that presented at least a small effect against the symptoms of the disease. Among them, there is Ivermectin: an antiparasitic that obtained favourable results in its first in vitro experiments to combat the new Coronavirus. In this way, the objective of the study is to present the possible therapeutic action of Ivermectin against COVID-19 and its long-term effects. This study is a literary review of publications made between 2019 and 2020 with the keywords "coronavirus infection, pharmacological treatment and Ivermectin." It culminated in the following results: The anti-viral potential of Ivermectin against various RNA viruses is due to the ability to inhibit nuclear transport mediated by α / β importin, which blocks the nuclear transport of viral proteins. Several RNA viruses depend on Impα / β1 during the infection process, so SARS-CoV-2 being an RNA virus, must have a similar mechanism of action. However, it is essential to consider that the fact that this drug has activity in vitro is not decisive to ensure success in vivo treatment. Therefore, it can be concluded that despite the promising results in vitro of Ivermectin, it is necessary to carry out more controlled studies (preclinical and clinical) to define the reliability of this therapy in vivo and to avoid damage to the user.

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INTRODUCTION

COVID-19, known previously as 2019-nCoV pneumonia or disease, has emerged as a global public health crisis, joining severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS) in a growing number of corona virus-associated illnesses which have jumped from animals to people (Smith, 2020). Symptoms of the disease range from mild (like flu), to severe cases, with life-threatening pneumonia (Chaves, 2020). The global situation is dynamically evolving; on 30 January 2020, the World Health Organization declared COVID-19 as a public health emergency of international concern (PHEIC), and on 11 March 2020, it was declared a global pandemic (Smith, 2020).

The transmission of the virus occurs through droplets of saliva, sneezing, coughing or physical contact with an infected individual. This disease mainly affects the elderly and the immunosuppressed. Therefore, until the present time, the main ways of prevention are social isolation and quarantine, while there is not safe and effective therapeutic schemes (Sharun, Khan, 2020). With the increasing number of sick, people started to use any drugs that could help with the symptoms of the disease. Medicines that, for the most part, are not aimed at treating the illness or killing the virus. Nowadays, there is not completed research about the efficacy of antiparasitic and antibacterial drugs for the cure of COVID-19. Therefore, it is necessary to inform the effects of medications and their likely consequences. Among several medicines found in the early

stages of studies, there is Ivermectin (Sharun, Khan, 2020). An effective drug to exterminate worms and parasites, and which obtained favorable results in its first experiments when fighting a new coronavirus carried out by Monash University in Australia (Tay, 2020). The research followed succeeding, especially after the doc published in the journal Antiviral Research, which states that the researchers infected cells with the new Coronavirus and thenadded Ivermectin. In the first 24hours,there was a 93% decreaseinviral genetic material; after 48hoursofstudy, the ratereduced to 99,9%. However, only these studies are not enough to determine if results would be positive also in humans (Tay, 2020). Hence, the objective is to present a therapeutic action of Ivermectin against Coronavirus and its long-term effects.

METHODOLOGY

This study is a literature review, based in articles published among 2019 and 2020**.** The database used to this search were: Science Direct, Cochrane Library, PubMed and Nature. The terms "coronavirus infection, pharmacological treatment, parasitology and Ivermectin" were used. Furthermore, we have done a search in medicine leaflets about the pharmacological action of Ivermectin and the local activity. As inclusion criteria, the articles would approach the anti-viral response of Ivermectin, show the invasion mechanism of Sars- CoV-2, introduce the use of Ivermectin in the treatment of Covid-19. As exclusion criteria, the articles would not approach: be experience reports and surround a combined use of Ivermectin and other drugs.

THEORETICAL REFERENTIAL

General aspects of Coronavirus: Human coronaviruses are enveloped viruses, with a morphology characterized by large projections on the surface, suggesting a crown shape. The virus that causes COVID-19 is called coronavirus 2 of the severe acute respiratory syndrome (SARS-CoV-2). Its genome consists of a strand of positive polarity RNA, causing the synthesis of mRNAs to occur from a discontinuous transcription of negative polarity RNA complementary to the genome (Chaves, 2020). The montage of the new viruses occurs anchored to the intracellular membranes, and the release happens through budding through the secretory pathway. There are many similarities between SARS-CoV-2 and SARS-CoV-1, both with protein S (spike) inserted in the viral envelope, which has a strong affinity for cells that express the Angiotensin-Converting Enzyme 2 (ACE-2), that is, epithelial cells of the pulmonary alveoli, increasing the transmission through small aerosols (Chaves, 2020).From this, pro-inflammatory cytokines and chemokines are generated, attracting monocytes, macrophages and T cells to the infection site. As a result, additional inflammation occurs, establishing a pro-inflammatory feedback loop (Jhimli Dasgupta, 2020).

General aspects of Ivermectin: The Ivermectin is a broad-spectrum antiparasitic that causes hyperpolarization and consequent muscle paralysis. It happens when the drug gets into chloride channels, via glutamate, in the nerves of invertebrates, with residual action in the gabaergic pathway. It is indicated for the treatment of filariasis, ascariasis, onchocerciasis, scabies and pediculosis (Smith, 2020). To a better understanding of the use of this parasiticide and its possible anti-viral action, it is crucial to know deeply its pharmacodynamics, pharmacokinetics and laboratory findings related to the use of the medication.

Pharmacodynamic: Ivermectin immobilizes the worms inducing tonic paralysis of the muscles. Paralysis is mediated by the potentiation and direct activation of the Cl-channels avermectin-sensitive, controlled by glutamate. These channels are present only in the invertebrates nerves and muscle cells, once potentiated, cause an increment of permeability in the cell membrane to chloride ions, with hyperpolarization of nerves or muscle cells, resulting in paralysis and death of the parasite (Revectina, 1999). Compounds in this class can also interact with mediation channels by other neurotransmitters such as gamma-aminobutyric acid (GABA). The lack of receptors with high affinity for avermectins in cestodes and trematodes may explain why these helminths are not fragile to Ivermectin. In cases of *Oncocerca* infestations, Ivermectin affects developing larvae and blocks the exit of the microfilariae from the uterus of adult worms. Its activity against *Strongyloidesstercoralis* is limited to the intestinal stages (Revectina, 1999). The selective activity of compounds in this class can be attributed to the fact that in mammals, ion channels mediated by GABA are only present in the brain, and Ivermectin does not cross the blood-brain barrier in typical situations. Besides, mammalian nerves and muscle cells do not have Cl- channels controlled by glutamate (Revectina, 1999).

Pharmacokinetics: The metabolization is hepatic, and the highest tissue concentration is found in the liver and adipose tissue. Shallow levels are found in the brain, despite the drug's liposolubility; it happens because Ivermectin does not cross the blood-brain barrier of mammals in typical situations. Ivermectin or its metabolites are excreted almost exclusively in the feces in an estimated period of 12 days, with less than 1% of the administered dose excreted in the urine in conjugated or unchanged form (Revectina, 1999).

Anti-viral potential: The Ivermectin's anti-viral action had been demonstrated in vitro against viruses as the HIV-1 (human immunodeficiency virus-1). It was identified as an inhibitor of the interaction between integrase protein and importin α/β1 heterodimer. As this heterodimer is responsible for import the integrase protein in the nucleus, the medicine in hibitsthe virus replication (Chaves, 2020). In one of the articles analyzed, the authors deduced that Ivermectin's nuclear transport inhibitory activity might be effective against SARS-CoV-2. It was based on studies about SARS-CoV proteins that revealed the importance of importin α/β1 to the virus in its infection mechanism. So, they performed in vitro tests to assess the possible action, and the results showed a decrease in viral replication. They hypothesize that this occurs by inhibiting the nuclear import of viral proteins mediated by importinα/β1, as demonstrated for other RNA viruses.So, they conclude the necessity of confirming this mechanism for SARS-CoV-2 infuture laboratory studies (Chaves, 2020). Ivermectin was previously found to inhibit flavivirus replication by specifically targeting the activity of non-structural 3 helicase (NS3 helicase) in vitro. It is a potent inhibitor of the yellow fever virus and a weak inhibitor of other flaviviruses. The broad-spectrum anti-viral potential of Ivermectin against several RNA viruses is due to its ability to specifically inhibit importin α/β-mediated nuclear transport, which in turn blocks the nuclear trafficking of viral proteins[5].
Several RNA viruses depend on Impα/β1 during the process of infection; therefore, SARS-CoV-2, as an RNA virus, is

expected to show a similar mechanism of action. The proposed anti-SARS-CoV-2 action of Ivermectin involves the binding of Ivermectin to the Impα/β1 heterodimer, leading to its destabilization and prevention of Imp α/β1binding to the viral proteins. This reaction prevents viral proteins from entering the nucleus and accomplishes the replicative process, according to Figure 1.

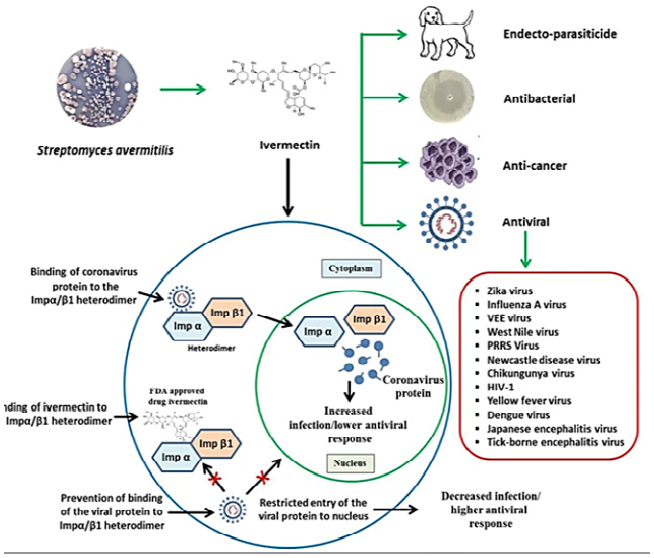

Figure 1. Potential modes of anti-viral actions of ivermectin

It is important to consider that the fact that a drug has activity in vitro experiments against some microorganisms is not decisive for ensuring success in vivo treatment.

DISCUSSION

Currently, research has turned to define how medications can act synergistically in the fight against Covid-19.Among the studies that have been promoted on the use of pre-available medications, Ivermectin has presented itself as a promising anti-viral. As shown before, Ivermectin acts impairing the replicative process (Centro de Estudos do Medicamento (CEMED), 2020). Its mechanism of action differs from medications such as hydroxychloroquine, which inhibits the entry of the virus into the cell. In addition, like any medicine, it is important to warn about the need for proper use of them, since the indiscriminate use of medication, without guidance from professionals in the area, can bring some health risks[4]. Therefore, institutions that use this therapy should be aware that the use of any of these drugs for Covid-19 is without a license and provisions for the legal protection of the institution and its professionals (Chaves, 2020). Furthermore, all studies emphasize the relevance of continuing research, seemed its reliability for use in humans is not fully defined yet.

With this in mind, some authors argued that until there was more information about the use of Ivermectin, it was preferable not to do it[4]. While others, support its use as a provisional measure until the development of an own vaccine or medication against Sars-CoV-2 (Sharun, 2020).

Conclusion

Based on the review carried out, it is concluded that faced with a critical situation, in which we consider the severity and high transmissibility of the virus, it is understandable the increasing use of several drugs as immediate protection. The absence of a vaccine or medication suitable for Sars-CoV-2 raised the importance of conducting numerous researches on pre-existing drugs on the market. Among them, Ivermectin was one of the drugs that gained prominence because from in vitro analysis, it was found that it has inhibitory effects on viral replication. Nevertheless, despite the promising results, it is relevant that governments continue to invest in scientific research in order to achieve conclusive results on the use of Ivermectin and other drugs against COVID-19 in humans. Preclinical controlled studies, and later clinical studies, are still essential to define the dose to be used in this situation, to prevent indiscriminate use and cause harm to the user.

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