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Mini Review

Ivermectin, a Drug to be Considered for the Prevention and Treatment of SARS-CoV-2 Brief Literature Review

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Abstract

On December 31, 2019, authorities in Wuhan City, Hubei province, China, reported 27 cases of acute respiratory syndrome of unknown etiology. On January 7, 2020, they reported that a new coronavirus (2019-nCoV) was identified as the possible etiology. Cases were rapidly reported in other Asian countries and progressively in other regions of the world. On 30 January 2020, the Emergency Committee convened by the Director-General of the World Health Organization (WHO), under the International Health Regulations (IHR (2005)), agreed that the outbreak of the new coronavirus (2019-nCoV) met the criteria for declaring a public health emergency of international concern. In February 2020 the new virus was named SARS-CoV-2. On 11 March 2020, COVID-19 was considered a pandemic, which has spread rapidly with high morbidity and mortality. The development of vaccines is still in progress, there are few alternatives with evidence of effectiveness, there is no experience with chemoprophylaxis at the population level, economic resources are limited, to acquire new drugs. In a recent *in vitro* study conducted in Australia, a 93% reduction in viral RNA present in cell cultures was observed within 24 hours when treated with Ivermectin. At 48 hours, a 99.8% reduction was observed in VERO-hSlam cell cultures treated with a single dose of Ivermectin after 2 hours of infection with CoV-2 SARS. This study showed that this single dose can decrease viral load by 99% in just 48 hours. The findings of this study in combination with its known safety profile suggest that Ivermectin deserves consideration as a possible SARS-CoV-2 antiviral.

Keywords: *Coronavirus; COVID-19; Ivermectin; SARS CoV-2; Treatment*

Introduction

On December 31, 2019, authorities in Wuhan City, Hubei Province, China, reported 27 cases of acute respiratory syndrome of unknown etiology [1,2]. On January 7, 2020, they reported that a new coronavirus (2019-nCoV) was identified as the possible etiology. Cases were rapidly reported in other Asian countries and progressively in other regions of the world [3,4]. On 30 January 2020, the Emergency Committee convened by the Director-General of the World Health Organization (WHO), under the International Health Regulations (IHR (2005)), agreed that the outbreak of the new coronavirus (2019-nCoV) met the criteria for a public health emergency of international concern [5]. In February 2020, the new virus was named SARS-CoV-2. On March 11, 2020, COVID-19 was considered a pandemic [5,6], which has spread rapidly with high morbidity and mortality. The development of vaccines is still in progress, there are few alternatives with evidence of effectiveness, there is no experience with chemoprophylaxis at the population level, and economic resources are limited for acquiring new drugs [7,8].

A recent *in vitro* study in Australia [9] showed a 93% reduction in viral RNA in cell cultures within 24 hours when treated with ivermectin. At 48 hours, a 99.8% reduction was observed in VERO-hSlam cell cultures treated with a single dose of Ivermectin after 2 hours of infection with SARSCoV-2. This study showed that this single dose can decrease viral load by 99% in just 48 hours. Treatment with ivermectin resulted in the effective loss of almost all viral material in 48 hours. It appears that the nuclear transport inhibitory activity of ivermectin may be effective against SARS-CoV-2. Overall, the findings of this study in combination with its known safety profile suggest that ivermectin deserves consideration as a possible antiviral against SARS-CoV-2. The entry of some RNA viruses into the nucleus of the host cell is facilitated by IMP (importins) proteins. Ivermectin has been identified as a potential inhibitor of the nuclear importation of viral proteins, mediated by one of these importins, the protein IMPα/β1. As the viral genome, the host cell nucleus, cannot be accessed, viral replication is not initiated, which is an important mechanism of action against SARS-CoV-2 [9-12]. Further studies with different protocols and clinical trials will be necessary to prove its efficacy in the proposed treatment in humans. This aspect motivated us to conduct a literature review with the aim of collecting updated information on ivermectin to promote its use in the prevention and treatment of SARS-CoV-2.

Origin and discovery of ivermectin

In 2009 the World Health Organization, the Bill Gates Foundation and the Carter Foundation declared it "the history of humanity's triumph over adversity", for having been able to eradicate onchocerciasis, which causes "river blindness" over such important diseases as AIDS, leprosy, malaria and dengue. Ivermectin, with more than 30 years of use in humans, was discovered at finales in the 1970s. In 1974 Omura's team isolated an organism from the soil of a golf course near the city of Ito and sent the samples to the MSD laboratories. William Campbell, a research veterinarian at Merck and Co.'s Animal Health Division, when evaluating soil samples sent by the Kitasato Institute in Japan in 1975 for possible agents of therapeutic value in animals, isolated avermectins, which proved to be surprisingly powerful against parasites, from a soil sample from a golf course in Japan [13,14]. Strains of *Streptomyces avermectinius* bacteria in the samples were shown to have strong activity against various intestinal parasites in mouse models. The compound responsible for this activity is called avermectin, a drug that is still being studied in other indications. Its safety is high; almost two billion doses have been given to humans with minimal side effects. It is excreted in the stool and is not nephrotoxic or hepatotoxic [13-15].

Action spectrum

It is the treatment of choice in AIDS patients, receiving HAART therapy for systemic strongyloidiasis and Norwegian scabies. It is used in children over two years of age or weighing more than 15 kilos. The dose is 200 micrograms/kg in oral form, 0.6% in drops (1 drop/kg of weight) and 400 micrograms/kg in topical form at 0.1% (0.4 cc/kg of weight). When Ivermectin was found to be safe and effective, Merck and Co in conjunction with the WHO in 1982 started a program to use the medication in humans. In 1987, when ended the clinical

trial stage, Ivermectin was indicated for human use orally in the form of 6 mg (6,000 µg) grooved tablets, thus starting the Onchocerciasis Control Program in African countries, indicating to affected people Ivermectin once a year, during 2 years which is the average life cycle of macrofilarias. In 1997, after the first decade of the program, over 18 million people were being treated annually with Ivermectin, through the combined efforts of WHO, the World Bank, over a dozen non-governmental development organizations, and numerous ministries of health. The above confirm exposed the safety of Ivermectin use in humans at the indicated doses, with no reported deaths so far attributable to it, to the extent that high-dose suicide attempts (megadoses of Ivermectin) have failed [14,15].

Its spectrum of action means that it can be indicated in the treatment of: Endoparasites: Microfilarias tissues of Onchocerca volvulus and *Strongyloides stercoralis*. Microfilarias of *Ancylostoma braziliense*, *Ancylostoma caninum*, *Brugia malayi*, *Gnathostoma spinigerum*, *Loa loa*, *Mansonella streptocerca*, *M. ozzardi*, *Wuchereria bancrofti*, *Ascaris lumbricoides*, *Enterobius vermicularis*, *Trichuris trichiura*. Ectoparasites: *Pediculus humanus*, *P. capitis* and *Phthirus pubis* and the mites *Sarcoptes scabiei* and *Demodex*, as well as in fly larvae: *Dermatobia hominis*, *Cochliomyia hominivorax* and *Hypoderma lineatum*. Truncular and multiple myasis: Larva migrans cutanea Demodicidosis, Gnatostomiasis, Neurocysticercosis, Tungiasis and Toxocariosis. Other possible indications are as an insect repellent (Malaria and Leishmaniosis) [13,14]. Ivermectin, an antiparasitic approved by the United States Food and Drug Administration (FDA) and considered on the WHO essential drug list, has antiviral action because of its nuclear transport inhibitory activity. In cell culture, a single dose reduces SARS-CoV-2 RNA by about 5000 times within 48 hours of administration [13-15].

Ivermectin, with the common name of 22,23-di-hydroavermectin B1, is one of the semi-synthetic derivatives of avermectin, was synthesized in 1975. It is a powerful antiparasitic, endo and ectoparasitic, broad spectrum, with conventional application in infections caused by nematodes, scabies and lice, its antiparasitic application is well established, its mechanism of action was not yet fully clarified, it is known, so far, that ivermectin affects the motility and feeding of nematode parasites by blocking the channels of chlorine ion, specifically those dependent on glutamate. In this way, it causes suppression of the nerve impulses and, consequently, paralysis. Its application in humans is considered safe. Antiviral application has been previously evaluated in Dengue, HIV-1 and Newcastle disease viruses [16,17]. Its antiviral mechanism is mediated by inhibition of nuclear importation of host and viral proteins. In addition, it has been shown to limit infection by retroviruses. The current virus causing the COVID-19 pandemic is a retrovirus, and literature findings suggest that the inhibitory activity of ivermectin may be effective against SARS-CoV-2 [18]. Chemistry: Ivermectin exists as an odorless, whitish powder with high lipid solubility but low water solubility. It is a mixture of at least 80% 22.23-dihydroavermectin B1a and not more than 20% 22.23-dihydroavermectin B1b. B1a and B1b have nearly identical antiparasitic activities [15,18].

Possibilities of use of Ivermectin in therapeutic strategies for VIDOC-19

Therapeutic strategies for VIDOC-19 should be based on the stage of infection. In stage I (mild phase) the virus multiplies and colonizes the host's respiratory tract, causing an influenza-like condition, with general malaise, fever and cough. Treatment is currently symptomatic. The best time to use antivirals in COVID-19, if approved, is in the preimmune acceleration phase, i.e. during stages I and II [17,19]. Stage II (moderate phase) is characterized by the development of pneumonia, which may be mild, moderate or severe, warranting admission for observation and treatment. Treatment consists mainly of respiratory support measures and available antiviral therapies [17-20].

Some existing drugs that are safe and effective against other diseases are emerging as possible treatments for IDOC-19, including Remdesivir, hydroxychloroquine and Ivermectin [19-23]. Commonly used drugs, such as azithromycin, chloroquine/hydroxychloroquine, Ivermectin or Nitazoxanide, have also shown positive effects that act on different targets of coronavirus action or at the host level by preventing the exaggerated immune response mainly the cytokine storm. Standardized doses have been used for more than 70 years, showing a degree of safety at the doses recommended by CDC and WHO. Some of these drugs can be used in the population-based chemoprophylaxis of IDOC-19, as proposed in India by malaria-like schemes for application to population groups [17,20]. The US FDA has

approved chloroquine and hydroxychloroquine for use in hospital patients with cardiac monitoring recommendations [16].

Studies show the efficacy of Ivermectin in the treatment of COVID-19 with FDA approval as an *in vitro* SARS-Cov2 inhibitor. Ivermectin is a long-standing veterinary antiparasitic that has been used in many different diseases due to its effect on arthropods, ectoparasites, mycobacteria and, importantly, on viruses such as flaviviruses, where the effect is to inhibit virus replication by acting on RNA helicase. Or also in the inhibition of the dengue with the same mechanism. The pharmacokinetics of ivermectin is characterized by its tendency to deposit fat tissue for up to 5 days, which is why it is used in prolonged therapies such as the eradication of river blindness by Onchocerca volvulus or the treatment of strongyloidiasis [14,15].

Main properties of ivermectin:

- The application of Ivermectin is oral, but there are many reports on subcutaneous or topical routes, which demonstrates its versatility, as well as the range of toxicity is very wide, so over dosage should be avoided The administration of a single dose of 200 µg/kg of ivermectin
- The maximum plasma concentrations are reached after four hours, following the intake of a 12 mg dose. Plasma levels increase proportionally to the doses administered. It is metabolized and excreted exclusively in feces within 12 days. The plasma half-life is 12 hours and that of its metabolites is three days.
- For people in the community in general, it is recommended that Ivermectin 200 ug/kilo (one drop of OV per kilogram of body weight) be used every 7 days (according to pharmacokinetics) until the pandemic ceases [22-24].

Conclusion

Currently there is no specific antiviral agent approved for COVID-19, but the participatory medical experience of experts (Physicians who do see patients with COVID-19, in their different specialties), has shown that it is a very helpful tool to avoid complications. It is being demonstrated that with the same doses that are used for pediculosis, clinical effects and promising results are obtained. This drug, in spite of having competition against it, has in its favor, the programs of control of onchocerciasis, where millions of people are treated annually and patients have taken millions of tablets of Ivermectin, without a serious side effect, so they should promote clinical trials with ivermectin to initiate early treatment of COVID-19.

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