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Mini Review

Prescribing Ivermectin in COVID-19: The Reality of a Panacea

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Abstract

The coronavirus disease 2019 (COVID-19), almost a year after the first case report, present in 190 countries of the world, with 45,683,708 infected and 1,190,516 deaths at the moment. The disease is classified into four spectra: mild, moderate, severe, and critical spectrum; based on its clinical characteristics and lung parenchyma affection verified by tomography. To date, there are no drugs designed for a specific treatment of severe acute respiratory syndrome caused by the new corona virus (SARS-CoV2), or vaccines that have been shown to be effective in preventing COVID-19. However, in a race against time, clinical trials of many drugs are ongoing. While cohort studies report consistent efficacy results for ivermectin; only the results of the large randomized clinical trials, with rigorous methodology that are being carried out or recruited, will be able to definitively establish how useful ivermectin is to treat COVID-19 or for its prophylaxis if applicable, alone or in combination. In the coming months, we must await the reports of the results of these trials and determine the antiviral viability of this drug, against SARS-CoV-2 and other viral diseases. Medical management must be focused responsibly, avoiding the unnecessary administration of drugs. The care of the patient with COVID-19 in any of the spectra of the disease should not be based on personal experience as a clinician, or on consensus; but rather in the physiological principles, in the natural history of the disease, in the pathophysiological mechanisms and in evidence-based medicine to be able to make the corresponding clinical decisions, honoring the words "primum non nocere" in each patient.

Keywords: *Covid-19; Severe Acute Respiratory Syndrome Coronavirus 2; Covid-19 Drug Treatment; Ivermectin; Evidence-Based Medicine; Evidence-Based Emergency Medicine*

Introduction

The coronavirus disease 2019 (COVID-19), which emerged in Wuhan, a district of China in December 2019 [1]; is, almost a year after the first case report, present in 190 countries of the world, with 45,683,708 infected and 1,190,516 deaths at the moment [2], being the most important public health emergency of the century, as it was in 1918-1920 the influenza pandemic [3].

Is classified disease basad to their clinical characteristics, with four spectra [4]: mild, which is characterized by symptoms affecting the upper respiratory tract, with no involvement of lung parenchyma or mild disease [5], lower than the 5% lung involvement confirmed by computed tomography [6]; moderate with hypoxia and lung parenchymal involvement up to 50%; severe with dyspnea, hypoxia and a pulmonary involvement greater than 50% and the critical spectrum, with respiratory failure, or with shock or with multiorgan dysfunction [7].

To date, there are no drugs designed for a specific treatment of severe acute respiratory syndrome caused by new corona virus (SARS-CoV2), and no vaccines that have been shown to be effective in preventing COVID-19 [8]. However, in a race against time, clinical trials of many drugs are ongoing [9], and research with vaccines from various patents against SARS-CoV2 remains dynamic [10].

The impact on world public health has had an economic cost to date of $ 1 trillion [11], in these months of pandemic during 2020 which has not ended yet; the number of infected continues to grow as well as that of deaths from COVID-19; and the world panorama is full of contrast for independent and indeterminate variables such as health systems, political situations, and economic systems; which allows a multidimensional approach to be made on which drugs to use against COVID-19, if there is still no treatment specifically designed for this disease.

International health leaders maintain efforts in research for an effective treatment against the COVID-19 pandemic, with a current focus on the repositioning or reuse of drugs, that is, research of existing drugs, with widely known therapeutic uses in other types of pathologies for new therapeutic purposes; with the aim of developing safe and effective treatments against COVID-19 [12].

From the drug repositioning approach, ivermectin investigations against COVID-19 were initiated due to its expectant properties against viral activity, which is not new and had been previously studied in other pathologies of viral etiology [13]. Ivermectin is a broad - spectrum antiparasitic a macrocyclic lactone B 22,23-dihydro from the bacterium Streptomyces avermitilis ; discovered in 1975 by William Campbell and approved as a treatment for parasitic-type infections in animals in 1981 [14]. Due to the importance of ivermectin in multiple infections of parasitic etiology, it is firmly on the List of Essential Medicines of the WHO (World Health Organizations) which is prescribed millions of times annually in the world [15].

Since 2012, the antiviral properties of ivermectin have been progressively documented in relation to RNA viruses, such as influenza, dengue, zika, chikungunya [16], and including human immunodeficiency (HIV) -1, and with greater connotation that of SARS-Cov-2 (COVID-19) [17], in addition to DNA-type viruses such as pseudorabies [18], polyoma and adenovirus [19].

Its property of ivermectin against viruses is based on its ability to bind and inhibit the transport function of importin protein α (IMP α) of the host. [20] So far it is known that IMPα is the mediator of nuclear import of multiple viral protein molecules that are key in the host. [twenty-one].

The safety of ivermectin as a drug is known in pathologies such as onchocerciasis and strongyloidiasis with single doses of 150 or 200 μg / kg, respectively [22]; or even with higher dosages such as 300-400 μg / kg in pathologies such as filariasis (in endemic areas, annually) [23]. It is assumed that the mechanism of action of ivermectin antiparasitic is potentiation of neurotrasmici or n GABA, being its selectivity which has an easy penetration into the central nervous system of mammals, which is GABA is a neurotransmitter key [24].

The key point to understand the role of the approach of ivermectin as a drug against viral diseases is the transport dynamics of eukaryotic cells, into and out of the nucleus; which is a central axis in viral activity, due to the fact that they sequester the system in order to generate an antagonism to the antiviral cellular response that is largely promoted by nuclear energy [25].

They are the IMPα, who perform the key functions as antiviral cellular response; the specific recognition of the cargo signal for nuclear import. This specific recognition allows the nuclear localization of multiple viral proteins, for example structural protein number five (NS5) from dengue [25]; distinctively, it is the binding property of ivermectin to IMPα that gives it the expectant focus as an antiviral drug, which extends to a large number of viruses, currently with greater relevance to SARS-CoV-2 [26].

The antiviral activity of ivermectin documented so far in a reproducible and demonstrable way is in the laboratory, with in-vitro investigations ; which involve the reproduction of high infections in non-physiological conditions and in monolayer-type cultures (Vero cells), which have no clinical relevance [27].

Sixty-eight (68) clinical trials have been conducted with ivermectin to date with the objective of determining its usefulness as a safe and effective drug against SARS-CoV-2; of which only eight (8) have been completed, four (4) are in progress, one (1) are enrolling by invitation, twenty-six (26) are recruiting research subjects, twenty-three (23) are not yet recruiting research subjects, and six (6) are active but without a recruitment process [20].

From the completed clinical trials, it has been found that the mean maximum inhibitory concentration of ivermectin is thirty-five (35) times higher than the maximum plasma concentration, compared to what was found *In-vitro*, which surprised with its effect of reducing the RNA of SARS-CoV-2 at values of 5000 times [28].

This century, despite technological and scientific advances, is experiencing eclipsing and chilling challenges for humanity, which have surpassed previous times. Thus, political leaders with the aim of preserving maximum health issues of their nations, have attempted to establish public health policies focused on fighting therapeutic the COVID-19, from its social, economic and cultural. However, it is evidence- based medicine that should support any health decision in order to preserve individual and population health status [29].

Different republics such as Peru [30], Bangladesh [31] or Bolivia [32] have included ivermectin with dosages in their public policies; However, it should be noted that the known dosages reported in multiple investigations are the results of laboratory replications and in most cases under non-physiological conditions; and in-vitro [27]. Although it is known that each republic maintains a committee of health authorities, an academic cohort that has allowed them to carry out the necessary literature reviews (it is assumed) to be able to dictate the recommendations as a state in the face of this pandemic; however, beyond a consensus of experts it does not have a sufficient level of evidence to be able to determine the use of the drug; Thus, concessions published as articles have as a recommendation the judicious use of the drug and as an urgent need the design of randomized clinical trials [33].

Until the moment of effective clinical trials, which include regimens of various dosages, combined therapies, not only a therapeutic effect of ivermectin but also a prophylactic effect against SARS-CoV-2 has been proposed; Only the results of the recently completed NCT04422561 [34] study reveal that two doses of ivermectin 72 hours apart, in a total of two hundred and three (203) research subjects; only 7.4% reported symptoms compared to the control of untreated subjects of which 58.4% of the subjects reported symptoms.

The NCT04422561 study was designed based on research subjects with the close contact condition of relatives of with confirmed COVID-19. This obvious difference between treated and control subjects highlights the potential of ivermectin as a prophylactic drug [34].

Although cohort studies report results of reduced mortality [35], negativization to SARS-Cov-2 more quickly, reduction of hospital stay, or reduction of the need for oxygen therapy [36]; and they are results consistent with the efficacy of ivermectin, only the results of large randomized clinical trials, with rigorous methodology that are being carried out or recruited, will be able to definitively establish how useful ivermectin is to treat COVID-19 or for its prophylaxis if as the case may be, alone or in combination. In the coming months, we must await the reports of the results of these trials and determine the antiviral viability of this drug, against SARS-CoV-2 and other viral diseases.

Medical management must be focused responsibly, avoiding the administration of drugs unnecessarily, being: antibiotics in outpatient and / or home care (even more if they are for hospital use); corticosteroids, anticoagulants different from those reported in the multiple investigations on COVID- 19 just because of the "idea of anticoagulation", ivermectin as if it were the "panacea" in these times.

The care of the patient with COVID-19 in any of the spectra of the disease should not be based on personal experience as a clinician, or on consensus; but rather in the physiological principles, in the natural history of the disease, in the pathophysiological mechanisms and

in evidence-based medicine to be able to make the corresponding clinical decisions, honoring the words "primum non nocere" in each patient.

Conclusion

The coronavirus disease 2019 (COVID-19) is currently present in 190 countries of the world, being a global public health emergency. Its clinical stratification has four spectra, from mild to critical; However, to date no specific medication has been designed to treat this disease; no vaccine to prevent it. However, current pharmacological research conduct is focused on the repositioning of drugs with known potential antiviral activity, including ivermectin.

However, while independent studies have shown a certain degree of efficacy of this drug, as well as prophylactic benefits; Only the results of large randomized clinical trials, which are still pending completion, will be able to reveal solid and concise data on their true therapeutic properties against viral diseases and SARS-CoV-2 infection; as well as prophylactic properties against this disease, if it had them. It must be remembered that the therapeutic management of the patient must be guided by medical practice based on evidence, on physiological principles, and not only on own or collective clinical experiences; this for the benefit of the patient.

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