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Use of ivermectin in the treatment of COVID-19: a review

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Abstract

Introduction: SARS-CoV-2 produces a respiratory syndrome that can range from a mild, self-limiting inflammatory condition to severe, progressive pneumonia. Prevention and treatment strategies have become a priority since the emergence of COVID-19. Noteworthy is the use of ivermectin, an anti-parasitic agent, which has been widely recommended by some health professionals for the prevention and treatment of COVID-19. **Objective:** To assess the evidence on the efficacy and safety of using ivermectin for the prevention and treatment of COVID-19, identifying its mode of action and the benefits and adverse reactions of using this drug. **Methods:** The search strategy for articles was based on a search in the electronic databases MEDLINE (NationalLibrary of Medicine, United States), LILACS (Latin American and Caribbean Literature in Health Sciences), Scielo, specialized libraries of Universities, PubMed, and Google Academic. The selected articles will be from 2015 to 2021. **Results and Conclusion:** Studies reveal that ivermectin is a broad-spectrum drug with high-fat solubility and has numerous effects on several parasites. In addition to having antiviral and antiparasitic effects, this drug also causes immunomodulation in the host. Ivermectin has already demonstrated its potent antiviral effects in vitro against several RNA viruses, such as influenza A, Zika virus, Newcastle disease virus, yellow fever virus, Chikungunya virus, dengue virus, among others. One way to delay viral transmission would be to stop the virus from replicating, thus reducing the viral load in infected individuals. Thus, studies have shown that ivermectin may have the potential for inhibiting and replicating SARS-CoV-2.

Keywords: COVID-19. SARS-CoV-2. Ivermectin. Treatment. Prevention.

Introduction

Found in several species of birds and mammals, coronaviruses are positive-sense, single-stranded RNA viruses (ssRNA+) surrounded by a lipid envelope. Some species are known to cause respiratory, enteric, neurological, and liver diseases. SARS-CoV-2 produces a respiratory syndrome that can range from a mild, self-limited inflammatory condition to severe, progressive pneumonia. The most severe cases can progress to multiple organ failures resulting in death [1].

In this context, the emergence of the new coronavirus caused a great impact around the world, the effects of this disease are still incalculable for society, the health system, and the economy. The situation has evolved rapidly, and the global number of cases and deaths is increasing every day, putting the lives of thousands of people around the world at risk [2].

Also, COVID-19 emerged in Asia, more specifically in China, and quickly spread to Europe and the United States and, later, to South America and Africa, characterizing a pandemic, as decreed by the World Health Organization (WHO) in early 2020 On July 9 of the same year, more than 11.8 million cases and 544,000 deaths were reported worldwide [3,4].

The search for effective treatments mobilized researchers from all over the world, viral replication inhibitor molecules, endocytosis inhibitors, protease and protein inhibitors, neutralizing antibodies, among many means have been considered and widely studied. Prevention and treatment strategies have become a priority since the emergence of COVID-19. Among those non-pharmacological, related to the reduction of viral transmission, are social isolation, quarantine at home, the use of masks, and hand washing. Among the pharmacological strategies, there is the use of ivermectin, an anti-parasitic agent, which has been widely recommended by some health professionals for the prevention and treatment of COVID-19 [3].

Besides, in vitro studies found that exposure of the coronavirus that causes COVID-19 to ivermectin generated destruction of almost all viral particles after 48 hours. According to the authors, the drug could inhibit the transmission of viral proteins to the interior of cells [5].

Therefore, the objective of this study was to evaluate the evidence on the efficacy and safety of using ivermectin for the prevention and treatment of COVID-19, identifying its form of action and the benefits and adverse reactions of using this drug.

Methods

The search strategy for articles was based on searching the electronic databases MEDLINE (NationalLibrary of Medicine, United States), Lilacs (Latin American and Caribbean Literature on Health Sciences), Scielo, specialized libraries of Universities, PubMed, and Academic Google. The selected articles will be between the period 2015 to 2021.

Results - Major findings

Pharmacological Aspects Of Ivermectin

Ivermectin has been used for several years to treat many infectious diseases, has a good safety profile, and has low adverse effects when prescribed orally. Ivermectin was identified in the late 1970s and was first approved for use in animals in 1981. Its use in humans was confirmed a few years later [6].

Studies reveal that ivermectin is a broad-spectrum drug with high liposolubility and has numerous effects on several parasites, arthropods, nematodes, mycobacteria, flaviviruses, and mammals through various mechanisms of action. In addition to having antiviral and antiparasitic effects, this drug also causes immunomodulation in the host. Studies have shown its effectiveness in inhibiting the proliferation of cancer cells, as well as in regulating glucose and cholesterol in animals. Despite the different pharmacological effects of this drug, many of its underlying mechanisms are not yet known [5].

The Action Of Ivermectin As Prophylaxis To Covid-19

Ivermectin is a drug with a wide range of bioactivity and has been used for over 30 years to treat parasitic infections in humans. Ivermectin is used at a dose of 0.15mg/kg - 0.2mg/kg body weight for most parasitic infections as an oral pill and is well tolerated by the body. It is not the first time that ivermectin's antiviral properties have been tested against human viruses. Ivermectin has demonstrated its potent antiviral effects in vitro against several RNA viruses, such as influenza A, Zika virus, Newcastle disease virus, yellow fever virus, Chikungunya virus, dengue virus among others [7].

One way to delay viral transmission would be to stop the virus from replicating, thus reducing the viral load in infected individuals. The antiparasitic drug ivermectin has been reported in several studies due to its inhibition of SARS-CoV-2 replication in vitro, although the authors highlight the need for further studies to determine the dosage for potential use in patients with COVID-19. This is particularly important as the serum levels used in their study far exceeded what would be achieved as commonly administered safe doses [8].

The anti-SARS-CoV-2 of ivermectin probably occurs through inhibition of viral IMPα / β1 mediated nuclear import, which decreases virus replication and, therefore, viral load. Caly et al. (2020) [9] showed the in vitro benefit of ivermectin in SARS-CoV-2 infected Vero-hSLAM cells. The authors found that a single dose of ivermectin was able to effect an approximately 5,000-fold reduction in viral RNA in 48 hours. The authors used a molecular docking and molecular dynamics simulation approach to explore the mechanism of action of ivermectin and doxycycline in inhibiting SARS-CoV-2 and revealed that the combination of ivermectin and doxycycline may be performing the effect by inhibiting viral entry and increasing viral load clearance by targeting various viral proteins.

In order to understand how the inhibition of SARS-CoV-2 by the ivermectin in vitro translates in humans, these concentrations are first evaluated in comparison to the lung concentrations predicted in humans following oral administration of ivermectin. Theoretically, only unbound drugs in plasma could access the lungs and other tissues through passive diffusion. Ivermectin that reaches the lungs after oral dosing may be related to lipophilicity, low ionization at physiological pH, binding of ivermectin to lung protein that is still unknown, and any carrier that can help maintain tissue distribution that is also unknown [10].

Case Studies Involving The Use Of Ivermectin

Rajter et al. (2020) [11] concluded that ivermectin is the best choice for the treatment of patients with mild to moderate COVID-19 disease. In a retrospective study of 280 patients with SARS-CoV-2 infection treated with ivermectin (n=173) or standard care (n=107), the authors found lower mortality in the ivermectin group (25.2% versus 15, 0%, OR 0.52, 95% CI 0.29-0.96). They also reported lower mortality among patients with severe lung disease (n=75) treated with ivermectin (38.8% versus 80.7%, OR 0.15, CI 0.05-0.47, p=0.001), however, no significant differences were found in successful extubation.

A study carried out by Ahmed et al. (2020) [12] enrolled 72 patients hospitalized in Dhaka, Bangladesh, who were assigned to one of three groups: oral ivermectin alone (12 mg once daily for 5 days), oral ivermectin in combination with doxycycline (12 mg of single-dose ivermectin and 200 mg doxycycline on day 1, followed by 100 mg every 12 h for the next 4 days), and a placebo control group. The average duration of hospitalization after treatment was 9.7 days in the placebo group, 10.1 days in the ivermectin and doxycycline group, and 9.6 days in the ivermectin alone group. None of the participating patients needed oxygen or had serious adverse events with registered medications. The mean duration of viral clearance was 9.7 days, 5 days for the ivermectin arm, 11.5 days for ivermectin + doxycycline, and 12.7 days for the placebo arm. Kaplan-Meier survival analysis showed that the proportion of patients at risk for SARS-CoV-2 was significantly reduced in the 5-day ivermectin group.

Conclusion

Studies reveal that ivermectin is a broad-spectrum drug with high-fat solubility and has numerous effects on several parasites. In addition to having antiviral and antiparasitic effects, this drug also causes immunomodulation in the host. Ivermectin has already demonstrated its potent antiviral effects in vitro against several RNA viruses, such as influenza A, Zika virus, Newcastle disease virus, yellow fever virus, Chikungunya virus, dengue virus, among others. One way to delay viral transmission would be to stop the virus from replicating, thus reducing the viral load in infected individuals. Thus, studies have shown that ivermectin may have the potential for inhibiting and replicating SARS-CoV-2.

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Data sharing statement

No additional data are available.

Conflict of interest

The authors declare no conflict of interest.

References

1. Ferreira LLG, Andricopulo AD. Medicamentos e tratamentos para a Covid-19. Rev. Estudos Avançados, v. 34, n. 100, p.7-27, 2020. Disponível em: < https://www.scielo.br/pdf/ea/v34n100/1806-9592-ea-34-100-7.pdf> Acesso em: 05 mar. 2021.
2. Marra LP. Ivermectina para Covid-19. Revisão sistemática rápida. 24 f., 2020. Disponível em: < https://docs.bvsalud.org/biblioref/2020/06/1099488/rs_rapida_ivermectina_covid19_06_05_20-1.pdf> Acesso em: 05 mar. 2021.
3. Person OC. et al. Intervenção com ivermectina para COVID-19 (SARS-Cov 2): sinopse baseada em evidências. 2021. 20f. Dissertação (Doutorado em Saúde) – UNIFESP, 2021. Disponível em: < https://preprints.scielo.org/index.php/scielo/preprint/view/1871> Acesso em: 05 mar. 2021.
4. Floriani ID. et al. Exposição de pacientes da emergência pediátrica a exames de imagem, na atualidade e em tempos de covid-19: uma revisão integrativa. Rev. Paul. Pediatr., v. 40, 2020. Disponível em: < https://www.scielo.br/pdf/rpp/v40/pt_1984-0462-rpp-40-e2020302.pdf> Acesso em: 05 mar. 2021.
5. Heidary F, Gharebaghi R. Ivermectina: uma revisão sistemática dos efeitos antivirais do regime complementar de COVID-19. Rev. The Journal of Antibiotics, v. 73, p. 593-602, 2020. Disponível em: < https://doi.org/10.1038/s41429-020-0336-z> Acesso em: 05 mar. 2021.
6. Kircik LHMD. et al. Mais de 25 anos de experiência clínica com ivermectina: uma visão geral da segurança para um número crescente de indicações. Rev. J Drugs Dermatol, v. 15, ed. 3, mar. 2016. Disponível em: <https://jddonline.com/articles/dermatology/S1545961616P0325X> Acesso em: 10 mar. 2021.
7. Pandey S. et al. Ivermectin in COVID-19: What do we know? Diabetes Metab. Syndr., v. 14, n. 6, p. 1921-1922, nov.-dez. 2020. Disponível em: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7521351/> Acesso em: 30 mar. 2021.
8. Hellwing MD, Maia A. Uma profilaxia COVID-19?

Menor incidência associada à administração profilática de ivermectina. Int. J. Antimicrob Agents, v. 57, n. 1, 2021. Disponível em: < https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7698683/> Acesso em: 30 mar. 2021.

9. Caly L. et al The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. Antivir Res., v. 178, jun. 2020. Disponível em: < https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7129059/> Acesso em: 30 mar. 2021.

10. Schmith VD, Zhou, J.; Lohmer, L. R. The Approved Dose of Ivermectin Alone is not the Ideal Dose for the Treatment of COVID-19. Clinical Pharmacology e Therapeutics, v. 108, n. 4, p. 762-765, out. 2020. Disponível em: < https://ascpt.onlinelibrary.wiley.com/doi/10.1002/cpt.1889> Acesso em: 31 mar. 2021.

11. Rajter JC. et al. Use of Ivermectin Is Associated With Lower Mortality in Hospitalized Patients With Coronavirus Disease 2019. Elsevier Public Heath Emergency Collection, v. 159, n. 1, p. 85-92, jan. 2021. Disponível em: < https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7550891/> Acesso em: 30 mar. 2021.

12. Ahmed S. et al. A five-day course of ivermectin for the treatment of COVID-19 may reduce the duration of illness. Int J Infect Dis, v. 103, p. 214-216, 2021. Disponível em: < https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7709596/> Acesso em: 31 mar. 2021.