Title	Summary of evidence: Ivermectin use in patients with COVID 19 disease
Identification code	04102020IHJA
Requesting area	COVID-191. Keralty Public Health Crisis Committee
Name	COVID-191. Keralty Public Health Crisis Committee
Answer Date	10 04 2020

Questions:

1. What is the evidence on the use of ivermectin in patients with COVID 19?
2. What is the evidence of the effect of ivermectin on the SARS-CoV-2 virus?

Methodology:
A fast-systematic search was performed (Fast Systematic Search Manual. Institute of Clinical Global Excellence. 2019)

Terms of search: COVID 19, Coronavirus, Ivermectin, SARS-CoV-2.

Types of studies: Scientific societies recommendations and leading national and international health organizations, systematic reviews, meta-analysis, clinical trials and other primary studies.

Source of information: Pubmed, Google Scholar,

Background: In the news, it was spread that the SARS-CoV-2 virus could be fought with ivermectin

According to Chosidow and Gendrel (2016) “Ivermectin is an antiparasitic drug, a derivative of avermectins and a product of the fermentation of an actinomycete, Streptomyces avermitilis. Its structure is associated with two avermectins. Ivermectin acts on chlorine-dependent channels of both glutamate and γ-aminobutyric acid, interrupting neurotransmission in invertebrates. In human beings, there are several mechanisms of brain protection for the potentially toxic effects of ivermectin, including P glycoprotein, present on the apical face of de blood barrier endothelial cells and encoded by the MDR1 gene. Ivermectin is currently used in the mass treatment of onchocerciasis, other filariasis, some intestinal nematode infections, but also scabies, and more rarely in resistant lice. "

A few days ago, the work of Caly et al. was published (2020). This author points out that Ivermectin “Originally identified as an inhibitor of the interaction between the human immunodeficiency virus-1 (HIV-1) protein integrase (IN) and the importing heterodimer (IMP) α / β1 responsible for nuclear import IN6, it has since been confirmed that ivermectin inhibits nuclear import IN and HIV-15 replication. Other actions of ivermectin7 have been reported, but ivermectin has been shown to inhibit nuclear importation of host proteins (e.g, 8, 9) and viral proteins, including simian virus SV40 large tumor antigen. (T-ag) and Dengue virus nonstructural protein (DENV) 55, 6. It is important to note that it has been shown to limit infection by RNA viruses such as DENV 1-44, West Nile virus10, Venezuelan equine encephalitis virus (VEEV) 3 and influenza2, and this broad-spectrum activity is believed to be due to the dependence of many different RNA viruses on IMPα / β1 during infection. Ivermectin has also been shown to be effective against DNA pseudorabia virus (VPR) both in vitro and in vivo, and treatment with ivermectin has been shown to increase the survival of mice infected with VPR13. No efficacy of ivermectin against Zika virus (ZIKV) was observed in mice, but the authors acknowledged that the limitations of the study justified the reevaluation of ivermectin activity against

ZIKV ”

Findings / Answers to Questions

1. To question 1. What is the evidence on the use of ivermectin in patients with COVID 19? No published evidence was found for the use of ivermectin in patients with COVID 19.
2. To question 2, what is the evidence of the effect of ivermectin on the SARS-CoV-2 virus? There is in vitro evidence that the inhibitory activity of ivermectin nuclear transport can be effective against SARS-CoV-2 (2), there is clear in vitro evidence that ivermectin affects the replication of SARS-Cov-2. In the article by Caly et al. (2020) it is stated that “To test the antiviral activity of ivermectin towards SARS-CoV-2, we infected Vero / hSLAM cells with the SARS-CoV-2 Australia / VIC01 / 2020 isolate at a MOI of 0.1 for 2 h, followed by the addition of 5 µM ivermectin. The supernatant and the cell granules were collected on days 0 to 3 and analyzed by RT-PCR for replication of the SARS-CoV-2 RNA (Fig. 1 A / B). At 24 h, there was a 93% reduction in the viral RNA present in the supernatant (indicative of released virions) from the ivermectin-treated samples compared to the DMSO vehicle. Similarly, a 99.8% reduction in cell-associated viral RNA (indicative of unreleased and unpackaged virions) was observed with ivermectin treatment. Within 48 h this effect increased to a 5000 fold reduction in viral RNA in ivermectin-treated samples compared to control samples, indicating that ivermectin treatment resulted in effective loss of essentially all viral material in 48 hours. "

Conclusions / general recommendations:

1. There is no evidence to consider that ivermectin is a COVID treatment 19.
2. There is no evidence to consider ivermectin as harmful in the treatment of COVID 19, at doses determined to be safe in the management of parasitosis. This is a single dose of 0.15-0.2mg / kg PO.
3. There is evidence of in vitro antiviral activity of ivermectin against SARS CoV-2, but there are no in vivo studies in animal models or studies in humans.
4. The treatment of COVID 19 is evolving as new evidence is acquired, and therefore it is suggested to be in a process of permanent updating.

Recommendations for health professionals:

1. The use of ivermectin in the management of COVID 19 has no evidence to recommend its use, since its clinical or antiviral effectiveness has not been established in clinical studies, nor has the recommended dosage schedule been established, nor the stage or clinical circumstance at which it might have an indication. However, it can be considered as part of the treatment according to the criteria of the treating physician.

Recommendations for the community:

1. Ivermectin is a medicine with a risk of toxicity, and can only be used under strict medical prescription.

SEARCH

Search: **ivermectin and covid-19** Filters: **in the last 10 years**

((((("ivermectin"[MeSH Terms] OR "ivermectin"[All Fields]) OR "ivermectine"[All Fields]) OR "ivermectins"[All Fields]) OR "ivermectins"[All Fields]) AND (((((("covid 19"[All Fields] OR "covid 2019"[All Fields]) OR "severe acute respiratory syndrome coronavirus 2"[Supplementary Concept]) OR "severe acute respiratory syndrome coronavirus 2"[All Fields]) OR "2019 ncov"[All Fields]) OR "sars cov 2"[All Fields]) OR "2019ncov"[All Fields]) OR (("wuhan"[All Fields] AND ("coronavirus"[MeSH Terms] OR

"coronavirus"[All Fields])) AND (2019/12/1:2019/12/31[Date - Publication] OR 2020/1/1:2020/12/31[Date - Publication])))

Translations

ivermectin: "ivermectin"[MeSH Terms] OR "ivermectin"[All Fields] OR "ivermectine"[All Fields] OR "ivermectin's"[All Fields] OR "ivermectins"[All Fields]

covid-19: "COVID-19"[All Fields] OR "COVID-2019"[All Fields] OR "severe acute respiratory syndrome coronavirus 2"[Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "2019-nCoV"[All Fields] OR "SARS-CoV-2"[All Fields] OR "2019nCoV"[All Fields] OR (("Wuhan"[All Fields] AND ("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields])) AND (2019/12[PDAT] OR 2020[PDAT]))

References:

1. Chosidow, A., & Gendrel, D. (2016). Tolérance de l'ivermectine orale chez l'enfant [Safety of oral ivermectin in children]. *Archives de pediatrie : organe officiel de la Societe francaise de pediatrie*, *23*(2), 204–209. https://doi.org/10.1016/j.arcped.2015.11.002
2. Caly, L., Druce, J. D., Catton, M. G., Jans, D. A., & Wagstaff, K. M. (2020). The FDA-approved Drug Ivermectin inhibits the replication of SARS-CoV-2 in vitro. *Antiviral research*, 104787. Advance online publication. https://doi.org/10.1016/j.antiviral.2020.104787