



Letters to the Editor

Antiviral and anti-inflammatory properties of ivermectin and its potential use in Covid-19[☆]

Propiedades antivirales y antiinflamatorias de ivermectina y su potencial uso en Covid-19

To the Editor:

The emergence of the new SARS-CoV-2 virus has led to the search for treatment alternatives among existing medicines, such as ivermectin. This is a semi-synthetic antiparasitic agent derived from avermectin B1 which has a broad spectrum of activity and a high efficacy and safety margin, and has already been used in more than 2 billion patients. *In vitro*, it inhibits the function of importin proteins (IMP) that recognize nuclear localization signals from viral proteins and promote their replication. Ivermectin inhibits HIV-1, DENV2 and other flaviviruses from entering the nucleus and replicating.¹

In *in vitro* studies, ivermectin administered at 5 μ M reduced RNA levels of SARS-CoV-2 5000-fold. However, the mean maximum inhibitory concentration (MIC₅₀) for the virus is 35 times higher than the maximum plasma concentration (C_{max}), so enthusiasm was lost and no further studies were performed. To achieve an MIC₅₀ in the lung, more than 25 times the approved weekly dose would have to be used.² However, when hydroxychloroquine was unavailable in Latin America, ivermectin was used with satisfactory outcomes. Comparing 704 hospitalized patients who received a dose of ivermectin (150 μ g/kg) with 704 controls, it was found lower mortality rates among mechanically ventilated patients who had received the medication (7.3% vs. 1.3%). Overall mortality was lower in cases (1.4%) than in controls (8.5%) with a hazard ratio (HR) of 0.2, 95% CI: 0.11–0.37 ($p < 0.0001$).³ This single-dose scheme has been conventionally used in various parasitological diseases; however, given that ivermectin is known to be safe and well tolerated, and a single dose may not be sufficient for viral diseases such as Covid-19, further studies are warranted.

Ivermectin has a demonstrated anti-inflammatory effect *in vivo* and *in vitro*, that works by reducing the production of TNF- α , IL-1 and IL-6, and suppressing LPS-induced NF- κ B translocation.⁴ In mice, the administration of 2 mg/kg of ivermectin suppresses mucus hypersecretion in the respiratory tract and decreases the recruitment of immune cells and the production of cytokines and IgE/IgG1 in bronchoalveolar lavage.⁵ This shows that ivermectin has an anti-inflammatory effect not only at a systemic level, but also on the lung tissue.

The disease caused by SARS-CoV-2 is divided into different phases: asymptomatic, mild symptomatic disease, and severe inflammatory respiratory disease. The first 2 are dependent on SARS-CoV-2 replication; the latter is attributed to the hyper-inflammatory state called the cytokine storm. Evidence suggests that this drug can act at different stages of the disease. Controlled studies must be conducted first to demonstrate the effect of ivermectin against Covid-19, then to determine if this effect is due to its antiviral action and finally to study if its administration is convenient also in hospitalized patients due to its apparent anti-inflammatory effect.

Conflict of interests

The authors state that they have no conflict of interests.

References

1. Wagstaff KM, Sivakumaran H, Heaton SM, Harrich D, Jans DA. Ivermectin is a specific inhibitor of importin α / β -mediated nuclear import able to inhibit replication of HIV-1 and dengue virus. *Biochem J*. 2012;443:851–6 <https://doi.org/10.1042/BJ20120150>
2. Schmith VD, Zhou J, Lohmer LR. The approved dose of ivermectin alone is not the ideal dose for the treatment of COVID-19. *Clin Pharmacol Ther*. 2020 May. <https://doi.org/10.1002/cpt.1889>
3. Patel AN, Desai SS, Grainger DW, Mehra MR. (2020). Usefulness of Ivermectinin COVID-19 Illness. Released April 19, 2020 (pre-print) (Patel et al. 2020). doi: 10.1056/NEJMoa2001282.5.
4. Zhang X, Song Y, Ci X, An N, Ju Y, Li H, et al. Ivermectin Inhibits LPS-induced Production of Inflammatory Cytokines and Improves LPS-induced Survival in Mice. *Inflamm Res*. 2008;Nov;57:524–9, <http://dx.doi.org/10.1007/s00011-008-8007-8>.
5. Yan Shuhan, Ci Xinxin, Na Chen, Chen Chi, Li Xiangchao, Chu Xiao, et al. Anti-inflammatory effects of ivermectin in mouse model of allergic asthma. *Inflamm Res*. 2011;Jun;60:589–96, <http://dx.doi.org/10.1007/s00011-011-0307-8>.

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