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Perspective

Ivermectin as a multifaceted drug in COVID-19: Current insights

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The Coronavirus Disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has ignited much research efforts towards repurposing of existing drugs as possible anti-viral agents in order to mitigate the adverse health and economic consequences. As a result, a great deal of dilemma has emerged in appropriate drug selection based on evidence and good clinical practice versus the prompt need for safe and effective treatment. Amidst fear of the pandemic, Ivermectin is being prescribed off-label for prophylaxis or as adjuvant therapy for COVID-19.

Ivermectin, a semisynthetic derivative of avermectin B1 is a broad-spectrum anti-microbial drug with anti-helminthic, anti-bacterial, anti-viral, anti-inflammatory and anti-cancer properties.[1] In addition, Ivermectin displays anti-diabetic activities by reducing blood glucose and cholesterol levels, and also by improving insulin sensitivity.[2] It has high lipid solubility and good safety profile with lowadverse effects, when administered orally.[3] As an anti-helminthic drug, its mechanism of action in invertebrates mainly involves the opening of glutamate-gated and gamma aminobutyric acid gated chloride channels, leading to increased conductance of chloride ions and causing subsequent motor paralysis in parasites.[4] The anti-inflammatory action of Ivermectin is attributed to inhibition of cytokine production by lipopolysaccharide challenged macrophages, blockade of activation of NF-kappaB, mitogen-activated protein kinases and p38, and inhibition of toll-like receptor 4 signalling.[5,6] The anti-viral properties of Ivermectin against various RNA and DNA viruses have been demonstrated in multiple studies. These RNA viruses include dengue, yellow fever, chikungunya, Zika, Avian influenza A, West Nile, Hendra, Newcastle, Venezuelan equine encephalitis, Semliki Forest, Sindbis, Porcine Reproductive and Respiratory Syndrome and Human immunodeficiency virus type 1. The various DNA viruses include Equine herpes type 1, BK polyomavirus, pseudorabies, porcine circovirus 2, and bovine herpesvirus.[1,4] With the outbreak of COVID-19 pandemic, Caly et al. conducted an in-vitro study and evaluated the anti-viral property of Ivermectin against SARS-CoV-2. In this study, single addition of 5 μM Ivermectin to Vero-hSLAM cells 2 h post infection with SARS-CoV-2 demonstrated ~5000-fold reduction in viral RNA at 48 h.[7] The anti-viral mechanism of Ivermectin in COVID-19 is attributed to inhibition of the importin (IMP) α/β receptor, which is responsible for transmitting viral proteins into the host cell nucleus.[4] A new hypothesis proposes Ivermectin as an ionophore which causes ionic imbalance between the external and internal environment of the viral membrane and consequent osmotic lysis.[3] Since significant effectiveness of Ivermectin is

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seen before the virus can adhere to the host cell, it is proposed that Ivermectin administration may be effective in the early stages or prevention. In an early systematic review and meta-analysis which evaluated 4 studies involving 629 patients, the authors found a significant reduction in mortality and time to clinical improvement with the use of Ivermectin.[8] A recent meta-analysis based on 18 randomized controlled treatment trials of Ivermectin in COVID-19 have found large, statistically significant reductions in mortality, time to clinical recovery, and time to viral clearance. Further, results from numerous controlled prophylaxis trials report significantly reduced risks of contracting COVID-19 with the regular use of Ivermectin.[9] A dose of 12 mg twice daily alone or in combination with other therapy for 5–7 days has been proposed as a safe therapeutic option for mild, moderate or severe cases of Covid-19 infection.[10] The time to reach maximum plasma concentration of 20–50 ng/ml, after a dose of 6 or 12 mg, respectively is approximately 4 h. The elimination half-life ranges between 12 and 24 h.[11] Pharmacokinetic studies in healthy volunteers have suggested that single dose up to 120 mg of Ivermectin is safe and well tolerated.[12] Although Ivermectin is tolerated well with few side effects, neurological adverse events of the drug (i.e. confusion, tremors, seizure, local swelling, vomiting), can occur rarely and continue for a week. The risk can also be potentiated by unknown drug–drug interactions.[13]

Recently, the use of steroids for the management of COVID-19 has increased drastically following the results of the RECOVERY trial which found a mortality benefit with the use of dexamethasone in hospitalized patients who received either invasive mechanical ventilation or oxygen alone at randomization.[14] Consequently, the side-effects of steroids are also expected to increase. Apart from the usual known side effects, a rare, but potentially severe complication of immunosuppressive therapy is Strongyloides hyperinfection or dissemination syndrome caused by *Strongyloides stercoralis*.[15] The current recommended dexamethasone dose from the COVID-19 Treatment Panel is 6 mg/day (≈40 mg of prednisone) for 10 days. In a recent study, the authors reviewed 133 individuals with Strongyloides hyperinfection and found that an average dose of 40 mg/day of prednisone was associated with hyperinfection syndrome in 83% of cases.[15] Again, it has been seen that, cases have occurred within 5 days of administration of the first dose of corticosteroids, following doses as low as 20 mg of prednisone and following a single dose of dexamethasone, leading experts to assert that the occurrence is independent of dose, duration, or route of administration.[16] Due to the high mortality associated with this syndrome and the availability of inexpensive and effective therapy, Ivermectin could be used as a preventive strategy for at risk patients. For patients with COVID-19 who are, or may become, candidates for dexamethasone, it is reasonable to consider presumptive treatment with Ivermectin for moderate-to high-risk patients not previously tested or treated for Strongyloides.

In the current COVID-19 pandemic, an explosion of skin diseases like scabies, psoriasis and urticaria have also been reported.[17] In scabies, permethrin failure has been observed due to complications in carrying out decontamination measures or in completing topical treatment as a result of high hospital bed turnover.[18] In such situations, oral treatment with Ivermectin is considered as the first choice for controlling infestation.[19]

While the findings by Caly et al. provide some promise, several pharmacokinetic factors limit the immediate translation of their findings, and there is no convincing evidence that the 5 μM concentration of Ivermectin used in their in-vitro study can be achieved in vivo.[7] Firstly, the maximum plasma concentration of Ivermectin that is achieved with a dose of 1700 μg/kg(i.e., 8.5 times the FDA approved dose of 200 μg/kg) is just 0.28 μM, approximately 18 times less than that found to have anti-viral effect in the in-vitro study.[12] Secondly, 93% of Ivermectin is bound to plasma proteins that limit its cellular uptake by endothelial cells. Considering both the total plasma concentration and protein binding, the free plasma concentration of Ivermectin would be 250 times lower than the concentration required to reduce viral replication of SARS-CoV-2 in vitro.[20] Thirdly, since there is no data on the tissue penetration of Ivermectin in human lungs, the total concentration of Ivermectin in calves injected with 200 μg/kg reached only 100 ng/g (approx. 0.1 μM) in lung tissue, which suggests that its accumulation would not be sufficient to achieve the antiviral effect with conventional doses.[21] The recently published interim results of the World Health Organization (WHO) Solidarity Trial did not demonstrate any mortality benefit, reduced initiation of ventilation or hospitalization duration with the use of remdesivir, hydroxychloroquine, lopinavir, and interferon beta-1a in patients hospitalized with Covid-19.[22] Had WHO also included Ivermectin in the study, there could have been better understanding of its anti-viral effects. Alternatively, based on the results of an experimental study, it is hypothesised that nebulized form of Ivermectin may be effective against SARSCoV- 2 to achieve desired IC50 levels at the target site of action. However, it needs vigorous preclinical and clinical testing before being claimed for use in COVID-19.[23] Considering the significant challenges surrounding the use of Ivermectin in the context of COVID-19, novel formulations employing micro- and nanotechnologies may address these concerns in coming future.

So far, research related to Ivermectin in COVID-19 has serious methodological limitations resulting in indecisive evidence.[24] The use of Ivermectin for prophylaxis or treatment for COVID-19 should be done based on robust evidence generated from multicentric randomised clinical trials.

Disclosure of competing interest

The authors have none to declare.

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