The broad-spectrum antiparasitic ivermectin against COVID-19

Nadia A. El Dib[a], Mona I. Ali[b]

[a]Department of Medical Parasitology, Faculty of Medicine, Cairo University, Cairo, [b]Department of Medical Parasitology, Faculty of Medicine, Beni-Suef University, Beni-Suef, Egypt

Correspondence to Mona I. Ali, MD, Department of Medical Parasitology, Faculty of Medicine, Beni-Suef University, Beni-Suef, 62521, Egypt. Tel: +20 122 196 9196; fax: 0020822318605; e-mail: monaib.para@yahoo.com

Received: 1 September 2020
Revised: 18 October 2020
Accepted: 28 October 2020
Published: 30 December 2020

Kasr Al Ainy Medical Journal 2020, 26:37–40

Ivermectin, the FDA-approved broad-spectrum antiparasitic drug, has recently shown excellent antiviral effects against many viral infections. This effect was especially important in the current pandemic infection of COVID-19. There are reports that ivermectin inhibited the replication of the virus *in vitro* in 48 h. Studies have been done on other viral infections and on this virus *in vivo* and *in vitro*. The results showed that it affects the viral replication by its effect on the protein transfer between the cytoplasm and nucleus inside the host cells. More information is still needed to approve its use in the treatment and prevention of COVID-19 pandemic, which will necessitate more studies to adjust the dose and mode of administration.

Keywords:
COVID-19, SARS-CoV-2, importin, ivermectin, RNA viruses, viral inhibition, viral replication

Kasr Al Ainy Med J 26:37–40

1687-4625

Introduction

Ivermectin is a famous broad-spectrum anthelminthic therapy for animals and humans. It also has a potent effect when used for entomological infestation, for example, scabies, pediculosis [1], and myiasis [2]. Most importantly, it has been implicated in malaria control programs by the WHO [3], as well as its antiviral effect against a wide range of viruses [4]. Molecular structure is shown in Fig. 1.

Ivermectin is one of the members of a family of natural products 'ivermectins,' from soil actinomycetes. It was first isolated in 1970s from the fermented broth of the bacteria *Streptomyces avermitilis* [5].

Since 1980s, several trials have been carried out to synthetize ivermectin and related compounds mainly after fermentation of the soil microorganism. Milbemycin is one of the related groups without carbohydrates that has been isolated as well. Ivermectin was found to be very effective against a wide number of parasites, including helminths and arthropods affecting man and livestock, and also it is prepared as lotions and creams against head lice in Australia. It is believed that it causes paralysis of these invertebrate parasites. Ivermectin is used in tablet form to treat nematode infection as well as scabies and rosacea, a skin condition with redness and visible blood vessels on the face [5]. The greatest effect of ivermectin is related to its famous use against onchocerciasis and river blindness in Africa.

After ivermectin was approved as antiparasitic agent by the FDA, it has shown a wide range of antiviral activity *in vitro*. It affects the RNA viruses and also shown great effect against DNA viruses *in vitro* and *in vivo* [6].

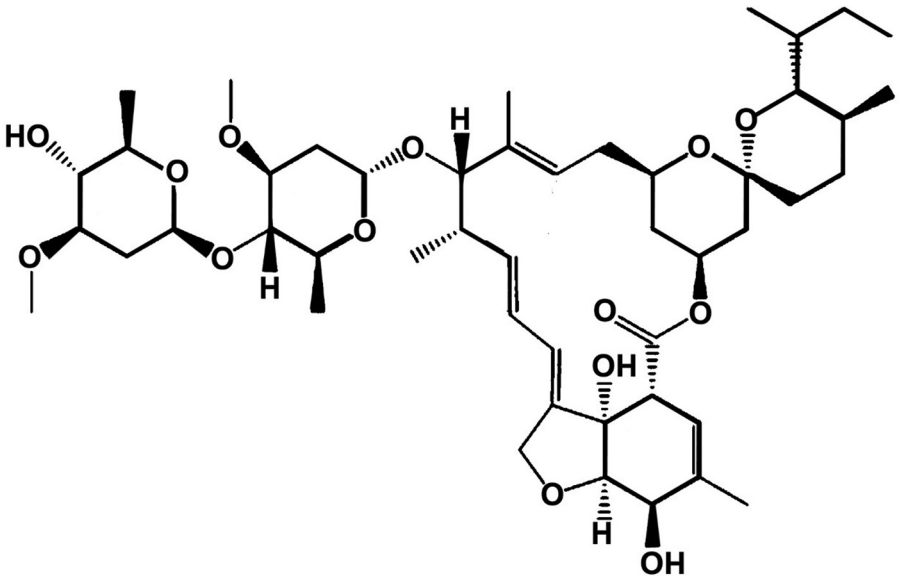
Ivermectin has attracted international attention for its use in the treatment of cases infected with COVID-19. In Peru, it was included in the national therapeutic guidelines for this pandemic. In Bolivia, there was a mass administration to 3 50 000 people for the treatment and prevention of COVID-19. Ivermectin market was restricted in Paraguay and Colombia for fear of mal-use [7].

Scientists suggest that the use of ivermectin against COVID-19 will need preclinical as well as clinical trials with enough funds to maintain the work [8].

A study was done in Latin America on 1408 PCR-confirmed COVID-19 hospitalized cases between the first of January and the end of March 2020. The data were collected from 169 hospitals in three continents. A single oral dose of ivermectin (150 μg/kg) was given to 704 cases, who were matched regarding their age, sex, race, and underlying morbidity, for example, history of smoking, obstructive lung disease, hypertension, diabetes, cardiac and coronary artery disease, and the taken medications including azithromycin, hydroxychloroquine, and corticosteroids. The group that was given ivermectin showed reduction in the need for mechanical ventilation and reduction in the death rate [7].

 DOI: 10.4103/kamj.kamj_37_20

Figure 1



The molecular structure of ivermectin [4].

In Bangladesh, some scientists claimed that a mixture of ivermectin in a single oral dose with the antibiotic doxycycline cured COVID-19-positive cases in less than 7 days without any adverse effects. They were especially proud of this finding owing to low cost of the combination of drugs [9].

The mode of action of ivermectin against viral infections is still not very clear, but it appears that it stops the processes that allow proteins to move within the virus. These proteins would normally modify the body's antiviral response, allowing the virus to replicate and enhance the infection [8–10].

A very nice and easy explanation of how the drug works was given by Dr Jans, who said, 'The main way ivermectin works is to target a key molecule of our cells that helps the virus to proliferate. By stopping this, the virus replicates more slowly, and so our immune system has a better chance to mount the antiviral response and kill the virus. Giving this or any antiviral drug early, is thought to give the body the best chance of beating infection' [11,12].

Members of the importin (IMP) superfamily of transporters of α-type and β-type are known to mediate the process of movement of protein between the cytoplasm and nucleus of the cells. This includes differentiation and development. Ivermectin was identified as one of the potent inhibitors of this process [10].

Wagstaff *et al.* [13] reported that ivermectin acts by inhibition of interaction between the HIV-1 integrase protein (IN) and the IMPα/β1 heterodimer responsible for IN nuclear import.

Other actions of ivermectin have been reported, but ivermectin has been shown to inhibit nuclear import of the host and viral proteins [14–16], including simian virus SV40 large tumor antigen and dengue virus (DENV) nonstructural protein 5 [10–13].

DENV was also proved to be affected by a single oral dose of ivermectin in Thailand [17].

Recently, Yang *et al.* [18] detected that ivermectin could dissociate the preformed IMPα/β1 heterodimer and prevent its formation. This was detected by binding to the IMPα armadillo repeat domain to affect IMPα thermal stability and α-helicity.

By using quantitative bimolecular fluorescence complementation, ivermectin was shown to inhibit NS5-IMPα interplay in cell context. All of these findings could restrict viral infections [18].

More studies showed that infection with RNA viruses, for example, DENV 1–4 [19], West Nile Virus [18] Venezuelan equine encephalitis virus [20], and influenza [21], was limited by the use of ivermectin.

These results were very promising as the virus responsible for the current COVID-19 (SARS-CoV-2), is a single-stranded positive-sense RNA [6].

Ivermectin is administered orally in the form of tablets or as an ethanolic extract. The bioavailability of the drug is affected by the ethanolic extraction and shows that it has a double availability as tablets or capsules. However, absorption was the same in all of these forms [22].

Ivermectin binds to plasma proteins with specific binding to serum albumin [23]. It was observed that the drug absorption was inefficient in cases with malabsorption of proteins and other nutrients as in cases with disseminated strongyloidiasis. The blood concentration of the drug in such cases was found less than in other healthy cases, indicating a need for other alternative route of administration. Thus, in cases, who cannot absorb oral medication, it is necessary to use the parenteral route to introduce ivermectin (which is not licensed for use in humans) [22]. The high lipid solubility of the drug makes it easily distributed in the body, especially in fatty tissue.

In vitro studies used a concentration of ivermectin in 2 μM. It led to inhibition of 50% of the proliferating viruses (IC_{50}). This concentration was measured to be 35 times more than the highest concentration in blood, after the administration of the approved dose of ivermectin (200 μg/kg). It is referred to as the total plasma concentration [24].

Ivermectin reaches the lungs, which are important target organs in cases with COVID-19, in an unbound form when administered in humans. There is a specific transport protein that keeps the drug in the lung tissue in certain concentration. The concentration of the drug in human lung tissue is difficult to be measured. Experimental work on cattle showed that the drug concentration in the lungs reached three times the concentration of plasma level. However, the researchers claimed that the lung ivermectin concentrations does not reach the IC_{50} after oral administration of the approved dose in humans [24].

Researchers from Australia used the ivermectin to treat cases with COVID-19, although they were not completely convinced. There was news about trials in London and Maryland, USA, under special occasions after conducting nonpublished animal studies [12].

In Latin America, the drug is used against common intestinal helminths known to modulate the immune responses that might affect the viral clearance. It is believed that if the use of the drug is not monitored properly in areas where it should be used to treat other diseases, nonsupervised doses of veterinary formulas could lead to some problems in mass-treatment regimens for the eradication of river blindness. There is also the false feeling of being protected [7].

Although ivermectin is approved by the FDA and is currently widely used to treat many parasitic diseases, showing a wide safety profile for human use [22,25], yet cases show some common adverse effects, including diarrhea, nausea, dizziness, and drowsiness. Less commonly, lack of energy, abdominal pain, constipation, vomiting, tremors, rashes, and itching may occur. Ivermectin may also interact with some medicines, such as the blood-thinning drug warfarin, or increase the severity of some conditions such as asthma [5].

If ivermectin is going to be used as a potential therapy against COVID-19, there will be some important questions to be answered regarding what is the proper dose? How it is delivered? What about its safety during pregnancy? Does it prevent COVID-19 infection? Does it reduce the severity of the illness? Does it shorten the time to recovery? [26].

These are very important reasons to recommend carrying out more studies before the drug is approved for the treatment of this serious pandemic.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

References

1 Coscione S, Esau T, Kekeubata E, Diau J, Asugeni R, MacLaren D, *et al.* Impact of ivermectin administered for scabies treatment on the prevalence of head lice in Atoifi, Solomon Islands. PLoS Negl Trop Dis 2018; 12: e0006825.

2 El-Dib N, Ali MI, Hamdy DA, Abd El Wahab WM. Human intestinal myiasis caused by *Clogmia albipunctata* larvae (Diptera: Psychodidae): first report in Egypt. J Infect Public Health 2019; 13:661–663.

3 The Global Technical Strategy for Malaria 2016-2030 was adopted by the World Health Assembly in May 2015, pp: 1–32, ISBN 978 92 4 156499 1

4 Heidary F, Gharebaghi R. Ivermectin: a systematic review from antiviral effects to COVID-19 complementary regimen. J Antibiot (Tokyo) 2020; 73:593–602.

5 McLachlan A. Head lice drug Ivermectin is being tested as a possible coronavirus treatment, but that's no reason to buy it. The Conversation 2020; XX:1–7.

6 Caly L, Druce JD, Catton MG, Jans DA, Wagstaff KM. The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. Antiviral Res 2020; 178:104787.

7 Chaccour CJ, Brew J, Garcia-Basteiro A. Ivermectin and COVID-19: how a flawed database shaped the pandemic response of several Latin-American Countries – Blog – ISGlobal, 19/6/2020.

8 Taylor M. COVID-19 treatment update: remdesivir, hydroxychloroquine, leronlimab, ivermectin, and more. Lab Equip 2020.

9 Bangladesh launches clinical trial of two-drug combination to. Available at: http://www.hindustantimes.com &z.rsquo; world-news &z.rsquo; bangladesh-launches-clinica

10 Wagstaff KM, Sivakumaran H, Heaton SM, Harrich D, Jans DA. Ivermectin is a specific inhibitor of importin alpha/beta-mediated nuclear import able to inhibit replication of HIV-1 and dengue virus. Biochem J 2012; 443:851–856.

11 Jans DA, Martin AJ, Wagstaff KM. Inhibitors of nuclear transport. Curr Opin Cell Biol 2019; 58:50–60.

12 Must read! COVID-19 drug research: ivermectin might emerge as one of the most suitable drug candidates for COVID-19-Thailand, 2020.

13 Wagstaff KM, Rawlinson SM, Hearps AC, Jans D. An alpha screen (R)-based assay for high-throughput screening for specific inhibitors of nuclear import. J Biomol Screen 2011; 16:192–200.

14 Mastrangelo E, Pezzulo M, De Burghgraeve T, Kaptein S, Pastorino B, Dellmeier K, *et al.* Ivermectin is a potent inhibitor of flavivirus replication specifically targeting NS3 helicase activity: new prospects for an old drug. J Antimicrob Chemother 2012; 67:1884–1894.

15 Kosyna FK, Nagel M, Kluxen L, Kraushaar K, Depping R. The importin alpha/beta-specific inhibitor ivermectin affects HIF-dependent hypoxia response pathways. Biol Chem 2015; 396:1357–1367.

16 van der Watt PJ, Chi A, Stelma T, Stowell C, Strydom E, Carden S, *et al.* Targeting the nuclear import receptor Kpnbeta1 as an anticancer therapeutic. Mol Cancer Ther 2016; 15:560–573.

17 Yamasmith E. He 34th Annual Meeting the Royal College of Physicians of Thailand. Chonburi, Thailand: Internal Medicine and One Health; 2018.

18 Yang SNY, Atkinson SC, Wang C, Lee A, Bogoyevitch MA, Borg NA, Jans DA. The broad spectrum antiviral ivermectin targets the host nuclear transport importin $\alpha/\beta 1$ heterodimer. Antiviral Res 2020; 177:104760. doi: 10.1016/j.antiviral.2020.104760. Epub 2020 Mar 3. PMID: 32135219.

19 Tay MYF, Fraser JE, Chan WKK, Moreland NJ, Rathore AP, Wang C, *et al.* Nuclear localization of dengue virus (DENV) 1-4 non-structural protein 5; protection against all 4 DENV serotypes by the inhibitor ivermectin. Antiviral Res 2013; 99:301–306.

20 Lundberg L, Pinkham C, Baer A, Amaya M, Narayanan A, Wagstaff M, *et al.* Nuclear import and export inhibitors alter capsid protein distribution in mammalian cells and reduce Venezuelan Equine Encephalitis Virus replication. Antiviral Res 2013; 100:662–672.

21 Gotz V, Magar l, Dornfeld D, Giese S, Pohlmann A, Hoper D, *et al.* Influenza A viruses escape from MxA restriction at the expense of efficient nuclear vRNP import. Sci Rep 2016; 6:23138.

22 Canga AG, Prieto AMS, Liebana MJD, Martinez NF, Vega MS, Vieitez JJG. The Pharmacokinetics and interactions of ivermectin in human – a mini-review. AAPS J 2008; 10:42–46.

23 Klotz U, Ogbuokiri JE, Okonkwo PO. Ivermectin binds avidly to plasma proteins. Eur J Clin Pharmacol 1990;39:607-608.

24 https://www.news-medical.net/news/20200427/Ivermectin-alone-not-useful-in-treating-COVID-19.aspx

25 Buonfrate D, Salas-Coronas J, Munos J, Maruri BT, Rodari P, Castelli F, *et al.* Mutiple-dose versussingle-dose ivermectin for *Strongyloides stercoralis* infection (Strong Treat 1 to 4): a multicentre, open-label, phase 3, randomised controlled superiority trial. Clinical trial, Lancet Infect Dis 2019; 19:1181–1190.

26 Navarro M, Camprubi D, Requena-Mendez A, Buonfrate D, Giorli G, Kamgno J, *et al.* Safety of high-dose ivermectin: a systemic review and meta-analysis. J Antimicrob Chemother 2020; 75:827–834.