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Narrative Review

A Review of the Antiviral Activity of Ivermectin and Its Use in the Treatment of Coronavirus Disease-2019

Christabel N. Hikaambo, MSc[1*]; Martin Kampamba, MSc[1]; Fernando Bwalya, BPharm[2]; Mutenje Mweemba, BPharm[3]; Chipo Siamutwe, BPharm[4]; Webrod Mufwambi, MSc[1]; Tadious Chimombe, MSc[1]; Michelo Banda, MSc[1]; Steward Mudenda, MSc, MPH[1]

[1]*Department of Pharmacy, University of Zambia, Lusaka, Zambia*
[2]*Kumera Pharmacy Operations, mPharma Zambia Limited, Lusaka, Zambia*
[3]*University Teaching Hospital, Lusaka, Zambia*
[4]*Solwezi General Hospital, Solwezi, Zambia*

[*]***Corresponding author***
Christabel N. Hikaambo, MSc
Department of Pharmacy, University of Zambia, P. O. Box 50110, Lusaka, Zambia; Tel. +260973760175; E-mail: xbellhikaambo@gmail.com; Christabel.hikaambo@unza.zm

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ABSTRACT

Background
The coronavirus disease-2019 (COVID-19) originated in China and was declared a pandemic by the World Health Organization (WHO) on 11th March 2020. Since its emergence in December 2019, there have been challenges in developing drugs that are effective against the virus. Currently, COVID-19 is managed using symptomatic and supportive therapies, antiviral agents, cellular and immunotherapy. Besides, most of the treatment modalities are still under investigation and treatment guidelines vary from one country to another. Ivermectin is among the drugs that are being used as part of treatment guidelines in certain countries like the Republic of Peru. However, the WHO recommends that ivermectin only be used in clinical trials.

Aim
The authors conducted this review to explore published studies on the possible therapeutic effects of ivermectin against active infection with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), a causative agent of COVID-19.

Methods
A literature search was conducted using Google Scholar, PubMed and EMBASE for articles published from 2016 to 2021. Search words used included ivermectin, antiviral, COVID-19, efficacy, safety, dosing, lower mortality rate, hospitalised patients and the Boolean operator 'AND'.

Results
A few clinical trials have shown that ivermectin is safe for use in humans at specific doses and reduces the severity of the infection. Ivermectin was seen to reduce the signs and symptoms associated with COVID-19 in some studies while others showed no significant reduction. However, more studies must be conducted to ascertain its use in treating COVID-19.

Conclusion
Since many clinical trials are being conducted on the use of ivermectin to treat COVID-19, full evidence will be used to support its use in humans. Currently, some countries that are using ivermectin for treating COVID-19 have reported it to be effective and reduces morbidity and mortality associated with the disease. Therefore, countries should collaborate and provide full evidence for the use of ivermectin in humans to manage COVID-19.

Keywords
Ivermectin; COVID-19; SARS-CoV-2; Clinical trials; Antiviral.

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INTRODUCTION

The World Health Organization (WHO) received reports of pneumonia of unknown aetiology diagnosed in Wuhan, Hubei province of China on 31st December 2019.[1,2] In January 2020, the causative agent of pneumonia of unknown aetiology was identified as a novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and the disease was later named coronavirus disease 2019 (COVID-19).[3,4] COVID-19 was eventually declared a global pandemic by the WHO on 11th March 2020.[5,6]

The signs and symptoms of COVID-19 vary depending on the severity and co-morbidities. The common signs and symptoms of COVID-19 are fever, dry cough, fatigue, sore throat, diarrhoea, headache, loss of taste and smell, dyspnoea, shortness of breath and chest pain or pressure.[7-13]

Different therapies are used for managing COVID-19 with variable treatment outcomes in patients. Antivirals, anticoagulants and anti-inflammatory agents that among agents used. Ivermectin is an antiviral agent and targets the host importin (IMP) α/β1 nuclear transport proteins responsible for nuclear entry of cargoes such as integrase and non-structural protein 5 (NS5)[14,15] and hence its use against COVID-19 which is being investigated in clinical trials.[16] In some countries such as the Republic of Peru and the North-eastern Beni region of Bolivia, ivermectin has been approved for treatment of COVID-19 in humans.[17] Notably, about 70 trials globally are presently testing the clinical benefit of ivermectin to treat or prevent SARS-CoV-2.[17,18]

METHODOS

Study Design

The literature used in this review was searched using Google scholar, PubMed and Excerpta Medica dataBASE (EMBASE). The keywords that were used in the search included ivermectin, COVID-19, antiviral activity, efficacy, safety, dosing, lower mortality rate, hospitalised patients and the Boolean operator 'AND'. This narrative review was performed from June 2021 to September 2021. We included all articles that were published in English from January 2016 to September 2021. We excluded all articles that had an abstract only. From a total of 65 articles that were retrieved, only 40 were used in our review based on the inclusion and exclusion criteria.

RESULTS AND DISCUSSION

Antiviral Activity of Ivermectin

Ivermectin is a Food and Drug Administration (FDA)-approved broad-spectrum anti-parasitic agent with demonstrated *in vitro* antiviral activity against some deoxyribonucleic acid (DNA)[19] and ribonucleic acid (RNA) viruses,[20] including SARS-CoV-2.[16,21-23]

The antiviral activity of Ivermectin is through the inhibition of nuclear import proteins of viruses as well as those of the host.[24,25] Ivermectin was originally noted to inhibit human immunodeficiency virus-1 (HIV-1) replication by inhibiting the interaction between the HIV-1 integrase protein and the importin (IMP) 1 heterodimer which is responsible for integrase protein nuclear import.[19,23] Ivermectin inhibits the transporter complex "*nuclear transporter mediated by a/β importin*", which is fundamental to the viral replication process; and binding to RNA-dependent RNA polymerases.[26,27] This prevents viral proteins from entering the nucleus, hence thereby reducing the inhibiting antiviral responses and leading to an efficient antiviral response.[20] Ivermectin also acts by inhibiting the nuclear import of *UL42* which is an accessory unit of DNA polymerase.[19,24]

Some studies done on SARS-CoV proteins have revealed that IMP α/β has a potential role during the infection in the signal-dependent nucleocytoplasmic shutting of the SARS-CoV nucleocapsid protein which may impact host cell division.[17,25,28] Most RNA viruses depend on IMP α/β for the transport of viral proteins at the time of infection, and ivermectin inhibits this import in thus enhancing antiviral activity observed in SARS-CoV-2 studies.[24] The transmembrane CD147 along with angiotensin-converting enzyme-2 (ACE-2) has been recognized as a major binding site for SARS-CoV-2 spike proteins.[24] Ivermectin has been shown to shield the spike proteins from the host receptor cells thereby interfering with the attachment of SARS-CoV-2 spike protein to the human cell membranes.[22,24]

It was proposed that human studies have to be conducted to fully observe the antiviral activity of Ivermectin earlier observed. Following-up, a pilot trial assessed the antiviral effects and safety of various doses of ivermectin in patients with mild symptoms of COVID-19. A total of 32 patients were enrolled who were randomly assigned to four groups that received standard of care treatment at hospital admission; standard of care treatment plus ivermectin 100 mcg/kg; standard of care treatment plus ivermectin 200 mcg/kg; or standard of care treatment plus ivermectin 400 mcg/kg.[29] In this study, the primary endpoint was testing negative twice for the SARS-CoV-2 reverse transcription–polymerase chain reaction (RT-PCR) test after 7-days of hospital admission. The results showed that those who received standard of care treatment plus ivermectin had a higher reduction in viral load compared to those who received standard of care treatment alone in a dose-dependent manner. This was also reported in a similar study by Pott-Junior et al.[16] This pilot study demonstrates that ivermectin combined with standard of care treatment in the management of COVID-19 presents an effective and adjuvant therapy. However, there is a need to conduct multi-centre studies to provide evidence that can be generalized to other patients.

Dosing of Ivermectin: Ivermectin Dose that Reaches the IC50 in the Lungs after Oral Administration

Ivermectin has a valuable clinical role in the management of different parasitic and helminthic diseases.[30] Ivermectin can be administered orally, subcutaneously, intramuscularly or topically at a dose range of 150-200 μg/kg in humans.[31] From some of the studies conducted, ivermectin has been reported to inhibit SARS-CoV-2 *in vitro* at certain concentrations. Caly et al[28] reported that Ivermectin inhibited SARS-CoV-2 *in vitro* causing a 5000-fold reduction in

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viral RNA at 48-hours with ivermectin at 5 μM. The concentration resulting in 50% inhibition (IC50) of 2 μM (1,750 ng/mL) is over 35 times higher than the maximum plasma concentration (Cmax) of 0.05 μM (46.6 ng/mL) after oral administration of the approved dose (~200 /kg μg) and ivermectin showed little to no activity at 1 μM *in vitro*. Because Ivermectin is highly bound to serum albumin (93%), the IC50 is in orders of magnitude higher than the unbound plasma Cmax after approved doses of ivermectin (0.0035 μM; 3.26 ng/mL).[20,28]

However, to translate the *in vitro* activity of ivermectin and relate it to the activity in humans, there is a need to evaluate these concentrations and compare them to the lung concentrations of orally administered Ivermectin.[32] For ivermectin to reach the lungs, all the pharmacokinetic parameters have to be considered as in theory, only the unbound drug reaches the lungs and other tissues through passive diffusion.[32,33] The likelihood of Ivermectin reaching the lungs after oral administration is related to its high lipophilicity, low ionization at physiological pH, protein binding capacity (about 93% serum albumin), as well as the transporters that maintain tissue distribution.[32]

Schmith et al[32] revealed that the total plasma concentration of ivermectin (bound and unbound) do not reach the IC50 as reported by Caly et al[28] even for a dose that is 10 times higher than the approved dose of ivermectin or after it is dosed repeatedly. The study showed that the plasma exposures did not increase substantially after repeat dosing with ivermectin accumulation in plasma after weekly dosing being very limited. The study showed that even with the high lung homogenate to plasma ratio, ivermectin is unlikely to reach the IC50 of 2 μM in the lungs after single oral administration of approved dose (predicted lung concentration being 0.0873 μM) or at doses 10 times higher than the approved dose after oral administration (predicted lung concentration being 0.820 μM). The study suggested that the approved dose of ivermectin alone has a low chance of being successful in the treatment of COVID-19.[32]

To reach the targeted concentration for the proposed mechanism of action for ivermectin, its IC50 is supposed to be 17 μmol/L.[14] Ivermectin antiviral concentrations expected to be effective are an overdose which could penetrate the blood-brain barrier and produce main adverse events especially doses earlier documented in preclinical mammalian testing.[34] In summary, the available pharmacokinetic data disapprove the use of ivermectin in the management of COVID-19, even though it is said to be a broad-spectrum antiviral agent, its potential is still *in vitro* and not *in vivo* as the SARS-CoV-2 inhibitory concentrations are practically not attainable in humans.[30]

The delivery of ivermectin by pulmonary route would provide high drug deposition in the airways and lungs. However, there is a need for investigations and new technology to overcome the mechanical, chemical, immunological and behavioural barriers that hinder the respiratory route of administration.

Efficacy and Safety of Ivermectin

Currently, the United States website ClinicalTrials.gov lists a total of 197 studies of Ivermectin worldwide, of which 81 related to SARS-CoV-2 or COVID-19 infection or sequelae. As of this writing, one trial to reduce viral load is underway, and 50 studies are not yet recruiting, recruiting by invitation only, or actively recruiting new study subjects.[i] Ivermectin has an established safety for human use and is FDA approved for some parasitic diseases.[17] The clinical efficacy of ivermectin in the treatment of COVID-19 has remained difficult to predict as we are dealing with a novel and frequently mutating virus.[20] Ivermectin has shown to be efficacious in the treatment of adult COVID-19 patients with mild symptoms.[16,35] The safety of ivermectin in animals and humans has been shown after oral, subcutaneous or topical administration at the recommended dose range (150-200 μg/kg in humans and 6-500 μg/kg in animals depending on species and formulation) and the indicated clinical applications. Within these dose ranges, pharmacokinetic characterizations have shown that attainable peak plasma concentrations increase with dose and may range from 20-81 ng/mL in humans.[31]

A study reviewing the safety and tolerability of escalating doses of ivermectin in healthy humans showed that a single dose (120 mg) that is 10-fold more than the clinically recommended dose (200 μg/kg) was well tolerated and it yielded a peak plasma concentration equivalent to 248 ng/ml with an elimination half-life of 19-hours.[23,31] Similarly, population-based pharmacokinetic modelling showed that ivermectin administered orally for 3-days at 600 μg/kg would yield maximal median plasma concentrations of 105-119 ng/ml (0.12-0.14 μM) and an elimination half-life of 3-5-hours.[23] These results suggest that even with extremely high doses of ivermectin, attainable peak plasma concentrations would remain markedly lower than the established IC50 concentrations for most viruses *in vitro*, though significantly higher than 0.5-1 ng/ml that is widely considered optimal for curative anthelminthic activity. The use of extremely high doses of ivermectin increases the prospect of adverse drug-drug interactions in patients requiring polypharmacy, as is often the case in treatment of viral infections and other infectious diseases.[31]

A recent randomised clinical trial assessed the efficacy of ivermectin at a dose of 300 μg/kg of body weight per day for 5-days *versus* the placebo. The main outcome of the study was complete resolution of symptoms within 21-days and the secondary outcome was the frequency of adverse events that were observed after using ivermectin in comparison to the placebo cohort. The results from this study show that additional multi-center research may be needed to demonstrate more robust evidence of a role for the use of ivermectin in the management of COVID-19 as there was no statistical significance in the resolution of symptoms between ivermectin and placebo. The guidance provided by the WHO says that ivermectin should only be used in a research setting such as clinical trials.[36] Therefore, all individuals using ivermectin should do so only for clinical trial purposes.

i. National Institutes of Health (NIH) U.S. National Library of Medicine. Web site. https://clinicaltrials.gov/ct2/results?cond=&term=ivermectin&cntry=&state=&city=&dist=. Retrieved October 3, 2021. Accessed October 3, 2021.

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Association of Ivermectin with Lower Mortality Rates in Hospitalised Patients

The use of ivermectin for the treatment of patients hospitalised with COVID-19 infections of mild-to-moderate severity has previously been shown to significantly lower mortality and morbidity rates associated with infection.[24] In an urgent search for useful treatments, this has led to the "off-label" use of this drug in the management of COVID-19 (i.e. unapproved by regulators such as the United States FDA for that particular clinical use). Studies have been conducted to demonstrate the relationship between the use of ivermectin and lower mortality rates in hospitalized patients.

A multihospital retrospective, unmatched cohort study by Rajter et al[27] conducted at a four-hospital consortium in South Florida reported that there was a reduction in the mortality rate of COVID-19 hospitalised patients who were treated using ivermectin. This observation was especially seen in patients who required higher inspired oxygen or support for ventilation. Analysis of results indicated that the mortality rate for those treated with ivermectin was 15% *versus* 25% in the usual care arm, with a significance level of p=0.03. There was a significant association of ivermectin with improved survival for patients who were admitted with COVID-19.[27] The positive association was also seen in the subject subgroups with severe pulmonary disease and other comorbidities. It also showed that the mortality for the subgroup of patients who had severe pulmonary involvement was lower in the ivermectin treatment group (38.8%) compared to the usual treatment group (80.7%) from the standard of care subject arm of the study, at a significance level of p=0.001. The length of hospital stay was not significantly different between the Ivermectin treatment group and the regular treatment group.[27] Because the cohorts were not matched and the study was not prospective, this study presents methodological limitations that may limit more than limited generalization to other settings or populations.

Ahmed et al[37] revealed that early intervention with ivermectin for the treatment of hospitalized mild to moderate COVID-19 infected patients may lower the amount of viral replication in the host. Early intervention in people with mild infection was associated with faster viral clearance, suggesting improved host immunity as well as the presumed lessening of viral transmission. Another study has also shown a reduction in mortality in ivermectin-treated patients with severe COVID-19 pulmonary involvement.[38] According to the pilot study conducted by Pott-Junior et al,[16] ivermectin used with standard of care (SOC) treatment was seen to reduce the risk of COVID-19 progression. The patients who were treated with standard of care treatment plus ivermectin at 200 mcg/kg or more had better clinical outcomes compared to those treated with SOC alone. Additionally, another clinical trial investigated ivermectin's potential to prevent hospitalisations in individuals with early COVID-19. The efficacy of ivermectin to prevent hospitalizations was evaluated as primary outcome. The results showed that ivermectin had no significant effect on preventing hospitalization of patients with COVID-19 and patients who received ivermectin required invasive mitral valve surgery (MVS) earlier in their treatment than those who were on placebo.[39] These findings are in agreement with a similar study where there was no improvement in symptom resolution among those that received ivermectin compared to the placebo.[29]

On the contrary to no significant group differences in the trial stated above, ivermectin was found in Rajter et al[27] work to reduce mortality rates in patients with COVID-19 especially those with severe pulmonary involvement. However, the authors recommended randomised clinical trials to prove these findings. Another study in Egypt found a reduction in hospitalisation among patients who received ivermectin in comparison to those who received the standard of care alone.[40] Noted reductions in hospital stay and mortality shows the potential benefits of using ivermectin in the treatment of COVID-19.

Despite studies showing the association of ivermectin with lower mortality rates in the management of COVID–19, other studies have shown no improvement or effect on time-to-resolution of the symptoms. In the double-blind, randomised trial conducted at a single site in Cali, Colombia, 200 patients were randomised to receive ivermectin, 300 µg/kg of body weight per day for 5-days whereas 200 patients received the placebo for 5-days.[29] The most important outcome in this study was that 82% of participants on ivermectin had their symptoms resolve by day 10 while 79% of participants on the placebo had their symptoms resolve by day 12.[29] A 5-day treatment course of ivermectin among adults with mild COVID-19 did not significantly improve the time to resolution of symptoms compared with placebo. The findings, thus, did not support the use of ivermectin for the treatment of mild COVID-19.[29] Therefore, studies have produced different findings on the use of ivermectin in the treatment of COVID-19. This means that there is a need for adequate evidence supporting or disputing the use of ivermectin to treat COVID-19. This is also supported by the WHO conclusion on the ability of ivermectin to reduce mortality rate which was found to be of very low certainty hence the suggestion that the drug only be used within clinical trials until more data is available.[36]

CONCLUSION

The use of ivermectin in the treatment of COVID-19 has been supported by two studies. However, large clinical trials are needed to provide sufficient methodological rigor and unequivocal evidence for the clinical use of ivermectin in the treatment of COVID-19 in humans. Multi-center clinical trials are warranted to support the use of this drug in humans confidently and also to ascertain its safety at different therapeutic doses in the COVID-19 patient population.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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