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COVID-19 and Ivermectin: Potential threats associated with human use

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ABSTRACT

Drugs re-purposing due to COVID-19 virus has declared a number of useful candidates for treatment and prevention of the virus. Ivermectin (IVM) has gained much popularity due to a strong background of magical applications against a broad spectrum of pathogens. The *in- vitro* studies of ivermectin have shown promise, the thorough clinical trials of its efficacy in the treatment and prevention of SARS-CoV-2 are still warranted. Useful strategies for analyzing projected use of IVM in human coronaviruses might be developed. It may be done by concluding ongoing clinical trials and culturing lessons from IVM usage in veterinary practice. The potential toxicity and careful dosage analyses are urgently required before declaring it as an anti-SARS-CoV-2 drug candidate. This manuscript overviews the background and potential threats associated with the off-label use of IVM as prophylactic drug or treatment option against COVID-19 virus.

1. Introduction

Ivermectin belongs to the group of Avermectins (Macrocyclic Lactones) mainly developed as pioneer endectocide for animals [1]. The mode of action of ivermectin is attributed to its binding affinity towards the glutamate gated ion channels, leading to hyperpolarization and paralysis of invertebrates [2]. It is investigated that ivermectin, being a bio-inspired drug has very efficient applications against the variety of parasites, disease vectors, viruses, bacteria and fungi [3,4,5]. To date, the U.S. Food and Drug Authority has approved the use of ivermectin against head lice, lymphatic filariasis, onchocerciasis, strongyloidiasis, rosacea and scabies [6]. 'Ivermectin' as an anti-parasitical has attracted great market potential, owing to the ease of use in the form of tablets, bolus, drench, pour-on, spot-on, injectables for animals and syrup, suspensions, creams and tablets for human beings.

Based on its magnanimous promise, it was distributed for successful prevention and control of Onchocerciasis and Filariasis in Africa [7]. Moreover, it has been proposed to employ mass drug administration (MDA) of ivermectin against malaria (*Plasmodium spp.*) in highly endemic regions of the world [1,8]. The need for repurposing ivermectin in malaria endemic regions ascended due to the resistance development against chloroquine (line of treatment for malaria). This strategy is most important to consider before promoting the excessive use of ivermectin in lower middle income countries having endemic parasite diseases.

The magnitude of global pandemic of COVID-19 virus signposted the urgency of declaring clinically efficient therapeutic candidatures [9]. Additionally, the high risk of aerosol infection of the virus indicated the need to re-purpose some drug having potential of protective prophylaxis. Among important anti-parasiticals, the projected *in-vivo* use of Hydroxychloroquine and Ivermectin, based on *in-vitro* studies gained a lot of research attention [10,11]. However, potential of highly potent ivermectin needs detailed clinical investigation before declaring the probability of its use against COVID-19 pandemic. The administration of vaccines, counteracting the severity of symptoms in SARS-CoV-2 challenge infections support this measure as being more useful and safe.

2. Pharmacological applications of 'ivermectin'

To the extent of laboratory scale *in-vitro* and limited *in vivo* experiments, IVM seems to be a wonder drug. Primarily, the drug

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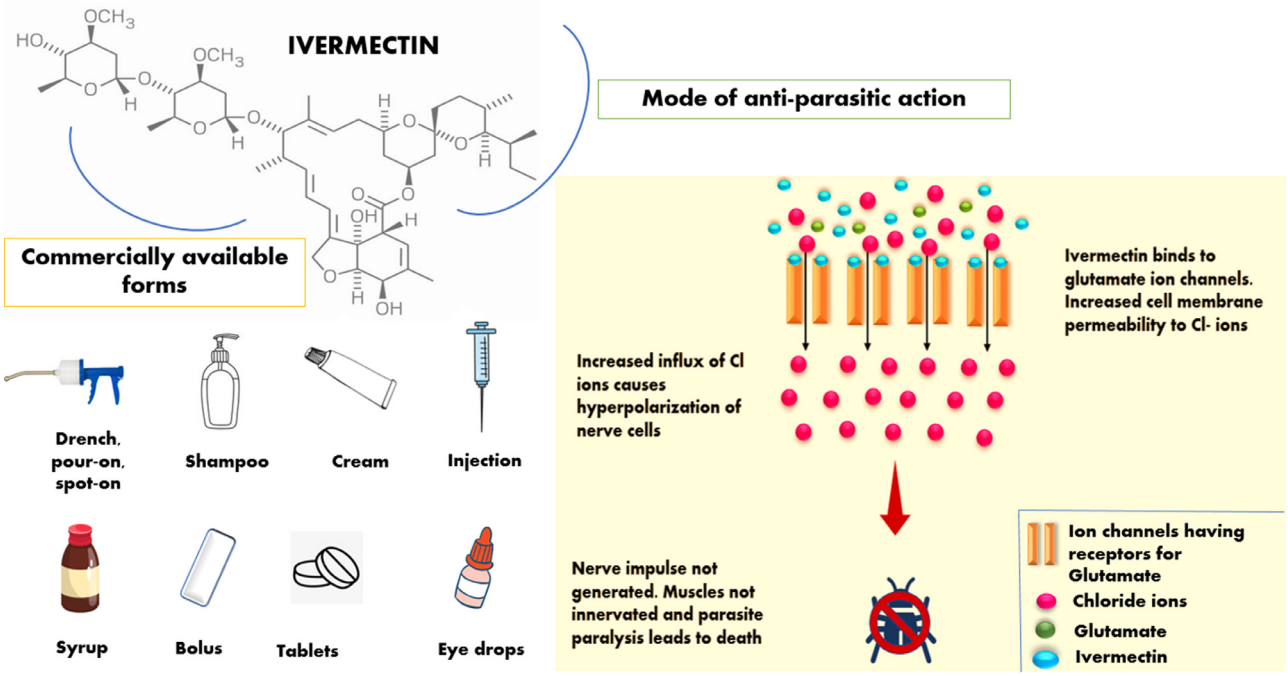

Fig 1. vermectin use and mode of action.

was developed to treat parasitic infections which were difficult to treat with other anti-parasitics [12]. It has been shown to inhibit a broad spectrum of bacteria, DNA and RNA viruses [13,14]. Based on the number of studies on efficacy of ivermectin are still lacking and warrant more investigation [15]. IVM has also been proposed to inhibit the transmission of mosquito vectored malaria [16]. Recently, it has been reported that high doses of ivermectin are required to kill *Aedes* mosquitoes, owing to the emerging resistance [17]. This fact substantially opposes the idea of using IVM in MDA strategies to reduce/eliminate mosquitoes and mosquito-borne diseases of Humans.

There's a limited understanding of complex pharmacodynamics of IVM in humans [18]. Based on current understanding, however, the drug is thought to be cleared in 2 cycles, leading to the subsequent plasma peak levels. The first one being hepatic P450 dependant and the recycling by enterohepatic route. The high lipohilic nature of 'ivermectin' leads to first peak within 3–5 h of oral administration [19]. IVM doesn't cross the blood brain barrier in vertebrates, owing to its high specificity in targeting the glutamate-chloride ion channels of neurons [7]. The summary of commercial preparations and mechanism of action as anti-parasitical has been given in **Fig. 1.**

'Ivermectin' has been shown to very precisely target the viral capability to import innate and host proteins, bringing major conformational variations [20,21]. Most recently, this drug has been widely re-purposed to be used as a potential candidate for COVID-19 treatment and prophylaxis [10,22,23,24]. IVM has been reported to specially inhibit the IMP α form and/or other enzymatic pathways, responsible for nuclear transport of viral proteins in human coronaviruses [25,26]. A number of reports and opinions have shown strong recommendations for the use of ivermectin against the global pandemic of COVID-19 virus. However, it is imperative to thoroughly test the efficacy of IVM in pre-clinical and clinical studies within validated models of the diseases [24]. Some reports however, owing to the bias influenced by confounding factors have shown lack of COVID-19 virus treatment by the utilization of approved therapeutic dose (200ug/kg) of ivermectin [27].

Therapeutic safety information of IVM use in children, elderly (more than 60 years age) and pregnant women is still very limited [28]. The adverse events (AE) of IVM in already parasitic infested individuals have also been reported [29,30]. The utilization of IVM against SARS-CoV-2 has not yet been declared to be clinically efficient. Recently, a study on non-severe SARS-CoV-2 affected patients using IVM has reported no significant contribution to the immunity, reduction in viral loads and ameoliration of symptoms [31]. The authors have reported the reduction in cough and hyposomia and changes in viral loads which have been lined to the requirement of more prospective trials of similar nature. However, the CDC and WHO (PAHO) have clearly dissuaded the use of IVM in the prevention or treatment of COVID-19 [32]. Since there is lack of well-researched, safe therapeutic window for IVM use in COVID-19 patients, the drug use may not be advocated. It is also timely to highlight the possible factors for failure of desired ivermectin action on the subjects in the parasite-pandemic regions of the world.

3. Lessons from use of ivermctin in veterinary practice

Extensive use of ivermectin in animals in developing countries have some lessons to learn, prior to going for the broad-scale administration of this drug. It is imperative to note that non-judicious use of this drug may create resistant and tolerant parasitic populations both in animals and human beings [16,33,34]. Repurposing IVM use, based on lack of resistance reports in Humans may not be a good scheme to confront emerging and re-emerging infectious diseases of Human concern. Another important feature of using sub-lethal doses of ivermectin in animals could be leading to the development of step-wise tolerance against other macrocyclic lactones [35].

Primarily, IVM had been designed against selected parasites of animal and human concern [36]. However, the unguarded use in various forms and combinations has led towards tolerance and eventually resistance in some parasites and disease vectors [37,38,39]. Inclusion of higher doses or combinational therapies with other anti-parasiticals has further worsened the scenario of

drug residues in farm animals. The IVM residues from milk of treated animals has been shown to contain residual concentration during/after cheese processing [40]. Drug withdrawl periods of anti-parasiticals are not well-observed in developing nations, owing to many factors. IVM residues in farm animal products signpost the probable development of resistance in Human consumers.

From this perspective, there arises a potential question of the levels of ivermectin resistance already circulating in Humans through animal products consumption, particularly in the developing nations where drug withdrawal periods are not always observed, let alone the deliberate use of this drug in Humans. It has been noted that there's a list of different ivermectin induced-idiosyncratic reactions in animals which might end up in severe toxicity even at approved therapeutic doses in animals.

An important approach for safety analyses and evaluation of IVM is determination of residues in environment. The exclusive fecal excretion of the drug indicate the potential hazard of sewage water contamination and possible transmission of drug residues in un-exposed subjects. There's dearth of research supported data on the effect of animal/Human IVM usage on the soil, air and water contamination. While this domain from One-health umbella remains unexplored, the MDA of IVM for prevention and treatment of diseases could create potentially hazardous aftermaths.

4. Ivermectin and COVID-19

The transmission of SARS-CoV-2 via aerosol route is indicative of it's preventable nature. However, the hospital acquired infections could be prevented by the use of protective vaccines. The druggability analyses of nCoV-19 has revealed promising candidates for drug efficacy [41]. To date, there's no complete treatment providing promising efficacy from clinical scenarios for SARS-CoV-2 virus [23,42]. It was shown that the short term and high dosage hydroxychloroquine failed to provide protection or treatmet against SARS-CoV-2 virus, after 4 days of exposure [43]. Inhalant form of IVM has also been re-purposed as more economical and efficient way to curtail the SARS-CoV-2 viral infection [44]. At this point of rapidfire ideas and lab scale research, it is required to extract clinically relevant data regarding the promise of IVM against COVID-19 virus.

The use of prophylactic drugs without complete efficacy and clinical evaluation can create serious aftermaths [45]. Ivermectin is a promising therapeutic agent against a variety of human and animal diseases [46]. Recently, an *in-vivo* study in mouse model has predicted the promise of IVM against a murine hepatitis virus [47]. The potential neurotoxicity and hepatoxicity are two major adverse reactions that should be taken into account before prescribing to weak and old age persons. There's still dearth of scientific support by *in-vivo* trials that could declare ivermectin as practically possible anti-corona therapy.

Most importantly, the safe therapeutic window of ivermectin for use in humans (as anti-parasitic) didn't show promise against viral pathogens [35]. Recommending or practically employing its usage at mass levels should be well-calculated by research and evidence [48]. The therapeutic and prophylactic doses may be carefully optimized before prescribing the drug at clinical levels. Unguarded, off label use of this drug may create increased surge of resistance at previously effective therapeutic dosage, in addition to concerns for prior mentioned toxicities. This situation may aggravate many clinical failures instead of promoting health and well-being of SARS-CoV-2 patients. Rapid popularity of any drug amidst deadly pandemic without strong data-base, declaring its safety can potentially aggravate the extra-label usage.

Moreover, the dose standardization in case of immune-compromised/ co-morbid, at risk and previously COVID-19 challenged individuals is still lacking. This is evident by one of the ongoing interventional trial to investigate the potential of IVM in preventing hospitalizations of COVID-19 patients [49]. The exclusion criteria of this clinical study eliminates kidney, liver or other chronic disease patients, pregnant and breast feeding individuals. Similarly, rheumatoid arthritis is routinely counteracted by the prophylactic dose of hydroxychloroquine in human subjects. The emergent idea of using these drugs, prescribed uncautiously could be a potential concern to frequent users [50]. Moreover, the inclination towards using an easily available and economical drug like IVM remains a serious concern of devolping and under developed nations of the world [51]. The subsequent aftermath of this off-label use may result in increased drug toxicities, resistance/tolerance and total exclusion of the drug from efficient therapeutic candidates eventually.

Owing to the high lipid solubility, the ivermectin reaches a maximum blood concentration of 20–80 ng/ml, when admistered orally [52,18]. Therapeutic doses of upto 2000 μg/kg in humans have been well-tolerated [19,28]. The lower plasma half life of 12 h also indicates the rapid solubility of the drug in humans [53]. However, the *in vitro* drug level required against SARS-CoV-2 was found to be in micrograms [54]. Currently, the trials are underway to confirm whether the therapeutic dose of 600–1200 µg/Kg for 5–7 consecutive days may efficiently treat the COVID-19 without adverse effects in the patients [55,56]. This much difference in the dosage of ivermectin indicates the urgent need of clinically evaluating the pharmacodynamics of this drug, before rapid firing it as a prophylactic candidate for healthcare/front line workers.

Modern technologies *viz.* micro and nanotechnology, for developing more efficient ivermectin formulations can help to overcome challenges associated with drug efficacy [57,58]. Approaches to standardize the current dosage of ivermectin may be critically evaluated to reduce the required dosage in humans. This could be made possible by the use of some drug potentiators enhancing efficacy of ivermectin. Nanomaterial-Ivermectin composites have been shown to enhance protective efficacy and long term stability in the blood against Zika virus *in-vitro* [59]. Recently, a study concluded the stability of non-immunogenic nanoparticles combined with ivermectin, tagged with immunoglobulin fragment (orally fed) as the treatment and prevention against SARS-CoV-2 [60]. However, the *in-vivo* safety and biodegradability of nanomaterials after being exposed to lung epithelia warrant more research focus. Another study has shown promising use of flavonoids against SARS-CoV-2 using molecular docking approaches [61]. The concern of synthetic nanomaterials use could be eliminated by employing nanoparticles arising from phyto actives [62,63]. Moreover, these compounds themselve can potentiate the anti-COVID-19 activity. Vaccine administration against COVID-19 has been declared safe and effective [64,65]. It can potentially help in reducing the symptoms associated with mild, moderate and severe infections with SARS-CoV-2 virus. The risk of virus transmission after the vaccine administration could also be lowered [66]. Many developed and developing nations have therefore employed anti-COVID-19 vaccine program on the urgent basis, owing to the emergence of most recent wave of COVID-19 virus.

Conclusions and future outlook

The transmission dynamics of this pandemic indicate the high probability of preventing infection by taking necessary precautionary measures. In synergy with these measures, the promise of anti-SARS-CoV-2 vaccines in clinical trials seems promising. The drug re-purposing trend may have some appearantly useful candidates to offer, whose clinical probing is highly warranted. CDC and WHO have clearly discouraged the use of IVM against COVID-19 viirus and this stance should be well-implemented at all levels of the healthcare system.

As a way forward, especially considering ivermectin's potential for nervous and hepatotoxicity in addition to drug resistance/tolerance, there's an urgent need for conducting more research, focused to rationalize the dosage on personalized basis of patient's condition, age-group, risk assessment and history. Surveillance of circulating and acquired levels of ivermectin resistance, specially at developing Nations is urgently needed, prior to ivermectin's use as anti-SARS-CoV-2. There's an urgent need to dessiminate the vaccine safety and efficacy information, for a widened spectrum of COVD-19 prevention. Taken together, the concerns associated with ivermectin's application in clinical settings may be adequately addressed to declare it as a safe anti-viral drug at a safe dosage.

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Tean Zaheer: Full writing and Analysis part of the manuscript
Kaushik Pal: Plan of research direction, polishing scientific illustrations
Rao Zahid Abbas: Research investigation and data analysis
María del Pilar Rodríguez Torres: Figures moderation and throughput contributions in the manuscript analysis

Declaration of Competing Interest

There are no conflict of interest along the authors to publishing this article.

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