IJNRD.ORG ISSN : 2456-4184
INTERNATIONAL JOURNAL OF NOVEL RESEARCH AND DEVELOPMENT (IJNRD) | IJNRD.ORG
An International Open Access, Peer-reviewed, Refereed Journal

Repurposing Ivermectin: Insight from Preclinical and Clinical studies

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ABSTRACT

Ivermectin is a sixteen-membered macrocyclic lactone that has been used extensively to treat parasitic infections in both humans and animals due to its wide range of antiparasitic properties and minimal toxicity. It is used "off-label" to treat a variety of worm-related parasite disorders, especially in domestic animals, in addition to its approved usage in treating human river blindness and strongyloidiasis and animal roundworm and arthropod infestations. Furthermore, a number of experimental investigations show that ivermectin exhibits strong antiviral, antibacterial, antiprotozoan, anti-trematode, and anti-insect properties. This review article describes the recent numerous researches in human and animals for its usage in therapy of parasite dieases in human and animals 40 years of study on the antiparasitic effects of ivermectin, and the use of the medicine in the treatment of parasitic disorders in humans and animals

KEYWORDS: Ivermectin, Antiparasitic activity, licensed use, “off-label” use, Experimental use

INTRODUCTION

Ivermectin, on the WHO’s List of Essential Medications, has been in clinical use since 1981 as an orally and topically active agent for treating a range of parasitic infections in humans, including river blindness and lymphatic filariasis. It is also widely used in veterinary practice

Anecdotally, the use of the standard clinical dose of ivermectin, 9mg once, has been associated with some cases of rapid clinical resolution in severe hospitalised COVID-19; clinical studies evaluating its utility in this regard are underway. Ivermectin is reported to inhibit the proliferation of SARS-CoV-2 in vitro, but the IC50 for this effect, 2μM, has been noted to be 35-fold higher than the maximal concentration achieved after the administration of the approved clinical dose (9mg) to humans, casting doubt on the utility of this agent as an antiviral drug in COVID-19 unless very markedly higher doses are used (1)

Ivermectin is a derivative of the 16-membered macrolide compound abamectin, which was first widely used in clinical practice as an antiparasitic drug. Ivermectin can increase the activity of γ-aminobutyric acid receptor or glutamatechloride ion channel (Glu-Cl), increase the influx of chloride ions, and cause the cell membrane hyperpolarization, thereby blocking signal transmission between neurons and muscles (Martin et al., 2021), which exerts its antiparasitic effects. Ivermectin could be used, in addition to as an antiparasitic drug, as antiviral agents such as Flavivirus, HIV-1 virus, and SARS-CoV-2 virus (2). Moreover, studies have shown that ivermectin has an inhibitory effect on various tumor cells and may be a potential broadspectrum antitumor drug (3). They have demonstrated that ivermectin is the most sensitive to breast cancer cells MDA-MB-231, MDA-MB-468, MCF-7, and ovarian SKOV-3; whereas ivermectin is the most nonsensitive to the prostate cancer cell line DU145. The induction of cell cycle arrest at G0/G1 mediates this effect of ivermectin on these sensitive

cancer cells. Furthermore, ivermectin can inhibit the proliferation of cancer cells through p21- activated kinase 1 (PAK1)-induced autophagy, Caspase-dependent apoptosis, or immunogenic cell death regulate the signal pathways, including Hippo, Akt/mTOR, and WNT-TCF pathways to inhibit cancer cell proliferation (4). As known, ROS plays a vital role in the apoptosis caused by oxidative stress. ROS is a by-product of normal mitochondrial respiration. Stimuli such as infection, drought, cold, and ultraviolet light result in increased ROS in cells. Then, accumulative ROS could induce cells mitochondrial dysfunction and promote apoptosis in cells. Evidence has shown that ivermectin-induced apoptosis is closely related to the production of ROS. Currently, there are few reports on the research of ivermectin in colorectal cancer (5)

Pharmcological Profile of Ivermectin:

Ivermectin is a widely used antiparasitic agent that has played a crucial role in the treatment and control of numerous parasitic disease in both human and veterinary medicine. Initially it discovered in the late 1970s as a derivative of avermectin which is derived from streptomyces avermitis, it is a member of the avermectin class of macrocyclic lactones and is known for its broad-spectrum officacy and safety profile. Ivermectin quickly emerged as one of the most important anti parasitic agent of a modern era. Intially developed for veterinary use , ivermectin was later approved for human use and has since become one of the most essential medicines globally, particulary in the treatment of neglected tropical disease. Its pharmacological profile is characterized by a selective mechanism of action favourable pharmacokinetics, and a generally well-tolerated safety profile, has led ti its inclusion on the World Health Organization list of essential medicines and extensive use in mass drug administration program for onchocerciasis and lymphatic filariasis. (6)

Chemical Profile

Ivermectin is a member of the avermectin family of 16-membered macrocylic lactones. It is a semi – synthetic derivative composed mainly of two homologous compounds ivermectin Bla (>80%) and Blb (<20%) – which is differ slightly in their side chain. These compounds are derived from the natural fermentation products of streptomyces avermitis and the chemically modified to increase potency and bioavailability.

The compound macrocylic lactone's structure confers high lipophilicity, contributing to its expensive tissue distribution and ability to penetrates parasite membrane. It is typically administrated orally in tablet form for human use (e.g.,3mg tablet), but it is also available in topical creams, lotions, and veterinary formulation, including injectables and pour – on liquid (7)

Mechanism of action

Ivermectin's antiparasitic activity is primarily mediated through its interaction with glutamate-gated chloride channels (GluCl), which are unique to invertebrates. These channels are found in the muscle and nerve cells of nematodes and arthropods. Upon binding to GluCl receptors, ivermectin enhances the influx of chloride ions into the cell, causing membrane hyperpolarization. This inhibits neuronal firing and leads to flaccid paralysis and ultimately death of the parasite.

In addition to GluCl channels, ivermectin also has a weaker affinity for gamma-aminobutyric acid (GABA)-gated chloride channels, which are present in both vertebrates and invertebrates. However, in mammals, ivermectin does not significantly affect these channels due to the blood-brain barrier, which limits the drug's penetration into the central nervous system. This selective mechanism contributes to the drug's safety in humans.

Recent research has proposed additional mechanisms of action that may underlie ivermectin's effects beyond its antiparasitic properties. For example, ivermectin has been shown to inhibit importin α/β1 nuclear transport proteins, a mechanism that may be relevant in its proposed antiviral and anticancer effects. However, these mechanisms remain under active investigation and are not yet considered central to its approved clinical uses. (8-13)

Preclinical Studies

1 Antiparasitic Activity

Ivermectin, a macrocyclic lactone derived from Streptomyces avermitilis, has long been recognized for its antiparasitic properties. Over the decades, extensive preclinical studies have explored its pharmacodynamics, toxicity, and potential repurposing in antiviral, anticancer, and anti-inflammatory contexts. These studies span in vitro experiments on cell lines and in vivo animal models, providing foundational insights into ivermectin's biological activities and therapeutic potential beyond parasitology.

In Vitro Studies:

In vitro studies using *Haemonchus contortus, Strongyloides stercoralis*, and *Onchocerca volvulus* larvae have shown that ivermectin at nanomolar concentrations can cause paralysis and inhibition of motility and reproduction.

Geary et al. demonstrated dose-dependent effects on motility in Brugia malayi larvae, with IC50 values as low as 2.1 nM. (14)

In murine models of *Strongyloides ratti* and *Brugia malayi*, ivermectin significantly reduced worm burden and fecal egg counts.

In cattle and sheep, ivermectin proved effective against gastrointestinal nematodes such as *Ostertagia ostertagi* and *Haemonchus contortus*, reducing worm counts by up to 99% (15).

2. Anticancer Preclinical Studies:

Researchers first noted the anticancer effects of ivermectin in 2015 through its ability to induce autophagy in cancer cells [16] . Mechanistically, the ubiquitination-mediated degradation route links ivermectin-induced autophagy in breast cancer cells to a reduction in P21-activated kinase 1 (PAK1) expression. When PAK1 is inhibited, Akt's phosphorylation level drops, which stops the Akt/mTOR signalling pathway. Ivermectin-induced cytostatic autophagy inhibits the growth of tumours in breast cancer xenografts. [17]. Various modes of action that support the theory that ivermectin induces apoptosis in certain cancers have recently been proposed [17-20]. The potential roles of ivermectin in the management of different cancers using ivermectin have been explored in gastric cancer, hepatocellular carcinoma, renal cell carcinoma, prostate cancer, *leukemia*, cervical cancer, ovarian cancer, glioblastoma, lung cancer, nasopharyngeal carcinoma, and melanoma [20].

3. Antiviral activity:

In the context of the most recent pandemic, ivermectin garnered significant attention due in Covid 19 because it can inhibit viral protein transportation through IMP-α/β1 [21]. In addition, the anti-inflammatory characteristic of ivermectin may explain its potential impact on infectious agents such as COVID-19. A cytokine storm in severe COVID-19 involves STAT-3 was shown to be inhibited in 48 hours upregulation of proinflammatory cytokines [22]. Ivermectin has been shown to inhibit STAT-3, so it may help treat severe cases of COVID-19. In vitro studies of ivermectin have demonstrated that it kills SARS-CoV-2 in 48 hours [22-23]. Marques et al. cite a single isolated study in which patients diagnosed with SARS-CoV-2 who received at least one dose of ivermectin during hospitalization were associated with lower mortality, particularly among those with increased oxygen and ventilatory requirements [23]. Jans et al. cite a study in Bangladesh that found that none of the 115 patients who received a single dose of ivermectin developed cardiovascular or pulmonary complications, while in 133 controls, 9.8% developed pneumonia, and 1.5% had an ischemic stroke [24].

However, Deng et al. conducted a meta-analysis of randomized controlled trials. They found that the use of ivermectin was not associated with a reduction in viral clearance time, hospitalization duration, mortality

incidence, or mechanical ventilation [25]. In a recent meta-analysis, Marcolino et al. evaluated 25 randomized clinical trials totaling over 6,000 patients and found that ivermectin does not reduce mortality risk or mechanical ventilation requirements [26].

4. Clinical Studies of Ivermectin in Onchocerciasis

The OCP, launched in 1974 and expanded to include ivermectin in 1987, it has eventually let to 95% reduction in microfilariae prevalence in endemic areas, Prevention of blindness in an estimated 600,000 individuals Restoration of 25 million hectares of arable land to safe habitation.

Longitudinal clinical evaluations indicated sustained suppression of skin and ocular microfilarial loads in individuals receiving ivermectin annually over 15–20 years (WHO, 2002).[27-28]

5.Antibacterial activity

Ashraf et al. found that ivermectin, but not levamisole or albendazole, demonstrated strong anti-staphylococcal action against two isolates at 6.25 and 12.5 µg/ml. It's interesting to see that one isolate was methicillin/cefoxitin sensitive, whereas the other was resistant.[29]

Xiao Wang it all reported Ivermectin (D) and its 4"-position amino substitution derivative (D4) were studied for their antibacterial/biofilm activity and mechanisms against MRSA. Compared to D4 (MIC=5 µg/mL), D's minimum inhibitory concentration (MIC) was four times greater at 20 µg/mL. According to the mechanism study, D4 was more effective than Dat at breaking down the bacterial cell wall, penetrating the cell membrane (6.25-36.17% vs. 1.92-6.04%), and attaching itself to the genomic DNA of MRSA. Furthermore, the percentages of biofilm dropped by 21.2-92.9% following a 24-hour incubation period with 10-40 µg/mL. Di, which was more efficient than D (no discernible change at 40 µg/mL. By controlling the expression of associated genes (RSH, reiQ, rsbl, sig, spA, and ical), the antibiofilm effect is produced.[30]

6. Antimalerial activity

Dziedzom K de Souza A CRCT that was randomized to two arms looked at the prevalence of malaria in Burkina Faso's right communities. Albendazole and a single dose of ivermectin (150–200 µg/kg) were administered to both experimental arms. Every three weeks, the communities in the intervention arm received five more doses of ivermectin. Children were checked for malaria infection on a regular basis while part of an active cohort. Over the course of the 18-week research, the main outcome was the cumulative incidence of uncomplicated malaria in a sample of children under the age of five. Because the methodology failed to take into consideration correlation or clustering among participants in the same town, we assessed the study as having a high risk of bias. Over the course of the 18-week research, the cumulative incidence of uncomplicated malaria in the group of children was not shown to be impacted by ivermectin (risk ratio 0.86, 95% CI 0.62 to 1.17; P=0.2607; extremely low-certainty evidence).[31]

7. Anti-Inflammatory activity

R.A. Accinelli it all shown anti-inflammatory action both in vivo and in vitro, which is achieved by inhibiting LPS-induced NF-kB translocation and lowering the synthesis of TNF-alpha, IL-1, and IL-6. Ivermectin at a dose of 2 mg/kg inhibits the generation of cytokines, IgF/IgG1 brunchoalveolar lavage, immune cell recruitment, and mucus hypersecretion in the respiratory tract in mice. This demonstrates that ivermectin has an anti-inflammatory effect on lung tissue in addition to the systemic level.[32]

8. Antiarthritis activity:

Muhammad Shahzad it all Ivermectin and dexamethasone treatment dramatically decreased the increase in IL-17, TLR-2, TNF, and NF-κB mRNA expression levels brought on by arthritic progression. In addition to demonstrating similar results to dexamethasone, a corticosteroid used to treat rheumatoid arthritis, ivermectin

treatment also shown a notable decrease in the degree of inflammation and joint degradation. Ivermectin shows notable antiarthritic effects and may be a new therapy option for people with rheumatoid arthritis who also have strongyloidiasis.[33]

Conclusion

An anti-parasite drug called ivermectin is used to treat parasitic illnesses. It is authorized by the FDA to treat a number of parasitic illnesses in humans, such as whipworm, hookworm, and parasitic worms. Ivermectin can also be used to treat intestinal strongyloidiasis, onchocerciasis, or river blindness, as well as a variety of other diseases and problems. Ivermectin has demonstrated antiviral action against a variety of RNA and DNA viruses, including dengue, Zika, yellow fever, and others.

This macrolide endectocide is effective against ectoparasites like Sarcoptes scabies, Pediculus humanus, Demodex folliculorum, and Cheyletiella sp. as well as endoparasites with cutaneous tropism (Strongyloides stercoralis, Ancylostoma braziliense, Cochliomyia hominivorax, Dermatobia hominis, Filaria bancrofti, Wucheria malayi, Onchocerca volvulus, Loa-loa, and Ancylostoma braziliense). Patients with various types of scabies, head lice, demodecidosis, cutaneous larva migrans, cutaneous larva currens, myiasis, and filariasis are all candidates for therapy with ivermectin.

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