Wonder drug for worms: A review of three decades of ivermectin use in dermatology

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Introduction

Ivermectin has evolved over the last three decades from being a veterinary "blockbuster" drug to a panacea for nematodal infestation and ectoparasitic diseases in humans.[1] This oral drug has breathed fresh life in the management of ectoparasitic infections which was conventionally based only on topical medications. In this review, we discuss the intriguing journey of this drug in dermatology.

History of Ivermectin

In early 1970, Omura and William Campbell identified a soil bacterium which was named *Streptomyces avermectinius*. The active component produced by the bacterium was termed as avermectin.[2] Ivermectin is a synthetic derivative of avermectin with a structural similarity to macrolide antibiotics.[3] It was first used in veterinary treatment in 1981, and now is being used to treat billions of livestock and pets around the world for varied nematodal infestations.[2] It was first used in humans after 1981 as a treatment against *Onchocerca volvulus*.[3] The role of ivermectin in dermatology was a serendipitous discovery which catapulted ivermectin to the zenith of anti-parasitic remedies.

Structure of Ivermectin

The structure of ivermectin is shown in Figure 1. The molecular formula of ivermectin is $C_{48}H_{74}O_{14}$.[4]

Pharmacokinetics

In humans, the oral route is the only approved route for administration of ivermectin, and it is usually recommended to be taken on an empty stomach with water. In the skin, the peak concentration of the drug was noted 8 h after a 12-mg oral dose, whereas the peak serum level is reached in 4 h after administration.[3] Between 6 and 12 h after the dose, a second peak occurs due to enterohepatic recycling of the drug.[5] It is extensively metabolized by cytochrome P450 and is excreted almost exclusively in feces.[3] The half-life of the drug is around 18 h, and the anti-parasitic activity lasts for several months after a single dose.[5]

Mechanism of Action

Ivermectin is an endectocide, which selectively binds to glutamate-gated chloride channels in invertebrates. This causes hyperpolarization of parasite neurons and muscles by increasing chloride ion influx, ultimately resulting in death of the parasite. It acts on endoparasites and ectoparasites by suppressing the nerve impulse conduction in intermediary neurons or in nerve-muscle synapses, respectively.[6,7] Due to the localization of these channels in the central nervous system and inability of ivermectin to cross the blood–brain barrier, humans are not affected except those with a history of undergoing shunt surgeries.[6]

Indications in Dermatology

The indications for ivermectin use in dermatology are summarized in Table 1.

Scabies

Ivermectin is the only recommended oral medication for scabies.[8] Two doses of oral ivermectin are given 7 days apart, to act on newly hatched scabietic nymph. In severe or resistant cases, it is often combined with topical medications like permethrin.[9] Two doses of topical ivermectin were also found to be as effective as two applications of permethrin.[10]

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In case of crusted scabies, multiple doses of oral ivermectin are given as shown in Table 2.[11]

Pediculosis

Ivermectin lotion (0.5%) is US Food and Drug Administration (FDA)–approved for the treatment of pediculosis capitis. A single application on dry hair without nit combing is recommended. Oral doses of ivermectin are preferred in difficult-to-treat cases of head lice.[12,13]

In phthiriasis palpebrarum infestation, oral ivermectin is found to be effective. The adult lice are eradicated in 2 days, but nits disappear gradually.[12]

In phthiris pubis, it is given as 250–400 µg/kg tablets 7 days apart depending on the severity. Topical ivermectin is also effective and a reapplication is recommended every 7–10 days until no live lice is identified for atleast 1 week after treatment.[14]

Demodicosis

Both oral and topical ivermectin are effective in cases of demodicosis.[3] In HIV-associated cases, oral ivermectin is the preferred option.[15]

Rosacea

Ivermectin 1% cream is now approved by US FDA for inflammatory rosacea. Ivermectin not only targets *Demodex folliculorum,* but also reduces the inflammation associated with the condition.[16]

Cheyletiella dermatitis

Ivermectin is effective in controlling infestations by *Cheyletiella* species in households having many cats. The dermatitis induced in humans regresses spontaneously within 3 weeks of elimination of the mites. Oral ivermectin can be given to prevent recurrence of the disease in humans.[3]

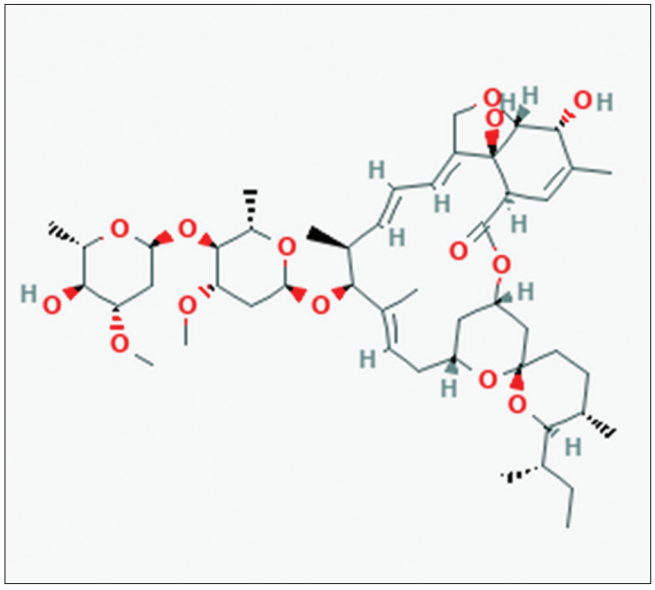

Figure 1: Structure of ivermectin

Myiasis

In case of furuncular myiasis, the treatment goal is complete removal of larva from the skin. It includes the usage of topical ivermectin followed by manual removal. Oral treatment is not recommended as an inflammatory reaction can develop to the dead larva in the skin. In case of migratory myiasis, oral ivermectin will mobilize the parasite to the body surface. Wound myiasis requires manual removal of the larva and debridement of necrotic tissues. Usage of short-contact topical ivermectin can cause reduction of pain in 15 min and death of a majority of the larvae. A single oral dose of ivermectin can facilitate removal of maggots of *Hypoderma lineatum* by causing spontaneous migration of maggots.[17]

Filariasis

Individuals with filariasis with a positive immunochromatographic test or those with microfilaremia, should be treated with an antifilarial drug. Ivermectin causes rapid disappearance of microfilaria but not the adult worm. The World Health Organization recommends the combination of both albendazole and ivermectin for effective management. Combination with diethylcarbamazine was found to be superior than the individual drugs.[18]

Onchocerciasis

Ivermectin is used to control endemic onchocerciasis. However, it kills only the larva and not the adult. It is given every 6 months as long as there is evidence of skin or eye infection. In case of recurrence, pruritus, rash, or eosinophilia, further doses should be given at 6–12 monthly intervals.[6]

Cutaneous larva migrans

A single oral dose of ivermectin ensures a 77%–100% cure rate. The cure rate increases to 97%–100% after one or two supplementary doses. The progression of tract formation stops in 2 days.[19] A single dose of ivermectin is less effective in case of hookworm folliculitis.[20]

Strongyloidosis

The first-line treatment for both acute and chronic strongyloidosis is oral ivermectin. Two consecutive days of oral ivermectin therapy is found to be more effective in cutaneous larva currens. In case of hyperinfection syndrome,

Table 1: Indications of ivermectin in dermatology

Scabies
Pediculosis
Onchocerciasis
Demodicosis
Rosacea
Filariasis
Myiasis
Cutaneous larva migrans
Strongyloidosis
Loasis
Cheyletiella dermatitis

Table 2: Ivermectin dosage in dermatology

Diseases	Recommended treatment regimens
Scabies	Classical scabies Oral ivermectin - two doses of 200 µg/kg, 7 days apart (not FDA-approved, used when FDA-approved treatment has failed or could not be tolerated) Crusted scabies: three regimens depending on severity Days 1, 2, and 8 (or) Days 1, 2, 8, 9, and 15 (or) Days 1, 2, 8, 9, 15, 22, and 29
Pediculosis	Pediculosis capitis Topical ivermectin 0.5% lotion Oral ivermectin - two doses of 400 µg/kg, 7 days apart Phthirus pubis Oral ivermectin - two doses of 250 µg/kg, 7 days apart Severe cases: oral ivermectin - two doses of 400 µg/kg 7 days apart Phthiriasis palpebrarum Oral ivermectin - two doses of 200 µg/kg, 7 days apart
Onchocerciasis	Oral ivermectin 200 µg/kg - every 6 months as long as the infected person has evidence of skin or eye infection
Demodicosis	Oral ivermectin 250 µg/kg (single dose)
Rosacea	Topical 1% ivermectin cream QD for 3 months
Filariasis	Albendazole 400 mg (single dose) with 150-200 µg/kg of ivermectin (single dose)
Myiasis	Furuncular myiasis: 1% ivermectin cream for 2 h followed by manual removal of larva Migratory myiasis: oral ivermectin 200 µg/kg (three doses) Wound myiasis - 1% ivermectin in propylene glycol solution for 2 h followed by washing with saline solution
Cutaneous larva migrans	Oral ivermectin 200 µg/kg (single dose) Second dose - during relapse
Strongyloidosis	Oral ivermectin 200 µg/kg for 1-2 days Hyperinfection syndrome: oral ivermectin 200 µg/kg/day until stool and/or sputum examinations are negative for 2 weeks along with stoppage of immunosuppressive therapy Cutaneous larva currens: oral ivermectin 200 µg/kg for 2 consecutive days
Loasis	Microfilaremia: <1000-2000 mf/mL - oral ivermectin 150 µg/kg (single dose), If co-infection with *Onchocerca volvulus*; treatment repeated every 3 months Microfilaremia: 2000-8000 mf/mL - oral ivermectin 150 µg/kg (single dose), repeated monthly until microfilaremia levels are <2000 mf/mL Microfilaremia: 8000-30,000 mf/mL - oral ivermectin 150 µg/kg (single dose), under close monitoring Microfilaremia: >30,000 mf/mL - oral ivermectin 150 µg/kg for 5 days under supervision in a hospital

FDA: Food and Drug Administration

immunosuppressive therapy should be stopped or reduced along with initiation of daily oral ivermectin, until stool and/or sputum examinations are negative for 2 weeks.[6,21]

Loasis

Ivermectin is used to reduce microfilaremia before the administration of DEC. However, administration of ivermectin may trigger encephalopathy in patients with *Loa loa* microfilaremia >30,000/mL. It is the preferred treatment when there is possible or confirmed co-infection with *Onchocerca volvulus*. It not only treats onchocerciasis, but also reduces pruritus and frequency of calabar swelling. DEC is the preferred drug and it is started after reducing the microfilaremia levels to <2000 mf/mL.[22] The treatment for *Loa loa* depends on the microfilaremia levels as given in Table 2.

The dosing schedule of ivermectin for various dermatological conditions is summarized in Table 2.

Contraindications

Pregnancy and lactation

The safety of ivermectin in pregnancy and lactation has not been established in humans. It is a pregnancy category C drug.[23]

Children

The safety and efficacy for use in children <15 kg has not been established; hence, it is not recommended for children under 15 kg and less than 5 years of age.[24]

Other Conditions

Ivermectin has to be avoided in those who have a history of seizure disorders and those who have had shunt surgeries in the past.[25]

Combination Therapy and Drug Interactions

Anti-parasitic agents are used in combination in view of increasing incidence of drug resistance. In case of onchocerciasis, the combination of ivermectin and doxycycline is highly effective in reducing microfilaremia levels more than ivermectin monotherapy.[6] In cases of filariasis, albendazole and ivermectin are preferred as they do not modify each other's kinetic behavior.[5]

Antibiotics like doxycycline, erythromycin, or azithromycin have a synergistic effect with ivermectin by increasing its intracellular concentration.[26] Alcohol can increase the plasma levels of ivermectin, whereas orange juice decreases the concentration of ivermectin by inhibiting certain drug transporters.[6]

Adverse Effects

Ivermectin is well-tolerated with minimal adverse reactions, and the degree of adverse events is independent of its concentration.[26,27] Common adverse events such as constitutional symptoms, pruritus and rash resolve spontaneously or might require symptomatic treatment.[3,6,28] A patient can also develop facial edema, headache, and abdominal pain. Rarely, encephalopathy and Steven–Johnson syndrome can develop.[3,6,28]

Mazzotti's Reaction

Mazzotti's reaction is an intense inflammatory response to the dead microfilaria, which occurs within 7 days of treatment with oral ivermectin, manifesting as fever and pruritus. The other manifestations may include urticaria, hypotension, tachycardia, tender lymphadenopathy, arthralgia, myalgia, and abdominal pain. This can be greatly reduced by adding low-dose corticosteroids at the initiation of treatment, without affecting the microfilaricidal activity.[29,30] A 6-week course of doxycycline preceding ivermectin, reduces the risk of Mazzotti's reaction by causing sterilization of female adult onchocerca.[30,31]

Toxicity

Ivermectin is considered to be relatively safe with no genotoxicity; but at a very high dose, it has been shown to cause embryotoxicity in animals.[3] The toxicity though rare, can be due to acute or chronic drug over-dose. It can occur at therapeutic dosage only when there is a defect in the ABCA1 gene which causes defect in P-glycoprotein.[32] Ivermectin toxicity manifests as increased salivation, diarrhoea, breathing difficulty, muscle fasciculation, drooping of lips, bilateral mydriasis, depression, ataxia, recumbency, reduced pupillary reflex, absent menace reflex and rarely encephalopathy and death.[30,33] Clinical signs usually progress during the first 36 h after administration.[33]

Resistance

Resistance to ivermectin has been reported in nematodes of horses, sheep, and other animals after 20 years of use.[3] An increasing trend of tolerance of scabies mite to ivermectin has been noted in endemic areas recently. Resistance is also noted in patients with crusted scabies who require repeated doses of ivermectin. The possible reasons could be the following:

1. Mutation in GluCl channel receptors which reduces the sensivity of ivermectin[3]
2. Mutation of ABCA1 gene resulting in alteration of P-glycoprotein[3]
3. Reduced efficacy of single-dose ivermectin, due to lack of ovicidal action.[3]

Future Perspective

Moxidectin is a macrolide lactone belonging to the Milbemycin subfamily produced by fermentation of *Streptomyces cyanogriseus*. Its affinity for P-glycoprotein is inferior to ivermectin. The half-life of moxidectin is more than 20 days with higher bioavailability because of its high lipophilicity and better penetration into the hyperkeratotic skin. Moxidectin also has a good safety profile with low resistance.[34]

Conclusion

Ivermectin has revolutionized the management of nematodal and ectoparasitic infection. The drug which spelt the death knell for onchocerciasis also had its impact on the treatment of many ectoparasitic infestations and will continue to do so in the future.

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Conflicts of interest

There are no conflicts of interest.

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