Review Article

Current Use of Ivermectin in Dermatology, Tropical Medicine, and COVID-19: An Update on Pharmacology, Uses, Proven and Varied Proposed Mechanistic Action

Abstract

Ivermectin is a broad-spectrum antiparasitic drug with anti-inflammatory, anti-viral, anti-bacterial, and anti-tumor effects. In this review, we discuss the history, pharmacology, multimodal actions, indications in dermatology and tropical medicine, therapeutic and prophylactic use of ivermectin in COVID-19, safety, adverse effects, special considerations, and drug interactions of ivermectin.

Keywords: *Action, COVID-19, cutaneous larva migrans, demodicosis, dermatology, dose, drug interaction, filariasis, ivermectin, malaria, nematodes, onchocerciasis, pediculosis, prophylaxis, rosacea, safety, scabies, side effects, tropical, uses*

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History

In the late 1960s, Satoshi Ōmura and William Campbell cultured bacteria from several soil samples, taken from a golf course in Japan, which lead to the discovery of a new species-*Streptomyces avermectinius*, a soil actinomycete that produced the active component avermectin.[1,2] Ivermectin (IVM) is the synthetic derivative of avermectin, which belongs to the broad-spectrum antiparasitic class of macrocyclic lactones. It is an antiparasitic drug with a structure similar to that of a macrolide; however, the antibacterial action is negligible.[3] Aziz *et al*.[4] in 1982 first tried IVM in humans against *Onchocerca volvulus (O. volvulus)* and IVM is now considered a phenomenal drug with several therapeutic applications. Most recently, it has found use in the ongoing COVID-19 pandemic.

Structure

IVM (MK-0933, 22,23-dihydroderivative of avermectin B1) is composed of 2 chemical compounds: 22,23-dihydroavermectin B1a (80%–90%) and 22,23- dihydroavermectin B1b (10%–20%).[5] The molecular formula of IVM is $C_{48}H_{74}O_{14}$ [Figure 1].[6] The modification of its structure [Figure 2] has led to the development of various molecules [Box 1].

Pharmacology and Pharmacokinetics

IVM is a white to yellowish-white, non-hygroscopic, crystalline powder, insoluble in water but soluble in methanol and 95% ethanol.[7] The preparations available in the country include 3, 6, and 12 mg tablets, 1% cream, 1% lotion, and 0.5% w/v shampoo.

IVM is absorbed rapidly, with an absorption half-life of 0.5 h to 2.5 h. It is generally given orally on an empty stomach, although a significantly higher absorption has been demonstrated with high-fat meals.[8] The plasma concentration decreases with orange juice and increases with beer.[9] Oral administration is the only approved route of administration in humans, and parenteral formulations are only approved for veterinary use. The half-life of IVM is 18 h, but the action of the drug can be observed several days after a single dose[10-12] consistent with the half-life of its major metabolites which can be up to 3 days.[12]

IVM undergoes pre-systemic metabolism in the gut via intestinal CYP3A4 enzymes and enterocytes contain an active efflux pump P-glycoprotein, located luminally, which transports IVM from enterocytes

How to cite this article: Mathachan SR, Sardana K, Khurana A. Current use of ivermectin in dermatology, tropical medicine, and COVID-19: An update on pharmacology, uses, proven and varied proposed mechanistic action. Indian Dermatol Online J 2021;12:500-14.

Received: 13-May-2021. **Accepted:** 16-Jun-2021. **Published:** 14-Jul-2021.

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Access this article online

Website: www.idoj.in

DOI: 10.4103/idoj.idoj_298_21

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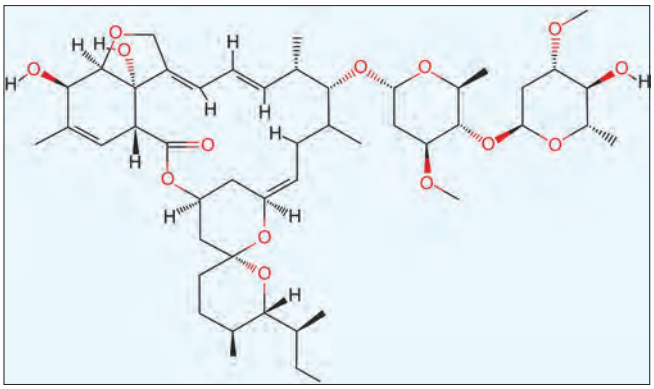

Figure 1: Structure of ivermectin

Box 1: Various analogues of ivermectin

Abamectin
Doramectin
Eprinomectin
Emamectin
Moxidectin
Milbemycin D

back into the lumen. The drug is extensively metabolized in the liver via CYP3A4 (major), CYP2D6 (minor), and CYP2E1 (minor) enzymes.[3,9] The presence of enterohepatic cycling can increase the total exposure and there is a high peak after initial administration as after being excreted into bile, it is reabsorbed again in the small intestine. This is responsible for the second peak between 6 and 12 h after the dose. Ivermectin binds strongly to plasma proteins (93.2%)[13] and thus higher free drug fraction is expected in patients with hypoalbuminemia. Less than 1% of IVM is excreted unchanged in the urine (i.e., renal insufficiency will have little impact on pharmacokinetics),[12] with most of the drug being eliminated through bile and feces.

A rapid and preferential sebum secretion of IVM has been demonstrated following oral administration.[14] After a single 12 mg oral dose, a peak concentration was noted in squames, sebum, and sweat on the forehead and the anti-thenar around 8 h which declined after 24 h. There is little transdermal absorption after topically applied IVM.

P-glycoprotein (P-gp) appears to be important in preserving the blood–brain barrier and preventing the accumulation of ivermectin in mammalian brain tissue.[15] As the expression of P-gp at the blood–brain barrier is likely at its lowest levels IVM in infancy, it is recommended not to administer the drug to children weighing less than 15 kg.

Notably, there are mass campaigns where there is coadministration of IVM with other drugs like albendazole and azithromycin. In a study where azithromycin, IVM, and albendazole were co-administered, IVM AUC and C-max were seen to be increased by 31% and 27%, respectively.

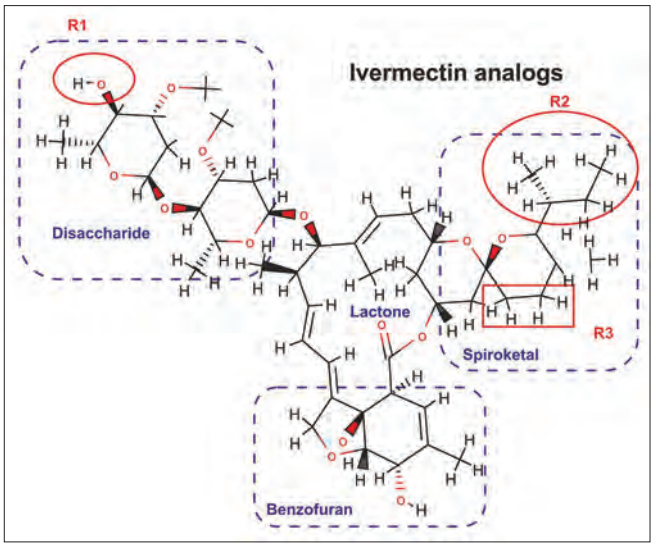

Figure 2: Ivermectin analogs

This has relevance in the COVID-19 therapeutic regimens where azithromycin is often combined with IVM which may serve to increase the blood levels and possibly the levels of the drug in the lung, which is the target organ in COVID-19.[16]

Mechanism of Action

Anti-parasitic action

Allosteric modulation of GluCl ion channels

Ivermectin is an endectocide (active against both endo and ectoparasites), which acts by selective and high-affinity binding to the specific neurotransmitter receptors, namely glutamate-gated chloride channels or γ-aminobutyric acid (GABA) gated chloride channels[17,18] found in peripheral motor synapses of parasites. This class of drugs are positive allosteric modulators (PAMs) that selectively open inhibitory glutamate-gated chloride ion channels in the membranes of pharyngeal muscles, motor nerves, female reproductive tracts, and the excretory/secretory (ES) pores of nematodes and muscle and nerves of insects and crustaceans. This leads to increased release of GABA at the presynaptic nerve endings and increased GABA binding to the motor neuron/inter-neuronic synapses. This causes hyperpolarization of parasite neurons and muscles by increasing chloride ion influx, resulting in paralysis and death. The effects of the drug are listed in Box 2.[19] While it acts on endoparasites (nematodes) by suppressing the nerve impulse conduction in intermediary neurons and ectoparasites (arthropods and insects) by suppressing the nerve impulse conduction in the nerve-muscle synapses,[20] it does not affect synapses gated by other transmitter substances, such as acetylcholine, norepinephrine, and serotonin.[21] Glutamate-gated anion channels and GABA-gated chlorides channels are localized only to the central nervous system (and not in the peripheral nervous system) of humans and hence, humans are not affected except

Box 2: The effect of ivermectin in nematodes and insects

Inhibition of pharyngeal pumping when the pharyngeal muscle is the target.

Inhibition of motility when motor nerves are the main target.

Inhibition of egg or micro filaria release when the female reproductive tract is the target site.

Loss of host immunosuppression when the ES pore cannot open to release host immunosuppressants.

those undergoing shunt surgeries.[3,22,23] This accounts for its selective action on paralyzing invertebrates.

Other actions

IVM inhibits the nematode parasite's ability to suppress the host immune system. It also acts as PAM on the histamine-gated Cl^-channels in *D. melanogaster*, *Sarcoptes scabiei*,[24] and the nematode pyrantel and levamisole nicotinic acetylcholine receptors (nAChRs).[25] In the brain, IVM targets the mammalian glycine receptors (GlyRs), GABA receptors, and AChRs.

Anti-inflammatory action

Lipopolysaccharide-induced production of inflammatory cytokines such as tumor necrosis factorα (TNF-α) and interleukin (IL)-1 is inhibited via nuclear factor-kappa B (NF-KB) pathway blockage. In addition, the production of the anti-inflammatory cytokine IL-10 is also enhanced. Topical IVM has shown to downregulate the proinflammatory genes IL-8, cathelicidin LL-37, HBD 3, TLR-4, and TNF-α in papulopustular rosacea along with its antiparasitic action against Demodex.[26,27]

Yan *et al*.[28] investigated the therapeutic potential of 2 mg/kg IVM for the treatment of allergic asthma in mice and found that it reduced the symptoms in mice by curtailing the recruitment of inflammatory cells and reducing the hypersecretion of mucus.

Antibacterial effects

Moderate antibacterial effects, against *Mycobacterium tuberculosis* and *Chlamydia trachomatis*, have been observed.[29] IVM, selamectin, and moxidectin were found to have bactericidal activity against mycobacterial species, including multidrug-resistant and extensively drug-resistant clinical strains of *Mycobacterium tuberculosis*.[30]

Anti-viral effects

IVM has broad-spectrum *in-vitro* antiviral[31] activity against many RNA and DNA viruses, including human immunodeficiency virus-1 (HIV-1), dengue virus (DENV), influenza, Venezuelan equine encephalitis virus (VEEV), a flavivirus, pseudorabies virus, and Zika virus.

The action is based on inhibition of the nuclear import of selected cytoplasmic proteins. IVM binds to the heterodimer protein importin (IMP) α/β1 and inhibits the binding of cargo proteins that are carried through the nuclear pore by IMP α/β1 into the nucleus. If IMP binding was not inhibited by IVM, IMP α/β1 + cargo protein would be able to pass through the nuclear pore.[32] Viral protein cargos known to bind to IMPα/β1 include:

(i) HIV-1 integrase, needed for HIV-1 propagation and incorporation into the host genome
(ii) DENV N55, a dengue virus nonstructural protein-5; and
(iii) the simian virus SV40 large tumor antigen.[33]

Half-maximal inhibitory concentration (IC 50s) in the 1–4 μM range have been found to limit the growth of the following RNA viruses in tissue culture: dengue virus, West Nile virus, and Venezuelan equine encephalitis virus (VEEV).[34] This broad-spectrum activity of IVM may be due to the reliance on IMP α/β1 for RNA virus protein transport during infection.[35]

At higher concentrations, IVM also exhibits activity against the DNA virus—pseudorabies virus (PRV) *in-vitro* and *in-vivo*.

Admittedly the role of IVM on select viruses is based on the *in-vitro* data. However, conventional doses and the normal therapeutic antihelminthic doses, may not always translate into clinical results except perhaps, for the yellow fever virus. The action on SARS-CoV-2 is discussed in the following sections.

Antimalarial Action

In addition to controlling filariasis, the mass drug administration (MDA) of IVM has also had effects on limiting the spread of malaria. The effect was both due to the effect on mosquito vectors of malaria and possibly direct inhibitory effect of IVM on the liver stages of malarial parasites. Singh *et al*.[36] found that IVM analogues inhibit *Plasmodium falciparum* erythrocyte stages *in-vitro*, with an IC 50 near 0.5 μM, and that an improved novel compound (analog19) had a better IC 50 of 0.05 μ M. The mechanism of this antimalarial effect involves signal recognition particles (SRPs), which are universal eukaryote ribonucleoprotein complexes that target proteins to the endoplasmic reticulum (ER).

A trial that studied repeated administration of IVM showed that frequent repeated mass administrations of IVM during the malaria transmission season can reduce malaria episodes among children without significantly increasing side effects. The dose used was IVM (150–200 μg/kg) at 3-week intervals over the 18-week treatment phase.[37]

Antitumor effects

There are various actions of IVM prominent being deregulation of the WNT-T cell factor (WNT-TCF) signaling pathway in cancers of the colon, skin, lung, breast, ovary, and prostate.[38] Li *et al*.[39] reported that IVM

inhibited protein expression levels of EIF4A3 and 116 EIF4A3-binding mRNAs in ovarian carcinoma cells.

Indications in Dermatology and Tropical Medicine

While the drug was initially discovered for its action against nematodes of veterinary importance, this was extended later to the cattle parasite *Onchocerca cervicalis* and this heralded its use for the treatment of onchocerciasis.[40] It is now accepted to be a potent drug against a wide range of helminths and ectoparasites and is the drug of choice for the treatment of onchocerciasis and strongyloidiasis. It is also a drug for the treatment of cutaneous larva migrans, head lice, and scabies. Although active against the intestinal helminths *Ascaris lumbricoides* and *Enterobius vermicularis*, it is only moderately effective in trichuriasis when given alone and has limited activity against hookworms. An overview of the various uses and dosimetry is listed in Table 1.[1,41-43,51,53-73]

Dermatological Indications

Scabies

Scabies, an infestation caused by *Sarcoptes scabiei var. hominis*, is labeled as a neglected tropical disease by the WHO. While permethrin is considered the most effective treatment and drug of choice for scabies in most parts of the world,[41,42] CDC recommends IVM (200 μg/kg, with a repeat dose two weeks later) which is equivalent to topical permethrin.[43] However, IVM is currently not FDA approved for the treatment of scabies. IVM has shown superiority over most topical agents including lindane, but not to permethrin.[44,45] IVM is also found to be well-tolerated in infants with an 80% healing rate in cases that failed two other topical treatments and may be considered for treatment of recalcitrant or relapsing scabies in infants.[46]

Although very effective against the adult stages of the mite, IVM is not ovicidal.[22] Thus, a single dose may be inadequate and the dose needs to be repeated within 1–2 weeks. Owing to the preferential secretion of IVM via sebum, Haas *et al*.[14] recommended that IVM preferably be taken in the evening to achieve the maximum surface concentration at night. Hot bath/washing or showering is not recommended after the drug intake as it may dissolve the surface lipids containing IVM.

Large scabies outbreaks in nursing homes and other facilities, nodular scabies (which is typically resistant to topical treatment), crusted clinical forms, and infestation in immunocompromised hosts are excellent indications for oral IVM.[47,48] More frequent dosing (2–3 doses, 1–2 weeks apart) is required in cases of crusted scabies[49,50] [Table 1] and a five-dose regimen with IVM administered on days 1, 2, 8, 9, and 15, with two additional doses on days 22 and 29 in most severe cases have been reported to be highly successful.[51] For refractory institutional and community outbreaks, a blanket treatment with topical permethrin and oral IVM for all symptomatic cases with classic or crusted scabies and a single oral dose of IVM, 200 μg/kg, for all exposed, asymptomatic residents, visitors, and staff is recommended.[52]

An interesting observation is that scabies patients often have secondary impetigo and this has been particularly noted in the Aboriginal regions of north-western Australia and throughout the South Pacific islands. A seminal trial undertaken by Romani and co-workers found that mass administration of oral IVM helped in marked decline in the prevalence of scabies with a concomitant decline of impetigo.[52]

Apart from oral IVM, topical IVM 1% (applied to the entire skin over one night, then repeated a week after) is also an effective anti-scabietic treatment.[22] Notably, earlier and higher cure rates have been observed with topical IVM 1% and permethrin 5%, as compared to oral IVM at weeks 1 and 2 post-treatment for scabies.

Pediculosis

IVM lotion (0.5%) is US-FDA approved for the treatment of pediculosis capitis and is based on a study where 79% of subjects remained louse-free for 15 days after the use of topical 0.5% IVM lotion as a single 10-min application on dry hair without nit combing.[53] IVM lotion is as effective as oral IVM (two 200-μg/kg oral doses of IVM given a week apart). An RCT showed that a single oral dose of IVM, 400 μg/kg of body weight, repeated at 7 days, revealed higher louse-free rates by day 15 as compared to two applications of 0.5% malathion lotion in patients with pyrethroid-resistant head lice infestations.[74] IVM is effective against permethrin-resistant head lice *in-vitro* and is capable of eliminating parasites partially refractory to malathion *in-vivo*.[74,75] Notably, short exposure intervals of body lice to sublethal amounts of IVM can induce upregulation of detoxification genes including cytochrome P-450 monooxygenase and adenosine triphosphate–binding cassette transporter genes leading to tolerance.[76] Thus overuse of IVM can lead to the development of resistance.

In pediculosis corporis, three doses of oral IVM 12 mg with a 7-day interval decreased the prevalence of subjects infested with body lice from 84.9% to 18.5% over 14 days but the effect was not sustained at 45 days.[77]

Rosacea

IVM 1% cream is now approved by US FDA for the treatment of inflammatory rosacea. IVM not only targets Demodex folliculorum but also reduces the inflammation associated with the condition. Results of a two-week controlled, investigator-blinded trials revealed that IVM 1% cream is superior to placebo in reducing inflammatory lesions in papulopustular rosacea, with near-complete

Table 1: Uses and dosimetry of ivermectin[1,43,51,53-73]

Food and Drug Administration (FDA)-approved indications	
Onchocerciasis	-Single oral dose of 150 µg/kg,
	Repeat q3-6 month until asymptomatic and no ongoing exposure
	A dose of 150 µg/kg/3 monthly is a good prophylactic dose
Lymphatic filariasis	-Children/adults >15 kg weight: 150-200 µg/kg one dose with another filaricidal drug
	- Ivermectin 150-400 µg/kg has better results against *W. bancrofti*
	Triple-drug treatment with Ivermectin (200 µg/kg body weight), DEC (6 mg/kg), and albendazole (a fixed dose of 400 mg) for brugian filariasis
Strongyloidiasis	-Oral ivermectin 200 µg/kg for 2 days (Larva currens)
	Disseminated: ivermectin (200 µg/kg daily ×14 days) or until stool and/or sputum examinations are negative for 2 weeks
Mansonella ozzardi/Mansonella streptocerca	-Ivermectin 200 µg/kg PO once (not effective against *Mansonella perstans*.)
Cutaneous larva migrans	-Children/adults >15 kg weight: ivermectin 200 µg/kg once daily for 1-2 days or
	Albendazole 15 mg/kg/day (400 to 800 mg/day orally) for 3 to 5 days
Rosacea	-Topical 1% ivermectin cream once daily (FDA approved 2014)
Off-label indications	
Scabies	-Classical scabies
	Ivermectin-two doses of 200 µg/kg, 1-2 week apart (should be taken at night)
	-Crusted scabies: three regimens depending on the severity
	Days 1, 2, and 8 (or)
	Days 1, 2, 8, 9, and 15 (or)
	Days 1, 2, 8, 9, 15, 22, and 29
	(Combined with 5% topical permethrin every 2 to 3 days for 1 to 2 weeks and alternating with keratolytic creams, such as salicylic acid or lactic acid)
Pediculosis	-Pediculus humanus capitis, 400 µg/kg/dose 7 days apart (2 doses)
	or topical ivermectin 0.5% lotion (≥6 months of age)*
	-Pediculus humanus corporis, 200 µg/kg/dose every 7 days (three doses)
	-*Pthirus pubis*, 250 µg/kg/dose every 7 days (two doses) or
	250 µg/kg/dose every 14 days (two doses)
Enterobiasis	-200 µg/kg single dose followed by a second dose after 10 days (cure rate of 85%)
Trichuriasis	-200 µg/kg daily for 3 days+ (Albendazole 400 mg PO ×3-7 days or mebendazole 500 mg daily or 100 mg PO BID ×3-7 days)
Demodex folliculorum	Ivermectin 250 µg/kg (single dose)
Ascariasis	-Ivermectin 150-200 µg/kg single dose
Gnathostomiasis	-Ivermectin, 200 µg/kg for two doses
Malaria	-Ivermectin (150-200 µg/kg) at 3-week intervals over 18-week treatment period
Loa loa	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- ivermectin 150 µg/kg (single dose),
	repeated monthly until microfilaremia levels are <2000 mf/mL
	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
Myiasis	2 doses of oral IVM (6 mg each) 24 h apart+Manual extraction
IVM dose in COVID 19**	

Contd...

Table 1: Contd...

Early outpatient protocol	0.2 mg/kg per dose-one dose daily, minimum of 2 days, continue daily until recovered (max 5 days)
Hospital Treatment	0.3 mg/kg per dose-daily for 5 days (take with or after a meal)
Protocol	(This is part of the MATH+protocol)
	IVM 12 mg/day for 5 days - mild COVID-19 (Ahmed *et al*.[68])
	IVM 12 mg single dose within 24 h of hospital admission-mild to moderate COVID-19 (Khan *et al*.).[69]
	IVM 200 µg/kg single dose/2 doses 7 days apart; (Rajter *et al*.)[70] (lowered mortality in a cohort with severe pulmonary involvement)
Prevention and Prophylaxis protocol	Prevention for high-risk individuals
	0.2 mg/kg per dose-one dose on day one, 2nd dose in 48 h, then one dose every 2 weeks
	-2 doses of IVM 300 µg/kg given 72 h apart
	- 12 mg monthly dose protocol of IVM (Alam *et al*.[73])
	-200 µg/kg on day one and second dose on day 2 or 3 for men aged more than 45 years (Chang *et al*.[72])
	-two doses of IVM 300 µg/kg given 72 h apart (Behera *et al*.[71])
	Post COVID-19 exposure prevention
	0.2 mg/kg per dose-one dose on day one, 2nd dose in 48 h

*US-FDA approved** The dose of IVM may change depending on data that is evolving and some trials are underway. The strength of tablet is 12 and 6 mg and thus the dose may vary between 12-18 mg in adults according to body weight

treatment response, and improving patient satisfaction and quality of life.[54] In addition, IVM 1% cream was found to be better than metronidazole 0.75% cream for decreasing the inflammatory lesion count, reaching "clear" or "almost clear" response and patient satisfaction.[78] IVM is also well-tolerated and beneficial for the treatment of perioral dermatitis.[79]

Demodicosis

Demodex folliculorum is a normal inhabitant of human skin and IVM (both oral and topical) may be useful in several disorders associated with Demodex overpopulation and immune dysregulation, including blepharitis, otitis externa, acne, and perioral dermatitis. In immunosuppressed patients, it causes facial or disseminated demodicosis affecting the pilosebaceous units where the host immune system is unable to keep the mite under control. While there is no specific approved dose regimen for demodicosis, 2 children with acute leukemia and disseminated demodicosis were treated successfully with a single oral dose of 250 µg/kg of IVM[55] and as a corollary oral IVM is preferred in HIV-associated demodicosis.[80]

Tropical infectious diseases

Onchocerciasis

Disseminated prurigo, lichenification, and subcutaneous nodules (onchocercomas) on the trunk and extremities are the cutaneous manifestations caused by *O. volvolus* infestation.[81] The drug penetrates well into nodules when given as a single dose and in animal model of onchocerciasis. High concentrations were detected in the capsule wall and inside the nodule after subcutaneous administration of 500 µg/kg.[82] Administered as a single oral dose of 150 µg/kg, IVM leads to rapid microfilaricidal effect, with most microfilariae being cleared by the end of the first week of therapy and within 1 month after treatment, the skin microfilarial loads decreased by 95%–99%.[56] This also prevented the production of new microfilariae by the adult female worms and accounts for its prolonged effect in suppressing microfilariae for up to 1 year after treatment. A periodic intervention has been suggested as adult *O. volvulus* worms may live up to 10 years; thus, the drug should be administered every 6 to 12 months for the life of the adult worm[57] though a recent paper suggests that a 3 monthly dose of 150 µg/kg has a better prophylactic role.[58]

Filariasis

Clinical manifestations of filariasis caused by *W. bancrofti* include acute lymphangitis of the legs, lymphadenitis, and orchitis, and finally, elephantiasis. A single dose of IVM is microfilaricidal against *W. bancrofti* for up to 3 months,[83] though with higher doses (150–400 µg/kg), microfilaremia takes longer to return, and the level of parasitemia is lower than baseline.[84] As IVM has been shown to be marginally inferior to DEC in producing a sustained reduction of microfilaremia in lymphatic filariasis, IVM is not effective against the adult worm, which explains why mass treatment campaign, with IVM resulted in a significantly smaller impact on hydrocele prevalence than DEC.[85] In endemic areas, a combination of IVM added to standard therapy with DEC and albendazole demonstrated greater reductions in

microfilaremia.[86] The high-dose twice-yearly combination of albendazole (800 mg) and IVM (400 μg/kg) is superior to standard-dose albendazole (400 mg) and IVM (150 μg/kg) in suppressing *Wuchereria bancrofti* microfilaremia and thus some experts recommend this combination regimen.[59]

The activity of IVM against *B. malayi* and *Brugiatimori*, the less common lymphatic filarial parasites, seems to be less than as compared to W. bancrofti and single doses of IVM, even as high as 400 μg/kg, result in slower clearance of microfilaremia. A recent trial showed that triple-drug treatment with an oral dose of IVM (200 μg/kg body weight), DEC (6 mg/kg), and albendazole (a fixed dose of 400 mg) was better than DEC and albendazole and this would seem to be a better option for brugian filariasis.[60,61]

Strongyloidosis

IVM is the first-line treatment for both acute and chronic strongyloidosis. A single dose is sufficient for most non-disseminated infections with a cure rate of 83%.[62,63] Larva currens is a cutaneous manifestation of strongyloidiasis in which two consecutive days of oral IVM therapy has been found to be more effective. Some experts recommend an additional dose given 7 to 10 days later and repeated courses are warranted in individuals with impaired cellular immunity, particularly patients infected with human T-cell lymphotropic virus type 1.

The difficulty in achieving adequate drug levels of IVM in patients with disseminated strongyloidiasis and intestinal ileus can be a serious clinical problem due to intestinal dysfunction. Here a subcutaneous injection of a veterinary formulation of IVM is indicated.[87,88]

Cutaneous larva migrans

Cutaneous larva migrans is caused by cutaneous penetration of larvae of animal hookworms (usually *Ancylostoma braziliense*). IVM is given in a dose of 150 to 200 μg/kg once daily for one or two doses.[64] Topical use of IVM has been found to be useful and may be useful in localized cases.[89]

Loa loa

Cutaneous manifestations of Loiasis include transient prurigo nodularis like swelling (Calabar swelling) which is seen on the upper extremities. IVM is the preferred treatment when there is possible or confirmed co-infection with O. volvulus.[90]

High doses of the drug (400 μg/kg) are required to clear microfilaremia,[65] and they clear slowly than bancroftian filariasis.[11] Serious adverse events, most notably fatal encephalopathy, have been reported when IVM was administered as part of an MDA program for control of endemic onchocerciasis. This is related to the high levels of microfilaremia (1% with 20,000 mf/mL, 10% with 50,000 mf/mL, and 30% with 100,000 mf/mL); therefore, IVM should be used with extreme caution in these patients.[91]

Myiasis and other parasitic diseases

Cutaneous myiasis is an infestation of humans by fly larvae *Musca domestica.* Various modes of treatment have been used including topical IVM, irrigation with IVM, and oral IVM. Manual extraction with the administration of two doses (24 h apart) of oral IVM (6 mg each) is an effective method to treat this disorder.[66]

A dose of 200 μg/kg/day for 2 days is effective in gnathostomiasis (cure rate of 100%).[67] The drug is also safe in *A. lumbricoides* (100 to 200 μg/kg),[92] pinworm infection caused by *E. vermicularis* (cure rate of 85% single dose 50 to 200 μg/kg.) but has limited activity in hookworm infection and ineffective for the treatment of infections caused by *T. trichiura*. Thus, a combination with albendazole appears to be a better option in such cases.[93]

Malaria

IVM kills malaria vectors[94] and a recent cluster-randomized clinical trial showed that mass administrations of IVM repeated every 3 weeks during a rainy season were shown to reduce the incidence of malaria episodes in children in the study by 20%.[37]

COVID-19

While a spate of drugs have been repurposed for use in COVID-19, very few have met the exacting standards of a double-blind randomized control trials (DB-RCT). The interest lies in drugs that are cheap and have a body of *in-vitro* data with a semblance of *in-vivo* translation. IVM is one such drug and here we critically analyze the data on this in COVID-19. It is worthwhile to mention here that although published studies are available on IVM use in COVID-19 on PubMed, many are only available on preprint servers. However, in this rapidly evolving scenario, therapeutic choices are now often made with the reliable emerging dataset from all sources; hence, such literature is also quoted here.

The interest in IVM in COVID-19 stems from an *in-vitro* study by Caly *et al*.[31] in which an almost 5000-fold reduction in viral RNA was observed within 48 h after addition of IVM to SARS-CoV-2 infected Vero-hSLAM cell lines. The drug was added to cultures 2 h post infection. Based on their results, the authors proposed a possible clinical use of IVM when given early in the infection course. IC50 of ivermectin was determined to be ~2 μM under these experimental conditions. Based on the previous studies on SARS-CoV and other viruses, the mechanism of IVM in COVID-19 was proposed to be inhibition of signal-dependent nucleocytoplasmic shuttling of the SARS-CoV nucleocapsid protein by an inhibitory effect on importins α/β [Figure 3]. The effect of IVM on importins has been previously demonstrated in experimental studies on many other RNA viruses[33] as well as some DNA viruses.[95] This effect likely leads to an impaired viral

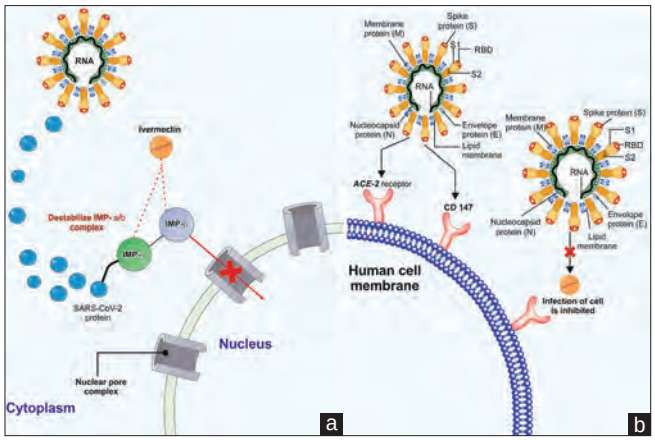

Figure 3: (a) IVM binds importin (IMP) armadillo (ARM) repeat domain causing thermal instability and helicity thus preventing IMPα-IMPβ1 interaction. Further, it can also dissociate IMPα-IMPβ1 heterodimers. This leads to impaired SARS-CoV-2 protein translocation into the nucleus via nuclear pore complex. An efficient nuclear transport of SARS-CoV-2 is essential for virus replication and downregulation of host immune response. (b) A second proposed mechanism is shielding of the SARS-CoV-2 spike protein thus preventing its binding to ACE-2 receptor and CD 147 receptor (basigin/EMMPRIN). ACE-2, a homologue of ACE, is an important cell surface receptor, which mediates SARS-CoV-2 infection by recognition of spike protein. The interaction with CD 147 has been recently recognized. CD147 is prominently expressed on red and white blood cells apart from the sites of expression of ACE2 receptor

replication and efficient host immune response against the virus.[96] Many other possible mechanisms have also been proposed, some of which are supported by experimental studies, while others are pure hypotheses [Table 2].[27,31,97-104] The studies conducted so far on the clinical utility of IVM as therapeutic as well as prophylactic regimen are given in Table 3.[31,68-73,105-115]

The literature available so far provides low-quality evidence of a modest effect of IVM in improving clinical outcomes in COVID-19, with some data on prophylactic use.[116] Notably, the antiviral activity of IVM in cell cultures has not been demonstrated in mouse infection models as yet.[117] Further, arguments have been raised on the inability of standard doses in achieving the IC50 (about 2.5 μM) determined by Caly *et al*. [31]

A standard 200 μg/kg dose achieves a Cmax of about 43 ng/ml, which is about 60 times less than the levels required to achieve the proposed antiviral effects.[118] With a dose of 120 mg (about 10 times the standard dose), Cmax achieved is about 247 ng/ml, which still falls about 10 times short of the desired level.[8] A perusal of the data shows that the drug has a definite role in the initial stage of viral replication. In real-life management protocols, the co-administration with azithromycin would increase the serum levels and may achieve the virological effect as demonstrated *in-vivo*. We would recommend avoiding the use of IVM with Vitamin C as that tends to reduce the serum levels of IVM. Also, additional emerging mechanisms of IVM, mainly the effect of shielding spike protein from binding to ACE2 receptor and CD 147 receptor (possibly responsible for the vascular

Table 2: Possible Anti-Sars-Cov-2 mechanisms of ivermectin[27,31,97-104]

Importin α/β heterodimer-prevention of heterodimer formation; dissociation of formed heterodimer [Figure 3]
Shields SARS-CoV-2 spike protein preventing its binding to the CD147 transmembrane receptor and ACE2
Allosteric modification of α7 nACh Receptor-(important component of the “Nicotinic hypothesis”)
Inhibition of SARS-CoV-2 RNA dependent RNA polymerase
Positive allosteric modulation of $P2X_4$ receptor
Anti-inflammatory and immunomodulatory effects: downregulates gene expression of pro-inflammatory molecules-IL-8, TNF-*α*, and cathelicidinLL-37
Prevention of Vitamin D receptor nuclear entry by inhibiting importin-4-resultant anti-inflammatory effects mainly mediated by downregulated LL-37 expression
Ionophore role

effects of SARS-CoV-2 infection) give support to continued use of the drug in COVID-19 till further conclusive clinical data is available.[119]

Pertinently we feel that the purists would wait for the ideal trial that would have to factor in the initial period of infection, severity, clinical parameters, and possibly a higher dose, but the emergent desire for administering a cheap drug supplants the rigors of such parameters. The drug has already found its way in many regional, state, and International protocols of clinical care though more evidence would be welcome to establish its role and as evidenced by the data in Table 3, a growing evidence of its use is being published and we feel it is one of the few drugs that has transcended in-vitro data to clinical applicability.

Safety/Toxicity Profile/Adverse Reaction

IVM has negligible adverse effects on mammals and is an extremely safe drug even at high doses.[120] Topical IVM lotion 0.5% is a particularly safe drug; the plasma concentrations (mean 0.241 ng/mL, maximum 0.97 ng/mL) detected after a single 10-min application for head lice treatment are much lower than those of oral IVM.[120]

The drug has been used safely in MDA programs for more than 25 years. Although high doses have been shown in certain animals to cause CNS toxicity manifested by emesis, mydriasis, and ataxia, its poor penetration of the blood–brain barrier prevents any toxic effect.[121] The acute lethal dose (LD) 50 toxicities are seen at 24000 μg/kg in monkeys and 80000 μg/kg in beagles.

As higher doses are given in cases of COVID-19, this is an aspect that needs to be analyzed. Doses up to 700 μg/kg have been shown to have a similar side effect profile as standard lower doses of 150–200 μg/kg.[118] Further, a recent systematic review, including a meta-analysis, demonstrated no significant differences in frequency or intensity of adverse effects with single-dose treatment using

Table 3: Studies conducted so far on the clinical utility of ivermectin as therapeutic as well as prophylactic regimen[30,68-73,105-115]

Author	Study Outcome
	***In vitro* study of IVM in COVID -19**
Caly *et al*.[30]	*In vitro* study in which almost 5000-fold reduction in viral RNA was observed within 48 hours after the addition of ivermectin to SARS-CoV-2 infected Vero-hSLAM cell lines. IC50 of ivermectin was determined to be ~2 μM under these experimental conditions.
	Clinical Studies of conventional dose of IVM In Covid -19 Disease
Ahmed *et al*.[68]	-Dose-IVM 12 mg/day for 5 days
	-Earlier virological clearance in mild COVID-19
Khan *et al*.[69]	-Dose- IVM 12 mg single dose within 24 hours of hospital admission
	-Earlier PCR negativity, and lower rates of oxygen requirement, respiratory distress, ICU admission, pneumonia, stroke and mortality in mild to moderate COVID-19
Rajter *et al*.[70] The Ivermectin in COVID Nineteen Study	-Dose IVM given as 200 μg/kg mg single dose/2 doses 7 days apart
	-Lowered mortality in a cohort with severe pulmonary involvement. All patients were also on azithromycin and hydroxychloroquine
Chowdhury *et al*.[105]	-Dose- Ivermectin (200 μg/kg mg single dose) + Doxycycline (100 mg twice daily for 10 days) versus Hydroxychloroquine-Azithromycin combination
	-No statistically significant difference in time to become symptom-free and time to negative PCR
Camprubí D *et al*.[106]	-Dose -200 μg/kg mg single dose at median of 12 days after symptom initiation - in severe COVID-19 patients
	-Effect of IVM is restricted to the early phase of the infection as there is a lack of clinical or microbiological (PCR negativity) effect when the drug was given later in the course of infection
Abd-Elsalam *et al*.[107]	-Dose-IVM 12 mg/day for 3 days versus standard care in hospitalized mild to moderate COVID-19 infected
	-No significant difference in length of hospital stay, requirement of mechanical ventilation or death rate
Okumuş *et al*.[108]	-Severe COVID 19 pneumonia patients randomised to receive
	IVM 200 mcg/kg/day solution for 5 days with reference treatment protocol comprising of -hydroxychloroquine + favipiravir + azithromycin versus reference treatment protocol alone (control group)
	-IVM group had lower mortality rate, a higher rate of clinical improvement and more marked reduction in d-Dimer, CRP and serum ferritin levels than the control group
Gorial *et al*.[109]	Patients who received IVM 200 μg/kg on admission, as an adjunct to treatment with hydroxychloroquine/ azithromycin, had notably lower hospital stays (7.62 days with adjunctive IVM vs 13.22 days without IVM)
	Clinical Studies of high doses of IVM and variable dose regimens of IVM (Therapeutic role)
Chaccour *et al*.[110] SARS-CoV-2 Ivermectin Navarra-ISGlobal Trial (SAINT)	-Non-severe COVID-19 patients utilizing a higher dose of 400μg/kg (single dose) given within 72 hours of symptom onset.
	-No difference in PCR positivity at days 4 and 7, although there was a tendency to lower viral loads and lower IgG titres (presumably reflecting milder disease) with a marked reduction in self-reported anosmia/ hyposmia in the IVM treated group
Krolewiecki *et al*.[111]	-Higher dose (0.6 mg/kg single dose) given within 5 days of symptom onset, in patients with mild-to-moderate disease, found no effect on viral load reductions at day 5 post-treatment.
Babalola *et al*.[112]	-Compared 6 mg IVM with 12 mg twice a week regimen vs control (Lopinavir/Ritonavir) arm.
	-The combined IVM arm had a significantly shorter time to PCR negativity compared to the control arm, but the difference between the 2 IVM arms was not significant.
Pott-Junior *et al*.[113]	-Dose comparison study comparing the effect of 100, 200, and 400μg/kg IVM in mild COVID-19 patients.
	-The proportion of patients who achieved 2 consecutive negative RT-PCR within 7 days of start of treatment were 71.4% in the 200 μg/kg group, 50% in the 100 μg/kg group, and 57% in the 400μg/kg group (lower than 200μg/kg group). This highlights an inconsistent dose-response effect.
Kory *et al*.[114] (Front Line COVID-19 Critical Care Alliance (FLCCC)	IVM 0.2 mg/kg for 3-5 days recommended for outpatient treatment.

Contd...

Table 3: Contd...

Author	Study Outcome
	Studies on prophylactic role of IVM
Behera *et al*.[71]	-A hospital-based matched case-control study among healthcare workers reported that two doses of IVM 300 mcg/kg given 72 hours apart led to a 73% reduction in SARS-CoV-2 infection in the following month. -The authors further reported that single-dose prophylaxis had no association with a reduction of SARS-CoV-2 infection.
Chang *et al*.[72]	-Two doses IVM 300 mcg/kg 72 hours apart reported a low (7.4%) incidence of COVID-19 infection in the intervention group compared to an almost 60% incidence in the non-intervention group. -Dose of IVM 200 μg/kg on day one, with an additional second dose of ivermectin on day 2 or 3 was studied for prophylaxis for men aged more than 45 years (presuming higher risk of severe disease in this subgroup). None of the 33 exposed healthcare workers given the prophylaxis developed the disease during the observation period
Alam *et al*.[73]	Reduction in disease development with a 12 mg monthly dose protocol of IVM, with only 6.9% of the treated group developing the disease compared with 73.3% subjects in the control group
Hellwig *et al*.[115]	Individual dosages for mass prophylaxis generally varied between 150 μg and 200 μg per kg, however, there seemed to be no notable difference in COVID-19 incidence among recipients of different dosages either

up to 800 μg/kg of IVM compared to standard approved doses.[122] A small number of patients in the study by Guzzo *et al*.[8] received doses up to 2000 μg/kg with a similar rate of adverse events than those receiving placebo.

As mentioned previously in cases with a high parasite burden—microfilariae in the skin (onchocerciasis) or blood (lymphatic filariasis or loiasis), post-treatment reactions including postural hypotension can be seen up to 36 h after treatment. In onchocerciasis, skin edema, pruritus, and mild eye irritation may also occur. Usually, recovery follows rapidly when the patient remains recumbent, and no specific therapy is needed. Occasionally patients may need symptomatic treatment with antipyretics or antihistamines.

A summary of side effects reported with oral and topical IVM and toxicity are listed in Table 4.[123-126]

Drug Interaction

A few drug interaction not much significant in routine clinical practice are listed in Table 5.[9,127-129]

Special Considerations

Resistance[130,131]

Though uncommon, there have been reports of poor parasitologic responses to the drug confirmed by parasitologic and epidemiologic evidence of IVM resistance.[132] In a study conducted in Cameroon, parasites obtained from individual patients demonstrated changes in the β-tubulin gene before and after the patients were treated with IVM.[132] The other mechanisms described include

(a) alteration of P-glycoprotein (via mutation of ABCA1 gene), which is a membrane protein that actively transports the drug across cell membranes;
(b) mutation in GluCl channel receptors which reduces the sensitivity of IVM;[133]
(c) lack of ovicidal action and reduced efficacy of single-dose IVM.

Novel agents like moxidectin have reduced affinity to P glycoprotein, a higher bioavailability and better penetration into the hyperkeratotic skin with a good safety profile and low resistance potential.[134] But it must be noted that macrocylic lactones are prone to cross-resistance and resistance to IVM leads to resistance to moxidectin, levamisole, and pyrantel as well.[135]

Pregnancy

Category: C

Although teratogenicity has been reported in animals with repeated doses 0.2, 8.1, and 4.5 times the maximum recommended human dose, no adequate and well-controlled studies have been performed in pregnant women. Thus, IVM should be avoided in pregnancy.

The use of IVM in mass treatment campaigns for more than 2 decades has occasionally resulted in the inadvertent administration of IVM to pregnant women with no adverse effects recorded.[136]

Lactation

The drug is excreted into breast milk and may attain concentrations of around 30% of that in plasma. But <10% of what goes into breast milk has been estimated to be taken up by the infant, which has been regarded as clinically insignificant.

Children and infants

IVM is conventionally not recommended for children under 15 kg and less than 5 years of age (see above) but clinical safety in infants and children has been demonstrated[46] in a recent large multicentric observational study. Levy *et al*.[137] reported data on 170 infants and children aged 1–64 months, with a bodyweight of 4–14·5 kg, who were treated with 1-2 doses of IVM for scabies. Only seven reported mild adverse events and there were no serious side effects.

Table 4: Adverse effects of IVM[123-126]

	Adverse effects
Oral ivermectin	-Systemic: Asthenia, arthralgia, myalgia, anorexia nausea, fever, headache, abdominal pain, and rarely encephalopathy, postural hypotension
	-Cutaneous: pruritis, maculopapular rash, edema/urticarial rash, lymph node enlargement, tenderness, facial edema, and rarely Steven-Johnson syndrome.
	-Laboratory: Increase in prothrombin time, decrease in blood pressure, flat T waves or prolonged PR times on ECG, eosinophilia, mild-to-moderate elevation of alanine aminotransferase
	-Mazzotti-type reaction: Intense inflammatory response to the dead microfilaria
Topical ivermectin	-Conjunctivitis, ocular hyperemia, eye irritation, dandruff, dry skin, and burning sensation.
	-Caution if there is previous hypersensitivity to IVM
Toxicity	-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.

Table 5: Drug interaction[9,127-129]

Mechanism	Drugs
Synergistic effect with IVM by increasing its intracellular concentration	Doxycycline, erythromycin, or azithromycin
Increase the plasma levels of IVM	Alcohol
Decreases the concentration of IVM by inhibiting certain drug transporters	Orange juice
Excessive hypocoagulability leading to hemorrhagic complications	Oral anticoagulant therapy with acenocoumarol
IVM potentiates other agonists of the GABA receptors	Benzodiazepines and sodium valproate
Alter IVM gastrointestinal disposition via enhanced P-glycoprotein-mediated intestinal transport	Rifampicin and phenobarbital

Renal failure

Renal elimination of IVM is negligible (<1%) and dosage adjustment in renal impairment is not expected to be necessary. However, IVM's pharmacokinetics in patients with renal impairment has not been studied in detail as yet.

Hepatic impairment

The drug is extensively metabolized in the liver (see above). Thus, although pharmacokinetic studies in liver function derangements are not available, hepatic impairment is likely to impair IVM's metabolism and elimination.

Conclusion

IVM is a drug that is safe, cheap, and widely available with multimodal action. The wide applicability with mass prophylaxis campaigns in various tropical disorders certifies its safety. The dermatological indications extend beyond scabies and pediculosis. The repurposing of this drug for COVID-19 is based on firm *in-vitro* data and therapeutic data suggests that it is a useful drug in the early virus replicative phase of the disease. It can be given at higher doses based on the available data which may achieve the ideal serum levels for an antiviral action. While it has established a firm place in the management of several nematodal and ectoparasitic infections, the anti-inflammatory, anti-cancer, and anti-viral/bacterial role of IVM make it a versatile drug, the full potential of it will evolve over the years.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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