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Authors

Zargari, Omid
Aghazadeh, Nessa
Moeineddin, Fatemeh

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Review

Clinical applications of topical ivermectin in dermatology

Omid Zargari¹ MD, Nessa Aghazadeh² MD and Fatemeh Moeineddin³ MD

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¹ Dana Clinic, Rasht, Iran

² Razi Dermatology Hospital, Tehran University of Medical Sciences, Tehran, Iran

³ Skin and Stem Cell Research Center, Tehran University of Medical Sciences, Tehran, Iran

Correspondence:

Nessa Aghazadeh, M.D.

Razi Hospital, Vahdat-Eslami St. Tehran Iran Tel. 9821-55633949

E-mail: n-aghazadeh@sina.tums.ac.ir

Abstract

Ivermectin (IVM) is a broad-spectrum anti-parasitic drug with significant anti-inflammatory properties. The emergence of treatment resistance to lindane, permethrin, and possibly malathion complicates the global strategy for management of common parasitic skin diseases such as scabies and head lice. In this regard, IVM has been safely and effectively used in the treatment of these common human infestations. In addition, IVM may be useful in inflammatory cutaneous disorders such as papulopustular rosacea where demodex may play a role in pathogenesis. Herein, we review the current applications of topical IVM in dermatology.

Key words: Ivermectin, Scabies, Pediculosis Capitis, Rosacea, Demodex

Introduction

Ivermectin (IVM) is a semi-synthetic derivative of a broad-spectrum class of antiparasitic drugs known as avermectins. Avermectins are a group of pentacyclic sixteen-membered macrolide antibiotics generated as fermentation products of *Streptomyces avermitilis*, a soil actinomycete. IVM is the most common avermectin, composed of two chemical compounds, namely 22,23-dihydroavermectin B1a (80-90%) and 22,23-dihydroavermectin B1b (10-20%) [1]. (Figure 1)

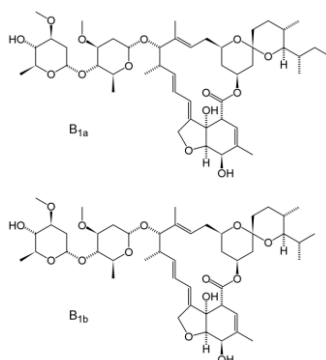


Figure 1. Chemical structure of the two components of IVM, 22,23-dihydroavermectin B1a and 22,23-dihydroavermectin B1b.

Oral IVM has been used for treatment of a wide range of endoparasites including *Strongyloides stercoralis*, *Ascaris lumbricoides*, *Ancylostoma braziliense*, *Gnathostoma spinigerum*, *Dermatobia hominis*, *Trichuris trichiura* and filariae including *Onchocerca volvulus* endemics, loiasis, and bancroftian filariasis. The interest of dermatologists in IVM particularly grew when promising results were observed in the treatment of ectoparasites such as *Sarcoptes scabiei*, *Pediculus humanus capitis*, and *Demodex follicularis* in animals and humans [2,3]. Oral IVM has been efficiently employed in the treatment of scabies [4-6]. Along with the growing concern of treatment resistance in head lice [7], oral IVM appeared as a valuable alternative for eradication of resistant head lice infestation in children [8,9]. The latter two indications remain off-label “oral” use of this medication. In 2012, FDA approved topical IVM 0.5% lotion for treatment of head lice in patients 6 months and older. The treatment is safe, convenient, and highly effective [10]. Recently, the anti-parasitic effect of IVM against *Demodex* mites and its anti-inflammatory properties proved to be advantageous in treatment of rosacea such that topical IVM 1% cream received FDA approval for once daily treatment of this inflammatory skin condition in 2014.

Mechanism of action

IVM binds selectively and with high affinity to glutamate chloride ion channels, commonly found in invertebrate nerve and muscle cells. It also stimulates the release of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) from presynaptic nerve terminals and encourages its binding to the postsynaptic receptors. The resultant increase in chloride ions leads to hyperpolarization of cells, and eventually paralysis and death of the parasites [11]. Topically applied IVM is absorbed by head lice and is actively transported across cell membranes by P-glycoprotein (P-gp). IVM exerts significant anti-inflammatory effects by inhibition of lipopolysaccharide-induced production of inflammatory cytokines such as tumor necrosis factor and interleukin (IL)-1 through inhibition of nuclear factor-kappa B pathway [12]. IVM also stimulates production of the anti-inflammatory cytokine IL-10 [13]. Such anti-inflammatory properties are comparable to that of other macrolide antibiotics [14]. Moderate antibacterial effects, against *Mycobacterium tuberculosis* and *Chlamydia tracomatis* have been observed [15].

Pharmacology, pharmacokinetics and safety

IVM is a white to yellowish-white, non-hygroscopic, crystalline powder, which is insoluble in water but soluble in methanol and 95% ethanol. Oral IVM is well-absorbed, reaching a peak plasma concentration of about 30-46 ng/mL, 4 hours post dose, with an elimination half-life of about 18 hours. The drug metabolism is primarily hepatic via CYP3A4 (major), CYP2D6 (minor), and CYP2E1 (minor), and some enterohepatic cycling has been proposed. IVM and its metabolites are excreted almost exclusively in the feces over an estimated 12 days, with less than 1% of the administered dose excreted in the urine [1,2].

IVM has negligible adverse effects on mammals. This safety margin is attributable to the fact that mammals do not have glutamate-gated chloride channels, the macrocyclic lactones have a low affinity for other mammalian ligand-gated chloride channels, and these lactones do not readily cross the blood-brain barrier [15]. The reported side effects observed in more than 10% cases include Mazzotti-type reaction (with onchocerciasis), pruritus, and fever, skin involvement including edema/urticarial rash, lymph node enlargement, and tenderness. The manufacturer and the Centers for Disease Control and Prevention (CDC) do not have safety data in children <15 kg [16].

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 single 10 minute application for head lice treatment are much lower than those of oral IVM. Additionally, IVM lotion is significantly less irritating than normal saline and sodium dodecyl sulfate, with minimal evidence of skin irritation or sensitization [17]. There are no reported contraindications for IVM lotion. However, caution may be justified if the drug is used to treat patients with known hypersensitivity to IVM or any of the product excipients (olive oil, oleyl alcohol, Crodalan AWS, lanolin alcohol, cyclomethicone, shea butter, sodium citrate, sorbitan tristearate, methylparaben, propylparaben, and citric acid) [18]. The most frequently reported (incidence rate of less than 1%) adverse reactions include conjunctivitis, ocular hyperemia, eye irritation, dandruff, dry skin, and burning sensation [19].

Minimal systemic absorption has been observed with IVM 1% cream; after 2 weeks of treatment, the highest plasma concentrations of IVM is 2.10 ± 1.04 ng/mL at 10 ± 8 hours. The half-life is 6.5 days in average. Adverse reactions, reported in $\leq 1\%$ of subjects, includes burning sensation in skin and skin irritation [20].

Use in pregnancy, lactation and Resistance

IVM has no genotoxic potential. Teratogenic effects have been observed in animal reproduction studies merely at or near maternotoxic doses to the pregnant female. However, there are no adequate and well-controlled studies in pregnant women. The manufacturers classify both oral and topical IVM as pregnancy category C, and neither form is recommended in pregnancy. Limited data indicate that IVM is poorly excreted into breast milk after oral administration. IVM tablets are not recommended for

use in lactating women, and caution is required with the topical drug in this group [16]. The safety profiles of topical IVM lotion in children less than 6 months and individuals older than 65 years of age are unclear. Impairment of the blood-brain barrier in both extreme age groups raises concerns regarding potential neurologic toxicity. The increased mortality rate reported with the use of oral IVM for scabies in an elderly Canadian facility [21] has been disputed [22].

Emerging IVM resistance in *Onchocerca volvulus* and animal nematodes have been reported endemic countries. Alteration of P-gp or chloride channel receptor may be responsible for the development of resistance [23,24]. Resistance of *Sarcoptes* scabies to oral IVM has been reported in two Australian patients with severe crusted disease who received exceptionally high doses of the medication (30 and 58 mg) [25].

Clinical Applications

Pediculosis Capitis

Pediculosis capitis is a common global health problem. It is estimated that about 6 to 12 million infestations occur each year in the United States among children 3 to 11 years of age [26]. Stigma and ostracism, parental anxiety, loss of income, and absenteeism from school are social problems associated with head lice [10,27]. Scratching the scalp and superimposed bacterial infection may contribute to morbidity [28].

The extensive use of pediculicides has led to the development and spread of resistant head lice with a varying resistance pattern depending on the geographic location. Increasing resistance to lindane and pyrethroids are well documented, and malathion resistance has been noted in the United Kingdom [7]. Therefore, the development of compounds with a different target site than that of conventional pediculicides was crucial. (Table 1)

Table 1. The mechanism of action of common pediculicides and resistance pattern

Pediculicide	Mechanism of Action	Resistance (Head Lice)
Permethrin	Modifies voltage-gated sodium channels by keeping the channel open for abnormally long periods, leading to spastic paralysis and death of the lice.	Permethrin resistance in head louse is widespread in various countries, including UK, USA, France, and Australia among others.
Lindane	Non-aromatic organochlorine insecticide, acts on γ -aminobutyric acid-gated chloride channel, stimulates the nervous system resulting in seizures and death of the parasite	Widespread resistance to head lice has been reported worldwide resulting in poor clinical response.
Malathion	Neurotoxic organophosphate, irreversibly inhibits cholinesterase activity	Less resistance in head lice than permethrin, lower rates in US than Europe
Ivermectin	Binds selectively to glutamate chloride ion channels, this increases cell permeability to chloride ions, causing hyperpolarization of the nerve or muscle cell, and death of the parasite	Head lice resistance not reported.

Studies point out that IVM is effective against permethrin-resistant head lice in vitro and is capable of eliminating parasites partially refractory to malathion in vivo [8,29]. Oral IVM 200-400 $\mu\text{g}/\text{kg}$, has been successfully used in treating pediculosis capitis. Both single treatment and two treatment (on days 1 and 8) regimens have been administered [8,9, 30-32]. However, systemic treatment is limited by dose limitation of less than 400 $\mu\text{g}/\text{kg}$, the need for repeated treatments to eliminate re-infestation from hatching eggs, and safety concerns in young children (less than 15 kg). Unlike the oral formulation, IVM lotion does not require a second dose because, the newly-hatched lice would die soon as they are unable to feed owing to pharyngeal muscle paralysis. Possible mechanisms for this are that the topically applied drug may penetrate the egg or that the hatching lice absorb the IVM on the outside of the egg [33].

Current evidence strongly suggests that topical IVM 0.5% lotion is safe and efficacious in treating head lice, achieving lice eradication of 94.9% on day 2 and 73.8% on day 15 post-treatment (Table 2) [10,34,35].

Table 2. Summary of studies of topical ivermectin in treatment of head lice

	Type of study	Participants	Method	Result	Adverse Events (AE)
Youssef et al ³⁴	case series	50 patients with clinically and parasitologically diagnosed scabies	single application of 0.8% ivermectin liquid, -dose: 15-25 ml for each patient	-apparently cured, clinically and parasitologically, within 48 hr - 50% of patients (males with widespread lesions),some degree of itching still present. Another application needed five days later	none reported
Halpert E ³⁷	Randomized study	208 infested individuals –2-25 years	Comparison of single application of 10 mL IVM 1% shampoo with 10 mL of lindane 1% shampoo - shampoos were applied for 10 minutes to individuals >5 years and for 5 minutes in those< 5 years	viable eggs not present at 4 to 6 hours or 15 days post treatment in the IVM group but were detectable in 15% at 4 to 6 hours and 30% at 15 days in the lindane group	-
Pariser et al ¹⁰	two multicenter, randomized, double-blinded, vehicle-controlled trials	-289 patients with at least 3 live lice* present - Other household members enrolled only if infested >1 live lice ** -6 month or older	single 10-minute application IVM 0.5% topical lotion or vehicle, no nit combing	-significantly more patients receiving IVM than vehicle were louse-free on day 2 (94.9% vs. 31.3%), day 8 (85.2% vs. 20.8%), and day 15 (73.8% vs. 17.6%) (P<0.001) -94.9% of IVM treated patients were louse-free on day - On day 2, pruritus reduced in both groups, with significantly more pruritus-free patients in IVM group than vehicle group (66.7% and 42.6%, respectively; P<0.001)	-frequency and severity of AE similar in IVM and placebo group - Pruritus, excoriation, and erythema most common AEs, frequency <1% in IVM group
Meinking et al ³⁵	Phase II, four-arm, randomized, double blind, parallel, placebo-controlled	-78 infected patients, 74 completed -age:2-62 years	comparison of single 10-minute application of three different concentrations (0.15, 0.25, 0.5%) of IVM and placebo	-All ivermectin groups showed greater head lice eradication than the placebo (P < 0.0091) : 8.7, 55.6, 50.0, and 73.7% of subjects in the placebo, 0.15, 0.25, and 0.5% treatment groups, respectively, were lice-free on day 15 - the highest level of eradication (73.7%) observed with 0.5% concentration -severity of pruritus decreased in all groups from baseline, including placebo with the greatest reduction in the 0.5% concentration group	-22 AEs reported by 20 subjects, all mild or moderate - none led to withdrawal - No ocular irritation -generally well tolerated
Ahmad et al ³⁶	Non-blinded observational trial	-62 patients with proven infestation - 5–47 years	-Comparison of single topical application of 1% IVM solution and single dose of oral IVM 200 µg/kg. -treatment repeated for non-responders after 1 week	-At week 1 after treatment, the eradication rates(88% vs. 45%, p = 0.002) and improvement of pruritus(90% vs. 55%, p = 0.0002) higher with topical vs. oral IVM -When second dose given to non-responders of each group, the cure rate reached 100% and 97%.	-AEs mild and rare among both group -none led to withdrawal

*, intention-to-treat analysis; **, extended intention-to-treat analysis

IVM: ivermectin

A single treatment with topical IVM may be associated with earlier response and higher cure rates than oral IVM [36]. Comparative studies with other pediculicides are lacking, however, 1% IVM shampoo appears to be superior to lindane in eliminating the viable eggs [37]. While permethrin and pyrethroids are the recommended first line of treatment for head lice [27], topical IVM 0.5% lotion can be used as a valuable second or third line treatment option [38], according to the local resistance pattern, ease of application, and cost. Topical IVM lotion is directly applied to the dry hair and scalp, left for 10 minutes, then rinsed thoroughly. Repeat application is not required.

Oral IVM (250 mcg/kg) has been used by some authors for treatment of *Phthirus pubis* and *Phthiriasis palpebrarum* [39]. However, topical formulation has not been studied.

Scabies

Scabies, an infestation caused by *Sarcoptes scabiei var. hominis*, is a common dermatologic disease both in developed and developing countries, with an estimated global prevalence of 300 million cases [40]. Currently, permethrin appears to be the most effective treatment and drug of choice for scabies in most parts of the world [41-43]. The CDC recommends IVM (200 mcg/kg, with a repeat dose two weeks later) as an equivalent to topical permethrin [44]. 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 may be excellent indications for oral IVM [4-6]. Higher doses may be required in the latter two settings [45].

Topical IVM is a welcome addition to the anti-scabietic armamentarium. Although it is very effective against the adult stages of the mite, IVM is not ovicidal. Therefore, a single application may be inadequate in treatment of scabies and repeated applications are often required within 1-2 weeks. IVM 1% solution is as effective as permethrin 2.5% cream at the 2 and 4 week follow up [46], but appears more effective than crotamiton 10 % at week 4 post treatment [46], and has been safely applied to infested children 1 to 10 years old [48]. More studies are required in the latter setting. 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 (Table 3) [49].

Table 3. Summary of clinical studies of topical ivermectin in treatment of scabies.

	Type of study	Participants	Methods	Results	Adverse Events (AEs)
Youssef et al ³⁴	case series	50 patients with clinically and parasitologically diagnosed scabies	single application of 0.8% ivermectin liquid, -dose: 15-25 ml for each patient	-apparently cured, clinically and parasitologically, within 48 hr - 50% of patients (males with widespread lesions),some degree of itching still present. Another application needed five days later	none reported
Yeruhama et al ^{84 *}	case series	10 patients with uncomplicated scabies	topical 1.87% IVM cream, weekly	marked improvement within 2 or 3 days of the first treatment, and clinical cure after 2 or 3 days of second treatment	-
Victoria et al ⁴⁸	case series	32 patients including 20 children (1-10 years)	-solution of IVM 1% 400 µg/kg/dose in 10cc of propylene glycol -applied twice one week apart	-All patients with clinically evident scabies were cured. -no sign of recurrence 6 weeks later	-no reported side effects -drug well tolerated
Goldust et al ⁴⁶	investigator-blind, randomized trial	380 patients, 4-72 years	Comparison of topical 1% IVM in propylene glycol at a dose of 400 µg/kg and permethrin 2.5% cream -both creams were applied twice at one week intervals. - if there was treatment failure at the 2-week follow-up, treatment repeated	-At week 2 , the treatment was effective in 120 (63.1%) patients in the IVM group and 125 patients (65.8%) in the permethrin group (P=0.68) - At week 4, cure rate was 160/190 patients (84.2%) in the IVM group and 170 of 190 (89.5%) in the permethrin group (P=0.43).	The main AE was irritation, reported by 30 in the IVM group and 20 in the permethrin, but this was not serious and did not affect compliance

Chhaiya et al ⁴⁹	randomized, comparative, parallel clinical trial -non-blinded	315 patients, 5 to 80 year	-Comparison of single application of permethrin 5% cream a, tablet IVM 200 mcg/kg as single dose, and single application of IVM 1% lotion - the same intervention was repeated at each follow up, if no sign of cure -All patients received hydroxyzine 10 mg or 25 mg twice-daily for pruritus	-At the end of week 1, cure rate was 74.8% in permethrin group, 30% in oral IVM group, and 69.3% in topical IVM group (P < 0.05). At the end of week 2, cure rate was 99% in permethrin group, 63% in oral IVM group, and 100% in topical IVM group (P < 0.05). At the end of week 3, 100% cure rate observed in permethrin and topical IVM group while 99% in oral IVM group (P = 0.367) - topical IVM and permethrin cause rapid improvement in itching compared to tablet IVM at week 1 and 2(P < 0.05)	-No major AEs with any medication -One patient in permethrin group developed burning sensation, relieved spontaneously -2 patients in oral IVM group developed mild headache and increase in pruritus, respectively, subsided without any medication.
Goldust et al ⁴⁷	investigator-blind, randomized trial	340 patients, > 2 years of age	Comparison of topical 1% IVM solution in propylene glycol (400 µg/kg), repeated once the following week and crotamiton 10% cream twice daily for five consecutive days -Treatment re-applied at week 2 in case of failure	-At week 2, the treatment was effective in 110 (64.7%) patients in the IVM group and 70(41.2%) in the crotamiton group (P = 0.72) - the overall cure rate at week 4 was 140 of 170 patients (82.3%) in the IVM group and 110 of 170 (64.7%) in the crotamiton group (P = 0.043).	The main AE was irritation, reported by 30 in the IVM group and 20 in the crotamiton but this was not serious and did not affect compliance
Ahmad et al. ⁵¹	Randomized trial	Uncomplicated scabies, >5 years of age	Comparison single topical application of 1% IVM solution to at night and single oral dose of IVM (200 µg/kg/dose) after food. Treatment was repeated after one week only in patients with persistent infection. Patients were assessed, clinically and by KOH smear, at 1, 2, and 4 weeks after starting treatment	At 1 week, 87.5% of patients in topical IVM group vs 73.5% in oral group were treated. (p<0.001 compared to baseline for both groups. The difference in cure rates between the two groups was not statistically significant Pruritus was resolved in topical IVM-treated patients more quickly than the oral IVM group (at week 1, 90.6% vs. 76.6%, respectively) AEs mild and rare, no treatment discontinuation required.	Both topical and oral IVM are safe and equally effective in treatment of uncomplicated scabies. topical IVM may provide faster cure of scabies and its related pruritus

IVM: ivermectin

*The authors were unable to access the full text of this paper

“Whole-body bathing method” has been proposed as a possible new method of application of IVM for treating scabies. When rats were bathed in the IVM 100 ng/mL fluid, the drug was effectively delivered to the skin in a concentration higher than that of oral IVM, without systemic absorption [50]. Recently, Ahmad et al compared the efficacy of single application or topical 1% IVM and single oral dose of IVM (200 µg/kg). The study showed that both topical and oral IVM are safe and equally effective in treatment of uncomplicated scabies, with topical IVM providing faster cure of scabies and its related pruritus [51].

Based on the above studies, we recommend treatment of scabies with a 1% solution of IVM (400 microg/kg) to the entire skin over one night, then repeated a week after. While permethrin remains the first choice in treatment of scabies, both oral and topical IVM can be safely and effectively used when the former fails to respond and resistance is suspected.

Diseases associated with *Demodex folliculorum*

Demodicidosis

Demodex mites are the most prevalent human parasites, enjoying a lifelong symbiotic residence in human beings. Human demodicosis is a skin disease of the pilosebaceous units associated with human *Demodex* mites (*Demodex folliculorum* and *Demodex brevis*) that predominantly involves the face and head and presents with a variety of clinical presentations including pityriasis folliculorum and conglobate, ocular, and auricular demodicosis [52-54]. The role of the *Demodex* mites as agents of human disease remains somewhat controversial because absolute proof of causation is difficult to achieve; prompt treatment

response is considered the strongest evidence of pathogenesis [55]. High-density *Demodex* mite infestation has also been reported as a possible cause of facial eruption in immunocompromised individuals [52], cutaneous eruption in patients receiving epidermal growth factor receptor (EGFR) inhibitor [56], perioral dermatitis [57], chronic blepharitis [58], and otitis externa [59].

IVM is acaricidal and is the treatment of choice for canine demodicosis [60]. Oral IVM has been successfully employed in treatment of human demodicosis including in the setting of AIDS [50,61]. A single oral dose of 250 mcg/ kg was successfully used in treatment of two children with acute leukemia and disseminated demodicosis; subsequent relapse was also responsive to IVM [2,62]. Oral 200 µg/kg IVM with subsequent weekly topical permethrin was effective for rosacea-like demodicosis [63]. The combination of oral IVM and metronidazole appeared more effective than the latter alone for treating skin lesions and anterior blepharitis associated with *D. folliculorum*. [58] Elimination of *D. folliculorum* may be useful in the treatment of ocular and eyelid discomforts of patients with Behçet's disease, even in the absence of any complaint [64]. A variety of other dermatological conditions have been associated with increased density of *Demodex* mites and hypothetical etiological significance including androgenetic alopecia, madarosis, lupus miliaris disseminatus faciei, and dissecting folliculitis among others [65]. The potential therapeutic effect of *Demodex* elimination has not been studied in these situations. However, IVM may be useful in a myriad of disorders associated with *Demodex* overpopulation and immune dysregulation, including blepharitis, otitis externa, acne, perioral dermatitis, demodicosis of immunosuppression among others.

Rosacea

Rosacea is a common, chronic skin disorder divided into four main subtypes: erythematotelangiectatic, papulopustular, phymatous, and ocular rosacea. The estimated prevalence of rosacea in fair-skinned populations is from 1% to 10% [66], with an overall incidence rate of 1.65 per 1,000 person-years in the United Kingdom [67]. Rosacea is associated with reduced self-esteem and negative impact on quality of life and social engagement [68]. The etiology of the disease is multifactorial; neurovascular dysregulation, augmented proinflammatory innate and adaptive immune responses, exogenous factors, and microorganisms such as *Demodex* mites have been implicated [69,70]. Rosacea patients have a 5.7 fold increase in *Demodex* density compared to healthy controls. Mites, or bacteria associated with them (*Bacillus oleronius*), could trigger both the innate (via toll-like receptor 2 and the inflammasome, stimulating active cathelicidin and IL-1 β) and adaptive immune responses in this disorder [71].

IVM is lethal to *Demodex* mites that reside in the pilosebaceous units of patients with papulopustular rosacea. In addition, the anti-inflammatory effects of IVM appear to play a dominant role in controlling the inflammatory lesions of rosacea. Results of two-week controlled, investigator-blinded trials have shown that IVM 1% cream is superior to placebo in reducing inflammatory lesions in papulopustular rosacea, achieving 'clear' or 'almost clear' treatment response, and improving patients satisfaction and quality of life [72]. A 40-week extension study showed that IVM was associated with less treatment-related dermatologic adverse events compared to azelaic acid 15% gel and provided efficacy and safety data for prolonged use up to 52 weeks [73]. IVM 1% cream was better than metronidazole 0.75% cream for decreasing the inflammatory lesion count, reaching 'clear' or 'almost clear' response, and patient satisfaction [74](Table 4). Based on the above mentioned studies, IVM cream is applied once daily at bedtime to the affected areas of the face. The effect of IVM on other clinical subtypes of rosacea including erythematotelangiectatic, phymatous or granulomatous has not been studied.

Myiasis and other parasitic diseases

Myiasis, is the infestation of live human and vertebrate animals by dipterous larvae. Conventional treatment consists of the removal of the larvae from the affected sites, although sometimes they may be difficult to access. Oral IVM has been successfully used in treating myiasis [75]. Topical IVM also led to successful killing of all larvae caused by *Cochliomyia hominivorax* after 24 hours in four patients with traumatic myiasis who received single topical treatment of 1% IVM for 2 hours [76].

Oral IVM is the treatment of choice for onchocerciasis, it has been widely and effectively used to kill the microfilaria, prevent blindness, and reduce the occurrence and severity of skin lesions [77]. Cutaneous larva migrans has been effectively treated with single dose of oral IVM [78], with higher efficacy in patients with only creeping dermatitis than in those with associated hookworm folliculitis [79]. To the best of our knowledge, topical IVM has not been studied in the latter parasitic infestations.

Cheyletiella dermatitis

Cheyletiella spp. are non-burrowing mites that feed on the keratin layer of the epidermis and hair in cats, dogs and rabbits. *Cheyletiella* mites are very mobile and contagious by direct contact. The infected animal is asymptomatic except for excessive dandruff on the back. Rarely, free-living *Cheyletiella* mites cause dermatitis in humans, characterized by intensely pruritic papules, necrotic lesions, vesiculobullous or blistering skin lesion characteristically distributed on areas of contact with the infested animal [80,81]. Treatment of the affected animal with weekly applications of topical acaricidal products such as pyrethroids is often sufficient. Naturally occurring cheyletiellosis has been effectively treated with twice, three-week interval of

subcutaneous 300 pg/kg IVM injection in dogs [82]. Topical selamectin, another avermectin antiparasitic agent with structural and functional similarities to IVM, has been successfully used to treat cheyletiellosis in cats [83].

Conclusion

IVM is an antiparasitic drug with significant anti-inflammatory effects. Topical application as cream or lotion is particularly safe. The evidence strongly supports its clinical application for pediculosis capitis and rosacea, and it can be considered for treatment of scabies, demodicidosis, and cutaneous myiasis.

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Tables 1-4 to be added - see version 'Topical Ivermectin in Dermatology AuthorEdit 8-12-16'. Figure was added as Figure 1 on page 1.