CURRENT USES OF IVERMECTIN IN DERMATOLOGY IN POST-COVID ERA

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Rezumat

Ivermectina este un medicament antiparazitar cu spectru larg cu aplicații medicale bine stabilite în dermatologie (cum ar fi, dar fără a se limita la rozacee/demodicoză, scabie și larva migrans cutanată), a câștigat atenție publică în ultimii ani, fiind înconjurat de controverse cu privire la tratamentul COVID-19. Acest articol își propune să ofere o trecere în revistă cuprinzătoare a utilizărilor medicale ale ivermectinei în dermatologie, oferind o perspectivă proaspătă și actualizată asupra mecanismului său de acțiune, farmacocineticii și aplicațiilor sale clinice cel mai frecvent întâlnite în practica medicală curentă. Indiferent de diferitele argumente în jurul utilizării sale în bolile respiratorii, dovezile actuale susțin utilizarea ivermectinei ca opțiune sigură și eficientă în tratamentul diferitelor afecțiuni dermatologice.

Cuvinte cheie: *dermatologie, ivermectină, demodex, scabie, rozacee.*

Summary

Ivermectin, a large spectrum antiparasitic drug with well-stablished medical applications in dermatology (such as but not limited to rosacea/demodicosis, scabies and cutaneous larva migrans), has gained traction into public attention in the last years, being surrounded by controversies regarding its effectiveness in the treatment of COVID-19. This article aims to provide a comprehensive review of the medical uses of ivermectin in dermatology, offering a fresh and updated perspective over its mechanism of action, pharmacokinetics and its clinical applications most frequently encountered in current medical practice. Regardless of the various arguments surrounding its use in respiratory diseases, the current evidence supports the use of ivermectin as a safe and effective option in the treatment of various dermatological conditions.

Keywords: *dermatology, ivermectin., demodex, scabies, rosacea.*

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Introduction

Since its registration for human use in 1987, ivermectin established in the medical practice as a broad spectrum antiparasitic drug, being used in treatment of onchocerciasis (*Onchocerca volvulus*), filariosis (*Loa-loa*) or strongyloidiasis (*Strongyloides stercoralis*). Apart of that, it harbors a wide array of applications in dermatology, such as but not limited to scabies, pediculosis or rosacea.[1] Given its immunomodulatory effects, ivermectin has gained traction into public attention in the last years, being surrounded by controversies, as a potential curative treatment for COVID-19. Popp et al found in a Cochrane systematic review that there is currently low- to high- certainty evidence that ivermectin has no beneficial effects for people with COVID-19, inconclusive whether ivermectin prevents exitus

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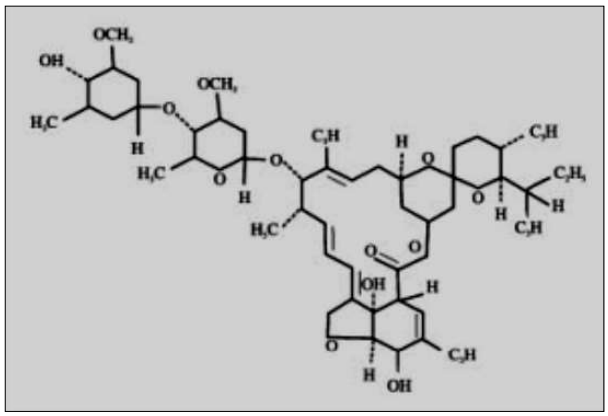

Figure 1 - Chemical structure of ivermectin [1]

or hospitalisations due to worsening of the conditions, also stating that there exists some low-certainty evidence that it has no beneficial effect regarding clinical improvement or viral clearance.[2] No evidence is, however, yet available on ivermectin ability to prevent SARS-CoV-2 infection.[3]

In this article, we aim to provide a comprehensive review of the medical uses of ivermectin in dermatology, offering a fresh and updated perspective over its mechanism of action, pharmacokinetics and most frequently encountered clinical applications in current medical practice.

History

Ivermectin (22,23-dihydroavermectin B1) is a macrocyclic lactone which is part of a class of highly effective, broad-spectrum antiparasitic agents called the avermectines[4]. Ivermectin shares a structural similarity with macrolide antibiotics, although it lacks antibacterial properties (Fig.1).[1]

Avermectin B was first isolated by fermenting a soil microorganism called *Streptomyces avermitilis*. in 1973 by Ômura.[5] For this extraordinary discovery, Satoshi Ômura together with William C. Campbell, were awarded the Nobel Prize in Physiology or Medicine in 2015.[5]

Since 1981, ivermectin has been used in veterinary medicine, to treat *Sarcoptes scabiei* in various animals such as pigs[6], calves [7], horses and dogs [8]. The treatment involved subcutaneous injection and has been proven to be both effective and safe. [4]

After 6 years since its first use on animals, ivermectin is approved by the FDA in 1987 for human treatment, for onchocerciasis. Thirty-six years after, ivermectin remains the first-line treatment for onchocerciasis. [9] Other parasites for which ivermectin is effective include ascaris, strongyloides, filariasis, cutaneous lavra migrans, head lice infections [10] and, of course, scabies. [11] Ivermectin is also effective on Demodex mite, an ectoparasite which is believed to be involved in rosacea pathophysiology. [12]

Table 1. Uses of ivermectin in dermatology. [35,29,45,49,54,57]

Disease	Etiological agent	Administration method	Dose	Treatment duration
Scabies	*Sarcoptes scabiae*	p.o.	200 mcg/kg	Second dose after 1-2 weeks
Rosacea		topical	Ivermectin 1% cream	12 weeks
Pediculosis	*Pediculus capitis* *Pediculus corporis* *Pediculus pubis*	p.o.	200-µg/kg per week	2 weeks
Cutaneous larva migrans	*Ancylostoma braziliense*	p.o	200 µg/kg	Single dose
Myiasis	*Cochliomyia hominivorax* *Dermatobia hominis*	topical	Ivermectin 1% cream	2 hours
Filariasis	*Wuchereria bancrofti* *Brugia malayi* *Brugia timori*	p.o	150 µg/kg	Single dose

Mechanism of action

The antiparasitic effect of ivermectin occurs by binding to the glutamate-gated chloride ions channels located in muscle and nervous cells, blocking the chemical transmission across the nerve synapses that rely on glutamate or μ-aminobutyric acid (GABA). This effect leads to cell death by increasing the permeability of the cell membrane to chloride ions. [11] Ivermectin also interacts with various receptors, including glycine, histamine, and nicotinic acetylcholine. [13] An important aspect is that ivermectin does not pass the blood-brain barrier easily, being safe in mammals. [11]

In addition to the antiparasitic effect, ivermectin has anti-inflammatory proprieties which have been studied in numerous preclinical studies. [14] One of the studies conduced by Zhang X. et al showed that ivermectin has reduced the production of pro-inflammatory cytokines, such as TNF alfa, IL-1b and IL-6 in mice, by inhibiting lipopolysaccharide (LPS)-induced production of citokines. [15] This effect was produced by blocking NF-kB pathway. They observed that ivermectin exhibits a dose-dependent inhibition of the NF-kB factor p65, which is translocated from the cytoplasm to the nucleus upon exposure to lipopolysaccharide (LPS). [15]

Another anti-inflammatory effect in produced by inhibiting LPS-induced of prostaglandin E2 and nitric oxide in macrophages in vitro. [16] The ability of ivermectin to inhibit the realease of macrophagal inflammatory mediators and its minimal impact on phagocytosis can have beneficial physiological outcomes at the organism level, leading to a reduction in symptoms associated with endotoxemia. [17]

Pharmacokinetics

Studies have shown that ivermectin has good oral bioavailability. After a rapid absorbtion which is better on an empty stomach, it is metabolized in the liver and the excretion is predominantly in the feces (98%) and urine (1%). [1] It was found that a small part is excreted in breast milk. [1] After oral administration, ivermectin reaches peak plasma levels at 4-5 h, with blood concentration around 30-46 ng/ml after a single dose and a half-time around 36h.1 In the situation where ivermectin is applied topically, such as severe papulopustular rosacea, steady-state plasma concentrations were attained after two weeks. The peak plasma concentration of ivermectin during steady state is attained approximately 10 hours following the application of the cream. [14] The primary metabolic pathway of the drug involves cytochrome P450, and it produces two significant metabolites known as 30-O-demethyl ivermectin and 4a-hydroxy ivermectin. [14] Patients who use ivermectin 1% cream once daily for a duration of 28 days exhibit a prolonged apparent terminal half-life of approximately 6 days on average. [18]

Minor and rare side effects have been reported, but these were mostly encountered after systemic administration of ivermectin, primarily in patients treated for filariasis. [19] Among the adverse effects, are included gastrointestinal manifestations like nausea, vomiting, diarrhea or abdominal pain; neurological symptoms like dizziness, somnolence or tremor; cutaneous reaction like pruritus, rash or urticarial and last but not least biochemical abnormalities like elevated transaminases or leucopenia. [20]

Uses in dermatology

1. Rosacea

Rosacea is a common, chronic inflammatory skin disorder with a variety of cutaneous manifestations which affects predominantly adults (over the age of 30 years, females > males). [21] Clinical manifestations include centrofacial erythema, telangiectasia, flushing, papules and pustules, phymatous changes and ocular features (Fig.2). [22] Besides these features, can be associated symptoms like roughness and scaling due to dry skin, burning sensations and edema. [23] The psychological impact of rosacea is significant due to its facial involvement across all types of the condition. This can lead to various psychological consequences, including depression and anxiety, ultimately resulting in a decreased quality of life for individuals affected by rosacea. [24]

The precise mechanisms underlying the development of rosacea are not fully comprehended. However, several potential

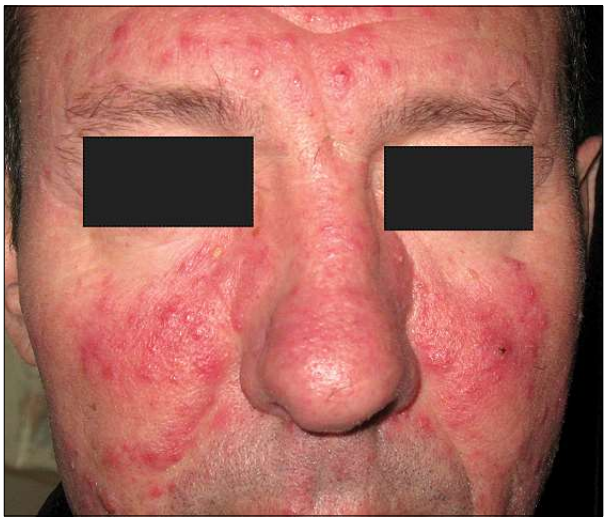

Figure 2 - Multiple erythematous papules on the cheeks and forehead of a patient with papulopustular rosaceea - (image from our clinic).

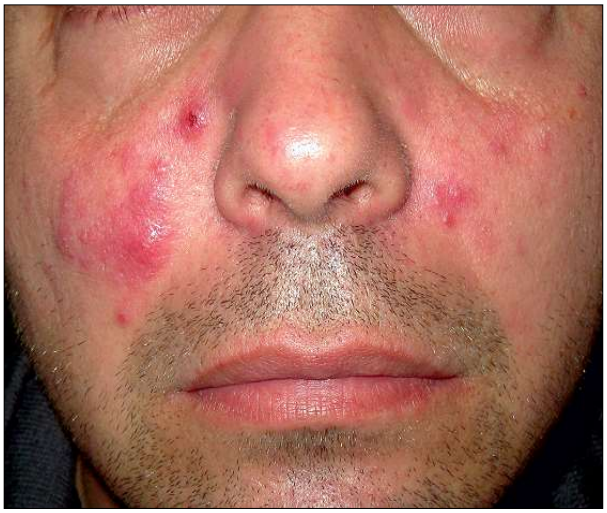

Figure 3 - Clinical manifestations of Demodex mites - (image from our clinic).

factors have been proposed to contribute to its onset. These include abnormalities in the immune system, inflammatory responses to microorganisms on the skin, vascular dysfunction, exposure to ultraviolet light, and genetic factors. [23] The Demodex mite, a natural inhabitant of human skin, has been identified as a common microbial factor associated with rosacea. Patients with papulopustular rosacea have been observed to have a higher prevalence of Demodicosis on their cheeks compared to individuals with healthy skin. [25] There are two types of Demodex mites, *Demodex folliculorum* and *Demodex brevis*, which are typically found in or near the pilosebaceous units causing inflammation and trigger immune reactions in the affected skin area. [26] While the parasite can be found on various parts of human skin, the mite has a particular preference for the facial region (Fig.3). [27] A diagnosis of demodicosis or Demodex infestation is typically considered when clinical signs and symptoms are observed, along with the presence of more than 5 mites/cm2 of skin or when the mites have penetrated into the dermis. [25] Demodex mites have the ability to penetrate into skin cells, specifically targeting keratinocytes that line the pilosebaceous follicles, and they feed on the contents of these cells sebum or cellular proteins. This feeding process is facilitated by salivary enzymes that contain proteases. [27] There are multiple ways in which Demodex mites might play a role in the development of rosacea: [25]

- → the excessive presence of Demodex mites can lead to the obstruction of hair follicles and sebaceous glands, potentially causing damage to the skin barrier and tissues;
- → the release of internal contents by dying Demodex mites is believed to trigger an immune response in the host, leading to subsequent inflammatory changes;
- → T-cell-mediated immune responses to Demodex have been reported to contribute to the development of rosacea;

The wide range of available drugs for rosacea makes it challenging to establish standardized treatment approaches. [28] The use of ivermectin 1% cream has gained significant relevance in the treatment of papulopustular rosacea, primarily due to its ability to target the altered microbiome. [26] To treat rosacea, the application of ivermectin 1% cream involves a once-daily routine. A small quantity equivalent to the size of a pea is applied to every affected area of the face, including the forehead, chin, nose, and each cheek in a thin layer over the skin. [29]

The effectiveness of topical ivermectin 1% cream in treating papular and pustular lesions of rosacea has been established through two high-quality, randomized trials with vehicle-controlled

comparisons. [30] These studies, conducted on adults with moderate to severe rosacea, provided evidence of the cream's efficacy in managing the specific symptoms associated with papular and pustular lesions. [31] In the initial trial, out of 451 patients, 173 individuals (38 percent) who received treatment with ivermectin achieved a state of being clear or nearly clear of inflammatory lesions within a span of 12 weeks compered to only 27 of 232 patients (12 percent) in the vehicle group. In the second trial, the outcomes were comparable, 184 of 459 patients (40 percent) treated with ivermectin versus 43 of 229 patients (19 percent) in the vehicle group reached a state of being clear or almost clear from inflammatory lesions after 12 weeks. [30]

One randomized trial study compared the effectiveness of once-daily use of ivermectin 1% cream versus twice-daily use of metronidazole 0.75% cream for a period of 16 weeks. The study was conducted on 962 patients with moderate to severe rosacea with papules, pustules and erythema. The study found that ivermectin 1% cream was more effective in decreasing inflammatory lesions. 29 Patients with severe rosacea at baseline demonstrated a slightly more significant difference in this outcome between the two treatment regimens. Specifically, 82.5% of patients receiving ivermectin compared to 63.0% of patients receiving metronidazole achieved the desired outcome. Similarly, among patients with moderate rosacea at baseline, the difference was also notable, with 85.4% of patients in the ivermectin group and 77.9% of patients in the metronidazole group experiencing the desired outcome. [14]

2. Scabies

Scabies is a parasitic skin infestation caused by the mite *Sarcoptes scabiei*. Scabies presents in two major clinical variants known as classic scabies and crusted scabies. The main clinical characteristic of classic scabies is intense itching (pruritus), which is typically more severe and pronounced during nighttime. [32] The pruritus is a result of a delayed-type hypersensitivity reaction to the mites, their feces, and their eggs. [33] The symptoms of scabies start to manifest approximately three to six weeks after the initial infestation occurs. [32] In this time, pregnant females create shallow tunnels known as burrows in the stratum corneum, and usually remain inside these burrows for the entirety of their lifespan, which lasts for about four to six weeks. During this period, they lay an average of two to three eggs daily. [13] In individuals who have been previously infested, symptoms typically manifest within one to three days after re-infestation, likely due to a cell-mediated immune response to mite antigens and mite products (prior sensitization). [13] The symptomatology includes numerous small erythematous papules, often accompanied by excoriation and burrows which can appear as thin, serpiginous lines measuring 2-15 mm in length, but the latter are not always visible due to excoriation or secondary infection of the affected skin (Fig.4, Fig.5). Other forms of presentation are vesicles, pustules or bullae. [32] The most frequently involved regions in scabies infestations are the sides and webs of the fingers, wrists, axillae, areolae and genitalia (Fig.6). [32] Nodular scabies is a less frequent presentation of classic scabies. It is characterized by the presence of persistent, firm, erythematous, dome-shaped papules that are highly pruritic. These papules typically have a diameter of 5 or 6 mm. [34]

Crusted scabies is a severe form of scabies characterized by a high burden of mites. It is commonly seen in individuals with underlying immunosuppression like AIDS, HTLV-1 infec-

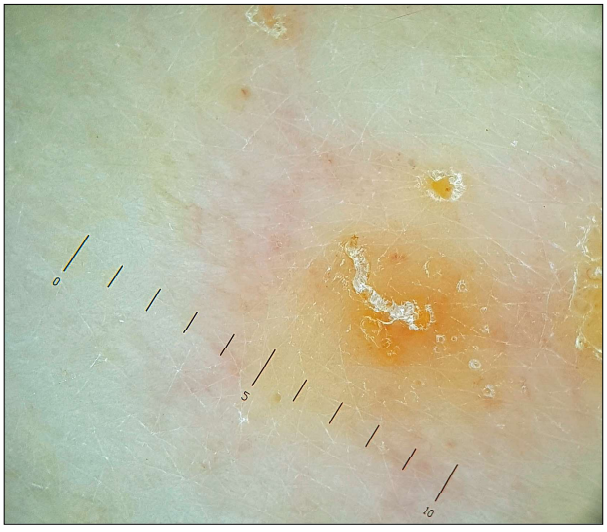

Figure 4 - Dermatoscopic image of a burrow (thin serpiginous line) - image from our clinic

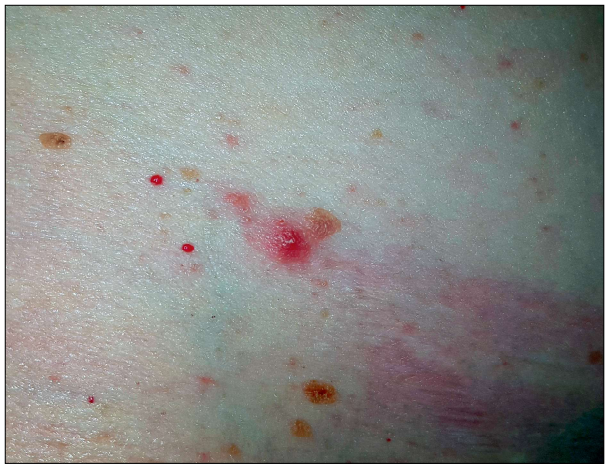

Figure 5 - Erythematous papule due to scabies (image from our clinic)

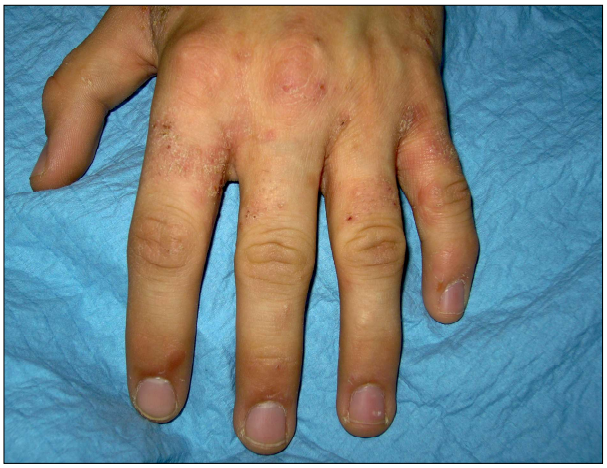

Figure 6 -Scabies- multiple erythematous papules and excoriations on the hand (image from our clinic)

tion, leprosy or lymphoma. Crusted scabies typically starts with indistinct, erythematous patches on the skin, which rapidly progress to the formation of thick, prominent scales. As crusted scabies progresses, the scales on the skin become warty in texture, particularly over bony areas of the body. Crusts and fissures may also develop, and the affected lesions tend to emit an unpleasant odor. Additionally, individuals with crusted scabies may experience thickening, discoloration, and dystrophy of the nails. [32]

The recommended treatment for classic scabies using ivermectin involves administering a single oral dose of 200 mcg/kg, followed by a second dose one to two weeks later. [35] The effectiveness of oral ivermectin is supported by multiple studies. One of the studies is double-blind trial conducted by Macotela-Ruiz and Peña-Gonzalez in Mexico compared a single dose of ivermectin at 200 mg/kg to a placebo. The study included 55 patients, 29 of them being treated with ivermectin. The result showed the effectiveness of ivermectin versus placebo, 79.3% of patients treated with ivermectin were cured within one week compared to only 15.4% of patients in the placebo group. [36] In Argentina was conducted a randomized double-blind study by Chouela et al. on 43 patients which compared 150-200 mcg/kg oral ivermectin with lindane 1%. After 15 days, 74% of the patients treated with ivermectin were cured compared to 54% patients in the lindane group. Patients who did not respond the first time to the treatment were given another dose and was observed on day 29 that 95% patients in the ivermectin group were healed versus 96% patients in the lindane group and it was concluded that after one month both drugs have the same statistical effectiveness. [37]

Although ivermectin is now considered safe for children weighing less than 15 kg, a syrup formulation containing ivermectin (400 µg/mL) has been developed as an improvised preparation specifically for this age group. [38]

Regarding crusted scabies, ivermectin has been documented as efficacious. The most effective approach appears to be administering repeated doses of ivermectin 200 mg/kg (administered for three, five or seven non-consecutive days based on the severity of the infestation), in combination with a topical scabicide (permethrin 5% applied every two to three days for 1-2 weeks). [35]

3. Pediculosis

Pediculosis capitis refers to a parasitic infestation of the hair and scalp caused by head lice. It is a significant public health worldwide issue, especially among children. Head lice are ectoparasites that depend on the human scalp for sustenance, warmth, moisture, and protection (Fig.7). [39] In the absence of blood meals, head lice can typically survive for approximately 55 hours when they are away from the human host. [39] However, lice eggs have the ability to survive

off the human body for up to 10 days. [40] Head lice reside in close proximity to the surface of the scalp and lay their eggs within 6 mm of the scalp. [40]

The most common symptom and most of the time the only one is the itching of the scalp. The sensation of itching commonly occurs due to sensitization to either the fecal or salivary antigens produced by the louse. [39] Symptoms typically manifest within 2-6 weeks in individuals who have not been previously infested. However, in cases of re-exposure, itching arises in less than 2 days. Clinically, it is possible to observe lice or lice eggs firmly attached to the hair near the scalp. [39] Lice eggs tend to be more frequently discovered in the postauricular or occipital areas. [41]

Figure 7 - Pthirus pubis - (image from our clinic).

For children, there are two forms of administration of ivermectin, either orally, or topically for the eradication of pediculosis capitis. [42] Topically, ivermectin exists in the form of a lotion and was approved in February 2012 by the FDA for children 6 months or older. [39] A single application of ivermectin 0.5% lotion is sufficient because nymphs that emerge from treated eggs are unable to feed due to paralysis of their pharyngeal muscles. [43] Side effects are rare and may include xerosis, dandruff, erythema, eye irritation or conjunctivitis. [43] Orally, a single dose of 200–400 μg/kg, followed by a second dose after 7 to 10 days, is an effective treatment for pediculosis capitis. [39] A study was performed by Glaziou et al. on [44] patients in French Polynesia, which compared the effectiveness of a single dose (100 mcg/kg) of ivermectin with benzyl benzoate 10% (topical treatment). After one month, 70% of the patients in the ivermectin group were cured versus 48% patients in the benzyl benzoate group. [44] This treatment scheme also applies to adults and is also useful in the case of pediculosis corporis or pubis (Fig.8). [45] Side effects are rare and include nausea, vomiting, diarrhoea or headache. [39] It is not recommended to use ivermectin during pregnancy or while breast-feeding. [39]

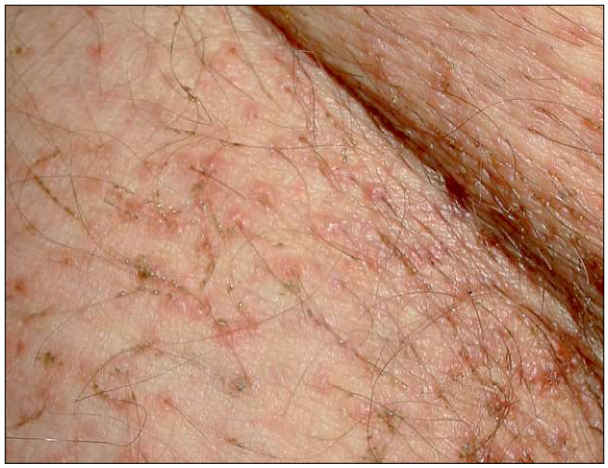

Figure 8 - Pediculosis pubis - numerous lice located around the pubic hair

4. Cutaneous larva migrans

Cutaneous larva migrans is the most prevalent migratory skin infection among travelers. Most frequently, this infection is caused after human interaction with the larvae of two hookworms, *Ancylostoma braziliense* and *Ancylostoma caninum*. [46] After contact, at the location where each larva penetrates the skin, a pruritic erythematous papule may develop. Within a few days, serpiginous tracts appear at the place where the larva migrates. These reddish-brown tracts are very pruritic and elevated, with a length of approximately 3 mm (can reach lengths of up to 15 to 20 mm). Typically, the larva itself can be found approximately 1 to 2 cm ahead of the visible skin

eruption. [47] The appearance of serpiginous lesions occurs within two to six days after exposure, although it is possible for them to manifest weeks or even several months after the initial exposure (Fig. 9). [48] As the larvae migrate, they trigger an inflammatory response along the cutaneous tract, which can persist for several weeks. [47]

One single dose of ivermectin (12 mg p.o. the equivalent of 200 μg/kg) has been sufficient for the treatment of the patients with cutaneous larva migrans (cure rates ranging from 94 to 100

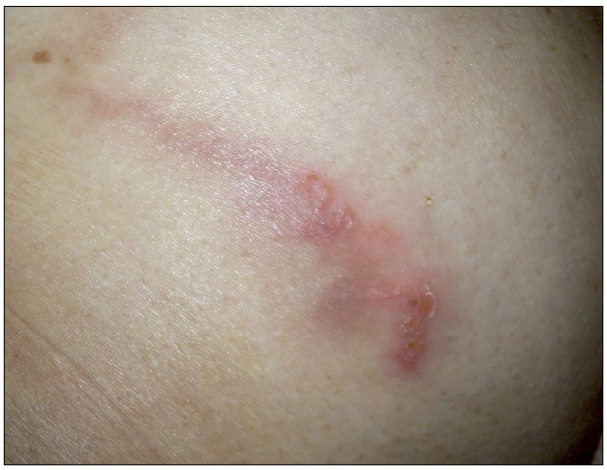

Figure 9 - Serpiginous lesion on the skin characteristic for cutaneous larva migrans (image from our clinic)

percent). [49] Albendazole can be considered as a suitable alternative treatment option (400 mg p.o per day, three days). [47] If the patients present hookworkms folliculitis, should be administeres two doses of ivermectin. [50]

5. Myiasis

Myiasis is an infestation with *Cochliomyia hominivorax* and *Dermatobia hominis*, two species of fly larvae which penetrate skin and grow in subdermal tissue.51 When the eggs come into contact with the skin, the warmth of the host's body triggers their hatching and the initial stage larvae penetrate the skin through tiny perforations, follicular openings, or intact skin without causing any pain. [52] Symptomatology begins with an apparent insect bite, a small, erythematous papule, that gradually increases in size over time, forming a nodule with a diameter of 1-3 cm and a small amount of serosanguineous fluid may be observed draining from the lesion. [53] Other sympthomes may include itching, a sensation of movement or noctural lancinating pain. [52]

Ivermectin has been used with success in the treatment of these infections. Administration methods depends on the species of fly larvae and include topical and systemic administration. Topical administration comprise 10% ivermectin solution on *D. hominis* and 1% ivermectin cream for *C. hominivorax*, applied for 2 hours with a decrease in pain after 15 minutes, the death of the larva after 1 hour and no viable larvae after 24 hours. [52, 54]. Systemic administration involve a single 200-g/kg oral dose of ivermectin, being effective on *C. hominivorax* myiasis. [52]

6. Filariasis

Filariasis is an infection of the lymphatic system and subcutaneous tissue caused by nematodes (Wuchereria bancrofti, Brugia malayi and Brugia timori). [55] Studies have shown that ivermectin tends to have a stronger impact on microfilariae than on macrofilariae and may have some potential effect in reducing worm fertility. [56] Filariasis treatment includes diethylcarbamazine, doxycycline, albendazole and ivermectin. It has been observed in a study conducted in South India that a single dose of ivermectin (150 microgram/kg) had similar effect as a 12-day regimen of diethylcarbamazine in suppressing microfilaremia for a period of three to six months. [57]

7. Other infections

Leishmaniasis is a collection of vector-borne diseases caused by a diverse group of protozoa belonging to the genus *Leishmania*. Clinical manifestations of leishmaniasis can vary and range from localized cutaneous ulcers to more severe systemic involvement affecting multiple organs. [58] Localized cutaneous leishmaniasis (LCL) starts as a pink-colored papule that gradually increases in size and transforms into a nodule or plaque-like lesion. Central softening may occur, resulting in the formation of a painless ulcer with a indurated border. [58] In the context of cutaneous leishmaniasis, ivermectin has greater efficacy compared to other drugs (such as pentostam, rifampicin, amphotericin B,

Figure 10 - Bedbugs - (image from our clinic)

metronidazole or nystatin) in killing *Leishmania tropica* parasites in vitro. Additionally, when administered via subcutaneous inoculation, ivermectin accelerates the healing of skin ulcers associated with the infection. [5] The combination of ivermectin with appropriate surgical wound dressing holds significant potential for the successful treatment and cure of cutaneous leishmaniasis. [59]

Bedbugs are parasitic insects that are dependent on blood for their survival and infest human habitats. The two primary species of bedbugs that commonly infest humans are *Cimex lectu-larius* and *Cimex hemipterus* (Fig. 10). [60] A typical manifestation of a bedbug bite is the presence of a 2 to 5 mm erythematous papule or raised area on the skin which often exhibits a central hemorrhagic punctum, usually pruritic (Fig. 11). In some cases, patients may only present with asymptomatic, purpuric macules at the locations where they were bitten by bedbugs. [60] Ivermectin has been shown to be highly effective against bedbugs and can be used to eliminate or prevent infestations caused by these insects. [61]

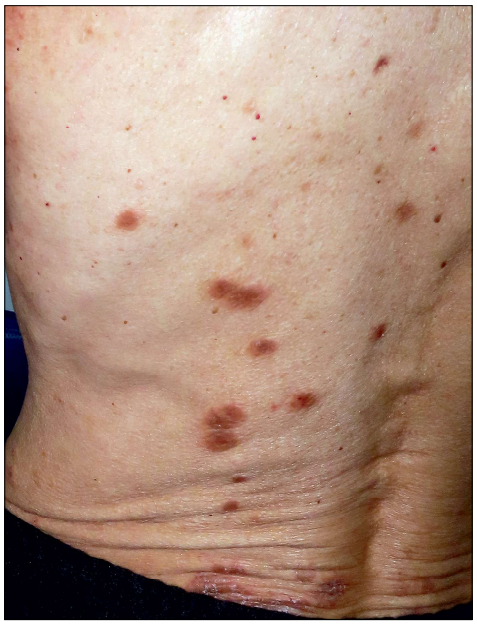

Figure 11 - Multiple erythematous papules with a central, hemorrhagic punctum on the trunk of a patient with bedbug bites - (image from our clinic)

Conclusions

Ivermectin has demonstrated significant effectiveness as an antiparasitic agent, providing successful treatment for numerous parasitic diseases that impact millions of individuals worldwide, with a particular focus on regions characterized by tropical and subtropical climates.

The current evidence supports the use of ivermectin as a safe and effective option in the treatment of various dermatological conditions such as papulopustular rosacea, scabies, pediculosis, cutaneous larva migrans, myiasis, filariasis, leshmaniasis or bedbugs bites. Taking on board the possible immunomodulatory effects of ivermectin, further studies may lead to discovery of new applications of ivermectin in dermatology.

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Conflict de interese
NEDECLARATE

Conflict of interest
NONE DECLARED

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