International Journal of Infectious Diseases 17 (2013) e343–e347

Contents lists available at SciVerse ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Evaluation of the efficacy of oral ivermectin in comparison with ivermectin–metronidazole combined therapy in the treatment of ocular and skin lesions of *Demodex folliculorum*

Doaa Abdel-Badie Salem [a,*], Atef El-shazly [a], Nairmen Nabih [a], Youssef El-Bayoumy [b], Sameh Saleh [c]

[a] *Medical Parasitology Department, Faculty of Medicine, Mansoura University, Gomhoria Street, Mansoura City, Egypt*
[b] *Dermatology and Andrology Department, Faculty of Medicine, Mansoura University, Mansoura City, Egypt*
[c] *Ophthalmology Department, Faculty of Medicine, Mansoura University, Mansoura city, Egypt*

ARTICLE INFO

Article history:
Received 16 April 2012
Received in revised form 9 November 2012
Accepted 18 November 2012

Corresponding Editor: Hubert Wong, Vancouver, Canada

Keywords:
Demodex
Ivermectin
Metronidazole
Blepharitis
Skin lesions

SUMMARY

Objective: To evaluate the efficacy of ivermectin and combined ivermectin–metronidazole therapy in the treatment of ocular and skin lesions of *Demodex folliculorum*.

Methods: One hundred twenty patients with skin lesions and anterior blepharitis, whose infestation was treatment-resistant and who had a Demodex count >5 mites/cm^2 for skin lesions or ≥3 mites at the root of each eyelash, were recruited. The treatment regimens were ivermectin and ivermectin–metronidazole combined therapy. We enrolled 15 patients from each of four groups for each treatment regimen. Demodex was detected by standardized skin surface biopsy for skin lesions. Three eyelashes from each affected lower eyelid were epilated and examined. The study subjects were followed-up once a week for four visits.

Results: There was a difference in the mite count between the subgroups taking ivermectin and combined therapy during all follow-up visits. At the last visit, in the combined therapy subgroup, 1.7% of patients showed no clinical improvement, 26.7% showed a marked clinical improvement, and 71.6% showed complete remission. In those on the ivermectin regimen, 27 patients had a mite count >5 mites/cm^2, 21.7% showed no clinical improvement, 33.3% showed a marked improvement, and 45% showed complete remission.

Conclusions: Combined therapy was superior in decreasing the *D. folliculorum* count in all groups and in reducing the mite count to the normal level in rosacea and in anterior blepharitis. On the other hand, the two regimens were comparable in reducing the mite count to the normal level in acne and peri-oral dermatitis lesions.

1. Introduction

Demodex folliculorum is the most common ectoparasite of man.[1] It is an elongated transparent worm-like parasite with an obvious head, neck, and a body-tail part, of which the former has four pairs of stumpy legs measuring about 0.35–0.4 mm in length; it has protruding stumpy sharp mouth parts.[2]Infestation with this organism may play a role in many clinical entities, such as rosacea-like demodicosis,[3] pustular folliculitis,[4,5] papulo-pustular scalp eruptions,[6] peri-oral dermatitis,[7] and hyperpigmented patches of the face.[8] In the field of ophthalmology, *Demodex spp* are thought to play a role in the etiology of blepharitis, chronic eczematous blepharitis (blepharitis acarica), madarosis (loss of eyelashes), and treatment-resistant chronic blepharitis.[9–12]

Ivermectin is a safe and effective orally administered antiparasitic drug. Its selective activity against human parasites is due to its high affinity for glutamate-gated chloride ion channels found in the peripheral nervous system of invertebrates; it does not readily cross the mammalian blood–brain barrier, where ligand-gated chloride ion channels are found in mammals, hence humans are spared from adverse central nervous system effects of the drug.[13] The binding of ivermectin to this ion channel in the nerve and muscle cells results in increased permeability of the cell membrane to chloride ions, leading to hyperpolarization with subsequent paralysis and death of the parasite.[14]

The acaricidal effect of metronidazole on the Demodex mite is not known. It has been proposed that metronidazole may act on the mite via one or more of its active metabolites formed in vivo.[15]

* Corresponding author. Tel.: +20 173811104.
E-mail address: dr_doaasalem@yahoo.com (D.A.B. Salem).

1201-9712/$36.00 – see front matter
http://dx.doi.org/10.1016/j.ijid.2012.11.022

The aim of this study was to evaluate the efficacy of ivermectin and combined ivermectin–metronidazole therapy in the treatment of refractory anterior blepharitis and skin lesions of *D. folliculorum*.

2. Methods

2.1. Study design

This was a randomized, single-blind, controlled clinical trial, comparing the efficacy of ivermectin and combined therapy with ivermectin–metronidazole in the treatment of anterior blepharitis and skin lesions of *D. folliculorum*.

2.2. Participants

This study took place in the Dermatology and Ophthalmology Clinic of the Mansoura University Hospitals between June 2011 and February 2012.

One hundred twenty patients were enrolled (mean age 36.71 ± 12.4 years) and categorized into four groups of 30 patients each (patients with acne vulgaris, rosacea, peri-oral dermatitis, and anterior blepharitis).

The selection criteria for patients with skin lesions were: a treatment-resistant infestation, with *D. folliculorum* mite density >5 mites/cm^2.

The potential criteria for the diagnosis of Demodex blepharitis are summarized as follows:[16] (1) clinical history: high index of suspicion when blepharitis is refractory to conventional treatments, or when there is madarosis or recurrent trichiasis; (2) slit-lamp examination: typical cylindrical dandruff at the root of eyelashes; (3) microscopic confirmation: detection and counting of Demodex mites in epilated lashes.

Patients with a mite density ≤5 mites/cm^2 for skin lesions or with <3 living mites/eyelash, a history of systemic or topical antibacterial or anti-inflammatory drugs in the 60 days before study entry, those with a known hypersensitivity to ivermectin or metronidazole, and pregnant women were excluded. In patients with anterior blepharitis, we also excluded those with posterior or mixed blepharitis, contact lenses, meibomian gland dysfunction, and any previous eye surgery.

2.3. Ethics issues

Informed consent was obtained from each of the participants, and the study was performed in accordance with the principles of our institutional ethics committee.

2.4. Sample size calculation

At the time this study was designed there were insufficient data to perform a reliable sample size calculation. So we anticipated that two groups of 60 patients each would be sufficient to indicate efficacy of the two regimens at 4 weeks. Based on the outcome of this pilot study, we will design a larger randomized controlled trial, including a large number of patients, based on a power calculation.

2.5. Randomization and blinding

The 120 participants were randomly assigned to either combined therapy or ivermectin treatment at a ratio of 1:1 (15 patients for each treatment regimen from each group) using a computer-generated randomization schedule. The assignment was done in a single-blinded manner, in which the subjects were blinded to the treatment assignment.

2.6. Hypothesis

Since metronidazole has an anti-inflammatory and acaricidal action, it is expected to have a better effect in combination with ivermectin and improve the outcome of treated patients.

2.7. Intervention

In each group 15 patients received combined therapy with metronidazole (does 250 mg three times per day for 2 weeks) and ivermectin (two doses of 200 μg/kg, 1 week apart), and 15 patients received ivermectin alone (two doses of 200 μg/kg, 1 week apart). All patients were then followed-up weekly for four visits.

2.8. Outcome measurements

For skin lesions, a standardized skin surface biopsy was performed for the detection of *D. folliculorum* in lesion areas. Subjects briefly washed their faces with a bland soap and water and then put on a pair of safety goggles. A drop (about 0.05 ml) of cyanoacrylate glue (Krazy Glue) was applied to one end of a plastic slide (1 × 3 inch plastic slides) and spread out to a uniform thickness using the nozzle of the Krazy Glue bottle. The slide was then pressed against a lesion area causing the glue to spread to a thin film the width of the slide (1 inch) and approximately half its length (1.5 inch). The slide was left in place for 5 min while the cyanoacrylate hardened as it polymerized. Initially a standard surface area of 1 cm had been drawn on the other side of the slide with a waterproof marker; the area of 1 cm was divided into four equal squares in order to make counting of the parasite easier after removal of the slide.[17]

For the detection of Demodex in anterior blepharitis, under a slit-lamp biomicroscope three eyelashes from each lower eyelid were epilated with fine forceps. Eyelashes were placed on a glass slide and mounted with a cover slip. Epilated eyelashes and skin samples were clarified with two to three drops of immersion oil and examined microscopically at standard magnifications (×40 to × 100) as soon as possible (within 2–4 h), as the movement of mites decreases with time and they may even disintegrate.[18] For eyelashes, determination of ≥3 living parasites at the root of each eyelash was diagnosed as infestation. The Demodex count was recorded as the total number of mites found in a total of three lashes per eye. For the diagnosis of a skin sample infestation, >5 living parasites in an area 1 cm^2 was required.[19] Patients were assessed prior to randomization and weekly for 1 month throughout the study.

The outcome measurements were done at the last visit. The primary outcome was a decrease in mite density for each treatment (≤5 mites/cm^2 for skin lesions and <3 living mites/eyelash). Secondary outcomes were clinical improvements in itching, burning, redness, and scaling at the root of the lashes in anterior blepharitis patients, and improvements in erythema, dryness, scaling, roughness, and/or papules/pustules in skin lesions.

Assessment of the outcome samples was done by two unblinded parasitologists and then reviewed by another independent blinded professor of parasitology to avoid bias.

2.9. Statistical analysis

Data entry and analysis were all done using SPSS software version 17 (Chicago, IL, USA). Results were expressed as mean ± standard deviation (SD), or number (%). Comparisons between the mean values were done using the independent sample *t*-test and Mann–Whitney test. The Chi-square test was used to compare the primary outcome in ivermectin and combined regimens and for