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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*

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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]

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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

comparison between categorical data (number (%)). The 95% confidence interval (95% CI) for the difference between independent proportions was calculated by the Wilson with continuity correction method. A p-value of <0.05 was considered statistically significant.

3. Results

3.1. Patient characteristics

One hundred twenty eligible patients were enrolled in this study; no patient missed any follow-up visit or discontinued treatment. Sixty patients were allocated to receive ivermectin and 60 to receive the combined therapy.

Baseline characteristics of the patients in each group are summarized in Table 1.

3.2. Efficacy

In the cases who received ivermectin alone, there was a gradual reduction in the mean follicle mite count at the first week visit (Table 2). However, rebound elevation in the mite count was evident in the third week in some patients with rosacea and those with anterior blepharitis lesions (Table 2).

In the combined therapy subgroup, the mean counts of Demodex were dramatically reduced in all patients within 1 week (Table 2).

In comparing the efficacy of the two regimens, we demonstrated that the combined therapy was superior in decreasing the mean count of *D. folliculorum* in all groups ($p < 0.05$) (Table 2) and in reducing the mite count to a normal level in rosacea (mite density $\leq$5 mites/cm^2) ($p < 0.001$; 95% CI 0.4–0.9) (Figure 1; Table 3) and in blepharitis (<3 mites/eyelash) ($p = 0.002$; 95% CI 0.2–0.8) (Figure 2; Table 3). The two regimens were comparable in terms of the reduction in mite count to a normal level in the acne group ($p = 0.1$; 95% CI −0.04–0.6) (Figure 3; Table 3) and peri-oral dermatitis group ($p = 0.5$; 95% CI −0.1–0.4) (Figure 4; Table 3) (mite density $\leq$5 mites/cm^2).

With regard to clinical improvement, at the last visit for those on the combined therapy regimen, 1.7% of patients showed no clinical improvement, 26.7% showed a marked clinical improvement, and 71.6% showed complete remission, while in those on the ivermectin regimen, 27 patients had a mite count >5 mites/cm^2, 21.7% of them showed no clinical improvement, 33.3% showed a marked improvement, and 45% showed complete remission.

At the end of the follow-up, one case on the combined therapy regimen had an infestation that continued to be treatment-resistant (the mites were persistent in their lesions) and after histopathological examination of the lesion, the case was diagnosed as lupus miliaris disseminatus faciei (LMDF).

4. Discussion

There are no standardized therapeutic recommendations for the treatment of demodicidosis. Although topical therapy alone is often not sufficiently effective, many reports have been written on the use of topical medications like lindane,[20] metronidazole,[21] benzyl benzoate,[19] permethrin,[22] hexachlorocyclohexane,[23] and camphor oil.[24] Few reports have been written on the systemic medications, e.g., oral ivermectin.[22,25] Hence the purpose of this study was to evaluate the therapeutic and clinical outcomes of the oral administration of an ivermectin regimen compared with combined ivermectin and metronidazole in the treatment of *D. folliculorum*-associated anterior blepharitis and skin lesions.

In the present work, during the first week of follow-up, no obvious change in the mite count was observed in all the groups receiving ivermectin, while through the third week, a rebound elevation in the mite count was observed in some cases in the rosacea and anterior blepharitis groups. However, in the fourth week there was a decrease in mite counts in all the studied groups.

These results agree with those of Holzchuh et al.,[26] who observed a significant improvement in the absolute number of *D. folliculorum* in the eyelashes after treatment with oral ivermectin.

Also, Baima and Sticherling[27] used oral ivermectin for skin lesions caused by Demodex, in combination with 4% pilocarpine gel in blepharitis, and reported a statistically significant reduction in the number of mites after treatment. Neither study pointed to a reduction in the mite count to the normal level after the administration of oral ivermectin in any of the studied cases.

These results, together with our results, strongly infer that an ivermectin regimen alone cannot eradicate a Demodex infection but only reduce the number of mites.

There are few reports on systemic metronidazole therapy for *D. folliculitis*. Studies on oral metronidazole alone for the treatment of Demodex skin lesions have shown a marked reduction in the inflammatory picture, but not of the Demodex population.[28,29] However in the study of Schaller et al.,[30] therapy with the oral administration of 250 mg metronidazole three times a day for 2 weeks resulted in a rapid and lasting recovery. Subsequent follow-up evaluation for the next 9 months showed excellent control of the disease. Repeated scrapings remained negative for *D. folliculorum* mites.

Other studies have reported complete recovery, with the disappearance of facial mites in treatment with combinations of oral and topical metronidazole; in a case of fulminant rosacea-like eruption with multiple *D. folliculorum* mites,[21] Grossmann et al.[31] used 750 mg/day metronidazole for 3 weeks in conjunction with 100 mg/day prednisolone, topical 2% metronidazole, and 0.15% lindane emulsion, and in a study by Anane et al.,[32] the patient was

Table 1
Age, gender, and Demodex mite density among studied groups

	Age, years, mean ± SD	Gender		Demodex density, mean ± SD
		Female, *n* (%)	Male, *n* (%)	
Acne group				
Ivermectin	34.9 ± 13.9	10 (66.7%)	5 (33.3%)	12.3 ± 3.2
Combined	32.5 ± 9.9	12 (80%)	3 (20%)	12.9 ± 6.1
Rosacea group				
Ivermectin	32.4 ± 9	12 (80%)	3 (20%)	51.7 ± 20.8
Combined	35.9 ± 8.3.1	8 (53.3%)	7 (46.7%)	51.5 ± 26.3
Peri-oral dermatitis group				
Ivermectin	43.7 ± 15.9	4 (26.7%)	11 (73.3%)	21.3 ± 7.5
Combined	36.8 ± 11.5	10 (66.7%)	5 (33.3%)	21.9 ± 6.8
Blepharitis group				
Ivermectin	38.4 ± 15.8	5 (33.3%)	10 (66.7%)	12.8 ± 6.8
Combined	38.6 ± 10.9	3 (20%)	12 (80%)	15 ± 5.7

SD, standard deviation.

Table 2
Comparing mite density of studied groups before treatment and through follow-up visits, using different therapy regimens

Mite density	Acne, mean ± SD	Rosacea, mean ± SD	Peri-oral dermatitis, mean ± SD	Blepharitis, mean ± SD
Pre-therapy				
Ivermectin	12.3 ± 3.2	51.7 ± 20.8	21.3 ± 7.5	12.8 ± 6.8
Combined	12.9 ± 6.1	51.5 ± 26.3	21.9 ± 6.8	15 ± 5.7
Mean difference (95% CI)	−0.6 (−4.2–3)	0.3 (−17.5–18)	−0.6 (−5.69–4.8)	−2.2 (−6.9–2.5)
p-Value	0.9	0.98	0.9	0.187
1st week				
Ivermectin	12.1 ± 3.2	50.5 ± 20.3	21.1 ± 7.6	12.6 ± 6.9
Combined	8.4 ± 5.1	37.7 ± 18.9	13.4 ± 4.9	7.6 ± 4.7
Mean difference (95% CI)	3.6 (0.4–6.8)	12.8 (1.9–27.5)	7.7 (2.9–12.5)	5 (0.5–9.5)
p-Value	0.02	0.04	0.009	0.04
2nd week				
Ivermectin	8.4 ± 2.6	41.1 ± 15.8	10.5 ± 3.9	8. 5 ± 7.6
Combined	5.6 ± 4.6	25.9 ± 22.6	5.8 ± 3.4	2.5 ± 2.9
Mean difference (95% CI)	2.8 (0.03–5.6)	15.2 (0.6–29.8)	4.7 (2–7.5)	5.9 (1.6–10.2)
p-Value	0.04	0.016	0.005	0.003
3rd week				
Ivermectin	5.3 ± 2.4	41.9 ± 21.4	5.2 ± 2.9	8.5 ± 6.3
Combined	2.1 ± 3.2	12.5 ± 25.6	1.3 ± 1.2	1 ± 1.7
Mean difference (95% CI)	3.3 (1.2–5.4)	29.4 (11.7–47.1)	3.9 (2.3–5.6)	7.5 (4.1–11)
p-Value	0.006	0.001	<0.001	<0.001
4th week				
Ivermectin	2.3 ± 2.7	31.4 ± 18.9	1.7 ± 1.7	5.3 ± 5.4
Combined	0.5 ± 1.2	5.5 ± 19.5	0.2 ± 0.4	0.2 ± 0.4
Mean difference (95% CI)	1.8 (0.2–3.4)	25.9 (11.5–40.3)	1.6 (0.5–2.7)	5.1 (2.3–8)
p-Value	0.02	0.001	0.003	<0.001

SD, standard deviation; CI, confidence interval; *p*-value, probability of error.

put on topical and oral metronidazole for 2 months and on yellow mercury ointment for 15 days. The facial mites disappeared and there was complete remission without recurrence.

Although this combination regimen has not been studied before, we found that in the combined therapy regimen, there was a reduction in the mite count from the first week and through the follow-up visits. With regard to the reduction in the mite count to the normal level, only one case continued to resist treatment, and after a histopathological examination the case was diagnosed as LMDF.

By comparing both regimens in terms of the decrease in mite count, we found that the reduction with combined therapy was statistically higher than that for ivermectin alone in all the studied groups. In addition, the combined regimen was significantly better at reducing the mite count to the normal level in the rosacea and anterior blepharitis groups.

The obvious improvement in the clinical picture in the subgroups receiving the combined therapy may be attributed to the fact that the mite *D. folliculorum* antigens could generate an immune response leading to the inflammatory changes. Since metronidazole is particularly effective against the inflammatory papulo-pustular component of the disease, its mechanism of action may involve an anti-inflammatory effect. Evidence has been presented that metronidazole has a direct pharmacological effect on anti-inflammatory influences on T lymphocytes,[33] and further, alterations in neutrophil cell function have been shown, inhibiting the generation of reactive oxygen species. Other investigators have provided evidence of an anti-inflammatory activity.[28] In addition metronidazole may have acaricidal activity, as it is degraded in vivo into at least five metabolites with potent biological activity (e.g., its 2-hydroxymethyl derivative is one-third- to 10-times more active as an antibacterial agent than metronidazole itself).[15]

So, we suggest that the combined therapy works better than ivermectin alone on cases with different skin lesions and anterior blepharitis.

In conclusion, the 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 blepharitis lesions, while the two regimens were comparable in reducing the mite count to the normal level in acne and peri-oral dermatitis lesions.

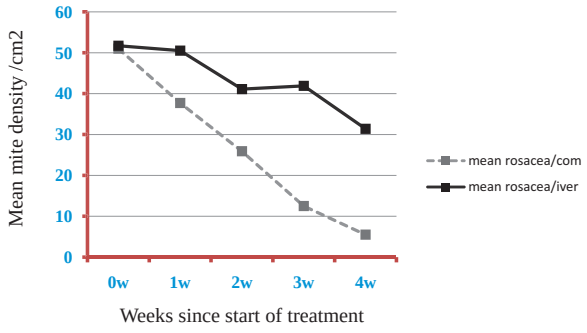

Figure 1. Mite density of rosacea group before treatment and through follow up visits using different regimen therapy.

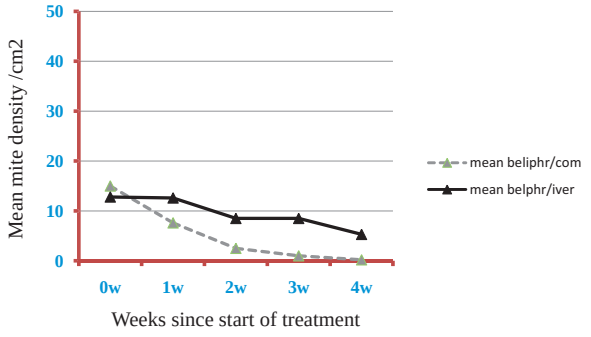

Figure 2. Mite density of blepharitis group before treatment and through follow up visits using different regimen therapy.

Table 3
Comparing the percentage of patients with a Demodex density reaching normal levels and patients with a Demodex density higher than the normal level among studied groups at the last visit, using different therapy regimens

	Ivermectin therapy	Combined therapy	Difference (95% CI)	*p*-Value[a]
Acne group	11/15 (73.3%)	15/15 (100%)	0.27 (−0.04–0.6)	0.1
Rosacea group	2/15 (13.3%)	14/15 (93.3%)	0.80 (0.4–0.9)	<0.001
Peri-oral dermatitis group	13/15 (86.7%)	15/15 (100%)	0.13 (−0.1–0.4)	0.5
Blepharitis group	7/15 (46.7%)	15/15 (100%)	0.54 (0.2–0.8)	0.002

CI, confidence interval (by Wilson with continuity correction).
[a] Chi-square test.

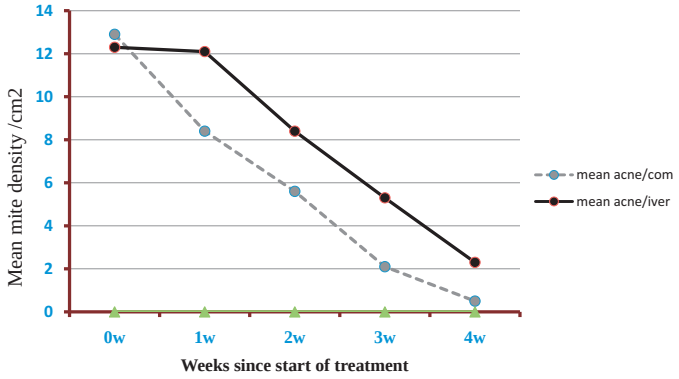

Figure 3. Mite density of acne group before treatment and through follow up visits using different regimen therapy.

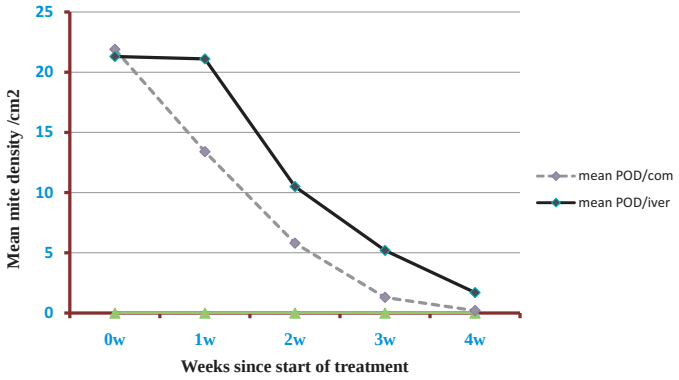

Figure 4. Mite density of peri-oral dermatitis group before treatment and through follow up visits using different regimen therapy.

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Conflict of interest: None.

References

1. Aylesworth R, Vance C. *Demodex folliculorum* and *Demodex brevis* in cutaneous biopsies. *J Am Acad Dermatol* 1982;**7**:583–9.
2. Spickett SG. Studies on Demodex folliculorum Simon (1942). Life history. *Parasitology* 1961;**51**:181–92.
3. El-Shazly AM, Ghaneum BM, Morsy TA, Aaty HE. The pathogenesis of *Demodex folliculorum* (hair follicular mites) in females with and without rosacea. *J Egypt Soc Parasitol* 2001;**31**:867–75.
4. Purcell SM, Hayes TJ, Dixon SL. Pustular folliculitis associated with *Demodex folliculorum*. *J Am Acad Dermatol* 1986;**15**:1159–62.
5. Karincaoglu Y, Bayram N, Aycan O, Esrefoglu M. The clinical importance of *Demodex folliculorum* presenting with nonspecific facial signs and symptoms. *J Dermatol* 2004;**31**:618–26.
6. Miskijan S. Demodicidosis (Demodex infestation of the scalp). *Arch Dermatol* 1951;**63**:282–3.
7. Dolenc-Voljc M, Pohar M, Lunder T. Density of *Demodex folliculorum* in perioral dermatitis. *Acta Derm Venereol* 2005;**85**:211–5.
8. Ayres Jr S, Ayres III S. Demodectic eruptions (demodicidosis) in the human. 30 years' experience with 2 commonly unrecognized entities: pityriasis follicularum (Demodex) and acne rosacea (Demodex type). *Arch Dermatol* 1961;**83**:816–27.
9. Pena GP, Andrade Filho JS. Is Demodex really nonpathogenic? *Rev Inst Med Trop Sao Paulo* 2000;**42**:171–3.
10. Damian D, Rogers M. Demodex infestation in a child with leukemia: treatment with ivermectin and permethrin. *Int J Dermatol* 2003;**42**:724.
11. Saint-Leger D. Normal and pathologic sebaceous function. Research in a shallow milieu? *Pathol Biol (Paris)* 2003;**51**:275–8.
12. Rodriguz AE, Ferrer C, Alio JL. Chronic blepharitis and Demodex. *Arch Soc Esp Ophthalmol* 2005;**80**:635–42.
13. Skopets B, Wilson RP, Griffith JW, Lang CM. Ivermectin toxicity in young mice. *Lab Anim Sci* 1996;**46**:111–2.
14. Kane NS, Hirschberg B, Qian S, Hunt D, Thomas B, Brochu R, et al. Drug-resistant Drosophila indicate glutamate-gated chloride channels are targets for the antiparasitics nodulisporic acid and ivermectin. *Proc Natl Acad Sci U S A* 2000;**97**:13949–54.
15. Schmadel LK, McEvoy GK. Topical metronidazole: a new therapy in rosacea. *Clin Pharm* 1990;**9**:94–101.
16. Liu J, Sheha H, Tseng SC. Pathogenic role of Demodex mites. *Curr Opin Allergy Clin Immunol* 2010;**10**:505–10.
17. Forton F, Seys B. Density of *Demodex folliculorum* in rosacea: a case–control study using standardized skin-surface biopsy. *Br J Dermatol* 1993;**128**:650–9.
18. English FP, Nutting WB. Demodicosis of ophthalmic concern. *Am J Ophthalmol* 1981;**91**:362–72.
19. Forton F, Seys B, Marchall JL, Song AM. *Demodex folliculorum* and topical treatment: acaricidal action evaluated by standardized skin surface biopsy. *Br J Dermatol* 1998;**138**:461–6.
20. Ashack R, Frost M, Norins A. Papular pruritic eruption of Demodex folliculitis in patients with acquired immunodeficiency syndrome. *J Am Acad Dermatol* 1989;**21**:306–7.
21. Hoekzema R, Hulsebosch HJ, Bos JD. Demodicidosis or rosacea: what did we treat? *Br J Dermatol* 1995;**133**:294–9.
22. Jansen T, Kastner U, Kreuter A, Altmeyer P. Rosacea-like demodicidosis associated with acquired immunodeficiency syndrome. *Br J Dermatol* 2001;**144**:139–42.
23. Rufli T, Mumcuoglu Y, Cajacob A, Büchner S. *Demodex folliculorum*: aetiopathogenesis and therapy of rosacea and perioral dermatitis. *Dermatologica* 1981;**162**:12–26.
24. El-Shazly AM, Hassan AA, Soliman M, Morsy GH, Morsy TA. Treatment of human *Demodex folliculorum* by camphor oil and metronidazole. *J Egypt Soc Parasitol* 2004;**34**:107–16.
25. Forstinger C, Kittler H, Binder M. Treatment of rosacea-like demodicidosis with oral ivermectin and topical permethrin cream. *J Am Acad Dermatol* 1999;**41**:775–7.
26. Holzchuh FG, Hida RY, Moscovici BK, Villa Albers MB, Santo RM, Kara-José N, et al. Clinical treatment of ocular *Demodex folliculorum* by systemic ivermectin. *Am J Ophthalmol* 2011;**151**. 1030–4.e1.
27. Baima B, Sticherling M. Demodicidosis revisited. *Acta Derm Venereol* 2002;**82**:3–6.
28. Shelley WB, Shelley ED, Burmeister V. Unilateral demodectic rosacea. *J Am Acad Dermatol* 1989;**20**:915–7.
29. Pallotta S, Cianchini G, Martelloni E, Ferranti G, Girardelli CR, Di Lella G, et al. Unilateral demodicidosis. *Eur J Dermatol* 1998;**8**:191–2.
30. Schaller M, Sander CA, Plewig G. Demodex abscesses: clinical and therapeutic challenges. *J Am Acad Dermatol* 2003;**49**(5 Suppl):S272–4.
31. Grossmann B, Jung K, Linse R. Tubero-pustular demodicosis. *Hautarzt* 1999;**50**:491–4.
32. Anane S, Mokni M, Beltaief O. Rosacea-like demodicidosis and chronic blepharitis. *Ann Dermatol Venereol* 2011;**138**:30–4.
33. Persi A, Rebora A. Metronidazole in the treatment of rosacea. *Arch Dermatol* 1985;**121**:307–8.