Contact Lens and Anterior Eye xxx (xxxx) xxx

Contents lists available at ScienceDirect

Contact Lens and Anterior Eye

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

Topical ivermectin 1.0% cream in the treatment of ocular demodicosis

Martin Smith [a], James S. Wolffsohn [b], Jeremy Chung Bo Chiang [b,c,*]

[a] Martin Smith Opticians, Lincoln, United Kingdom
[b] School of Optometry, College of Health and Life Sciences, Aston University, Birmingham, United Kingdom
[c] School of Optometry and Vision Science, Faculty of Medicine and Health, University of New South Wales, Sydney, Australia

ARTICLE INFO

Keywords:
Antiparasitic agents
Blepharitis
Demodex
Eyelashes
Eyelids
Ivermectin

ABSTRACT

Purpose: Ocular demodicosis can cause debilitating ocular surface disease. As ivermectin is effective at reducing Demodex proliferation in rosacea, this study investigated the efficacy of topical ivermectin 1.0% cream in treating ocular demodicosis.
Methods: This retrospective single-centre clinical practice chart analysis involved the off-label treatment of patients who had ocular demodicosis with topical ivermectin 1.0 % cream (Soolantra, Galderma Ltd, UK) applied nightly to the lid margins of both eyes for 3 months. Ocular surface health was assessed at baseline when the treatment was prescribed and followed up at 3 and 12 months after baseline. Slit lamp biomicroscopy was used to take digital images of the upper eyelid lashes. Manual image analysis with ImageJ was conducted by a masked assessor to quantify signs of ocular demodicosis including the number of lashes with collarettes, with visible Demodex tails and with follicle pouting.
Results: Data from a total of 75 patients with ocular demodicosis were analysed for this study (mean age 66.6 ± 13.9 years, 44 female). The numbers of lashes with collarettes (Median [Interquartile range]: 8 [4–13] at baseline to 0 [0–2] at the final visit, $p < 0.001$) and lashes with follicle pouting (3 [1–5] at baseline to 0 [0–1.8] at the final visit, $p < 0.001$) decreased with treatment. Any sign of lashes with visible tails was eliminated by the final visit ($p < 0.007$). Fluorescein staining severity score also improved, particularly from baseline (1 [0–2]) to the second visit (0 [0–1], $p < 0.001$).
Conclusions: The findings of this study show evidence for the efficacy of a 3-month course of topical ivermectin 1.0% cream in treating ocular demodicosis as indicated by reduction in collarettes, follicle pouting and visible Demodex tails. More research is warranted to improve the diagnosis, management and monitoring of this condition which is often overlooked or misdiagnosed.

1. Introduction

Demodex mites are ubiquitous symbionts of humans, living primarily within hair follicles (*Demodex follicularum*) and sebaceous glands (*Demodex brevis*) [1,2]. While these species do not usually cause harm to the human host, uncontrolled proliferation or infestation has been linked with the pathogenesis of potentially severe skin conditions such as rosacea, seborrheic dermatitis and acne vulgaris [3]. In the eyelids and lash environment, overpopulation of Demodex could contribute to the pathogenesis of ocular surface diseases including blepharitis and dry eye disease through deposition of necrotic tissue, waste products and moulting which has been suggested to induce aberrant bacterial growth, biofilm formation and proinflammatory processes [4]. Cylindrical dandruffs or collarettes, primarily found at the base of the lashes, are thought to represent these material depositions and are often considered the pathognomonic sign of ocular demodicosis [5,6]. Other methods have been investigated to aid in the diagnosis of ocular Demodex infestation including epilation or manoeuvring of the lash to reveal part or the whole of the mite visualised using slit lamp biomicroscopy, mounted under a light microscope or laser scanning confocal microscopy [7,8]. While these provide direct visualisation and quantification of Demodex mites, these may be limited to the few lashes investigated and some methods require specialised equipment not generally available in many clinical settings.

There is also currently an absence of a standardised approach for the treatment of ocular demodicosis. Tea tree oil of varying concentrations has historically been prescribed for this, however equivocal findings persist in terms of its benefits in improving clinical symptoms and signs

* Corresponding author at: School of Optometry, College of Health and Life Sciences, Aston University, Birmingham, United Kingdom.
E-mail address: j.chiang@aston.ac.uk (J.C.B. Chiang).

https://doi.org/10.1016/j.clae.2023.102099
Received 26 September 2023; Received in revised form 27 November 2023; Accepted 27 November 2023

as well as uncertainty in reducing Demodex mite population [9]. Terpinen-4-ol, a component of tea tree oil, has also been shown to be toxic to Meibomian gland epithelial cells [10]. Adverse effects associated with currently accepted treatments particularly those containing tea tree oil include tear film instability, ocular surface damage or staining and bulbar conjunctival hyperaemia [11]. Hence, more targeted interventions for ocular demodicosis have recently been investigated such as treatments which target Demodex mites including antiparasitic drugs such as ivermectin [12].

Topical ivermectin, an antiparasitic drug which has been approved for the treatment of Demodex infestation associated with rosacea within the past decade [13], has also shown recent clinical success in retrospective studies involving ocular Demodex blepharitis [14,15] although it is an off-label therapy and not currently approved for ocular application. Ivermectin has a broad-spectrum anti-parasitic impact and well as anti-inflammatory effects through reduction of immune responses [16]. While oral ivermectin was initially investigated for its efficacy in ocular demodicosis and showed some clinical improvements in reducing mite counts and symptoms [17,18], recent focus has been shifted to a more targeted approach in the form of topical ivermectin administration. The interest in this treatment also stemmed from its success in treating rosacea associated with proliferation in Demodex mites [19,20]. Some considerations for ocular use include application only along the base of the eyelashes as it could cause mild stinging sensation in some patients if the cream comes in contact with the ocular surface. There is currently an absence of standardized guidelines for dosing, although a single or double in-office application [15], and at-home instillation once weekly of ivermectin 1.0 % cream have been investigated [14].

It has been suggested that patients should be treated for 3 months to ensure they are treated at a susceptible stage in the life cycle of the Demodex mites during copulation [4]. Given that repeated applications are likely to be necessary to alleviate ocular demodicosis given the life cycle of the mite, the convenience of an at-home treatment over multiple 15-minute in-office treatments is substantial, saving clinician time and being more convenient and economical for patients. While previous studies with topical ivermectin have demonstrated some success, these involved relatively short follow-up periods of a few months with weekly application of the ivermectin cream which showed limited improvements in signs similar to controls [14] or were confined to reports of case series with crude judgement of ocular demodicosis signs [15]. The current retrospective study aims to investigate the treatment efficacy of nightly application of topical ivermectin 1.0 % cream for 3 months on alleviating clinical signs of ocular demodicosis and whether any potential improvements are sustained over a longer period of up to 12 months. This study also involved masked assessment with a widely available imaging analysis software to quantify potential treatment effects on ocular demodicosis characteristics captured with slit lamp biomicroscopy digital imaging.

2. Methods

2.1. Study design

This retrospective chart analysis, open-label, single centre, clinical study was approved by the institutional ethics committee and conducted in accordance with the tenets of the Declaration of Helsinki.

2.2. Patient selection and treatment regimen

All patients underwent thorough assessment of ocular surface health by a single clinician including fluorescein staining applied with impregnated strips moistened with saline to each eye and observed with a ~500 nm cut-off yellow filter. Patients were assessed at baseline when the treatment was prescribed and then followed up at 3 and 12 months after baseline. Severity grading was conducted according to the Efron scale (Grade of 0 indicating no staining to 4 indicating severe staining) [21]. The clinical records of consecutive patients who had ocular demodicosis and selected treatment with topical ivermectin 1.0 % cream (Soolantra, Galderma Ltd, UK) were analysed. Any lid hygiene regimen such as lid wipes or foam wash were discontinued at the point of prescription. Patients had been instructed to administer the ivermectin cream sparingly to both eyelids of each eye, rubbing down to the lid margin with the eyes closed just before bed at night, daily for 3 months from the baseline visit. If the patient got the cream in the eye, they were advised to use hyaluronate-based lubricating eyedrop (Hycosan Extra) to relieve any discomfort. Together with symptoms of itching or dry eye disease symptoms, either of the following signs or a combination of them indicated a diagnosis of ocular demodicosis, including collarettes around the base of lashes, visible Demodex tails, presence of Demodex mites through inspection of epilated lash follicle under light microscope (Brunel Microscope SP20D, Wiltshire, United Kingdom), or excessive pouting of lash follicles in those with good lid hygiene where Demodex was confirmed by secondary means such as visible Demodex tails or microscopic confirmation on lash epilation. The exclusion criteria include age of under 18 years, pregnancy or risk of pregnancy, sensitivity to ingredients in the ivermectin cream, and anticoagulant therapy with warfarin or Acenocoumarol given the potential for ivermectin to interfere with these therapies [22].

2.3. Slit lamp biomicroscopy digital imaging

Images for analysis were captured using a Topcon SLD-701 LED slit lamp biomicroscope with a BG-5 illumination attachment and DC-4 digital camera connected to the IMAGEnet ibase software. A magnification of between 10x and 25x was used to take the images, with the patient instructed to look down. The illumination column was then rotated so that it is parallel to the area of the eyelid being imaged, primarily focused on the central portion of the lid. Subsequent analysis was conducted on a randomly chosen eye for each patient.

2.4. Image analysis of ocular demodicosis characteristics

The Cell Counter plugin in ImageJ (version 1.54d, National Institutes of Health, USA) was used to mark the total number of lashes present. A lash was counted as part of the total if the lash base was in full view and not partially or fully obstructed by other anatomical features such as lid skin or other lashes, and was in sufficient focus. Three additional characteristics (Fig. 1) were then assessed from the marked images and recorded in a Microsoft Excel spreadsheet:

1. lashes with collarettes – number and percentage
2. lashes with distinct, visible tails – number and percentage
3. lash follicle pouting (distension of the surrounding skin tissue at the base of the lash indicating follicular hypertrophy thought to be due to an inflammatory reaction to accumulation of debris and impedance of normal lash growth [4]) – number and percentage

2.5. Statistical analysis

Statistical analysis was conducted with IBM SPSS Statistics (version 28.0.1.1) and graphs were generated with GraphPad prism (version 9.5.1). Normality of data was assessed with the Kolmogorov-Smirnov test. Repeated measures ANOVA, or the Friedman test followed by post-hoc analysis with Wilcoxon signed rank test and Bonferroni adjustment was used to assess within subject changes in clinical or ocular demodicosis findings for parametric and non-parametric data, respectively.

3. Results

A total of 194 patient records were reviewed for this study. 119

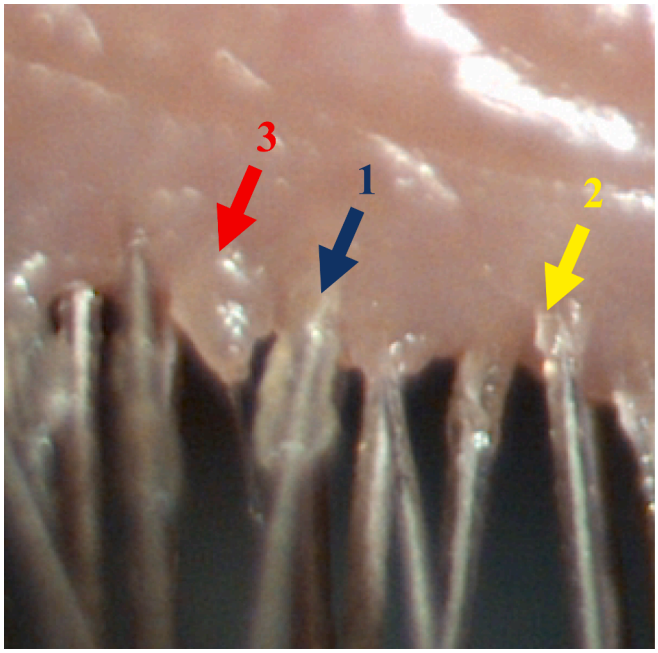

Fig. 1. A representative image of the base of lashes showing examples of a lash with collarette (labelled as 1 with blue arrow), a lash with visible tails of the Demodex mites (labelled as 2 with yellow arrow) and a lash with follicle pouting (labelled as 3 with red arrow). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

patients were not included for analysis due to: n = 12 (6 %) had discontinued following adverse side effects including mild irritation of the eyes or skin; n = 24 (12 %) were lost to follow-up; n = 12 (6 %) were non-adherent to the prescribed treatment and did not start or complete the course; n = 19 (10 %) patients attended follow-up out of the planned period; and n = 52 (27 %) patients did not have images that could be analysed due to insufficient focus of images for grading, contamination of other substances such as mascara, cream, or eyedrops on lashes, no lash bases visible or there were no imaging available. Data from a total of 75 patients were available for analysis in this study. The clinical and demographic data are shown in Table 1.

Of the 75 patient data analysed, side effects with the use of the treatment were reported in two patients (2.7 %), with one reporting mild skin irritation and the other reporting stinging upon application. Ocular surface therapies which were used prior to the prescription of ivermectin topical cream were: n = 51 (68 %) using lid wipes [37 (49 %) of these used wipes containing tea tree oil]; n = 33 (44 %) with preservative-free tear lubricants and n = 2 (3 %) with a lubricating gel with mild preservative; n = 20 (27 %) with warm compresses advised to be used once a day with either an Optase microwaveable mask or a'click and go' eye mask if the patient did not have access to a microwave; and n = 1 (1 %) with lid foam wash.

Table 1
Demographics and clinical characteristics of patients.

Demographics and clinical characteristics	Findings from patients
Age, years	66.6 ± 13.9
Gender, female	44 (58.7 %)
Laterality of eyes assessed	
Right eye	37 (49.3 %)
Left eye	38 (50.7 %)
Follow-up attendance	
3 months	70 (93.3 %)
12 months	44 (58.7 %)

Data reported as mean ± standard deviation or count (percentage %).

The mean number of assessable lashes were slightly higher in the second and third visits compared to the first visit (Table 2). Manual image analysis also showed reduction in all three ocular demodicosis characteristics, including the numbers and percentages of lashes with collarettes, visible Demodex tails and follicle pouting (Table 2). This significant reduction occurred as early as the second visit for all characteristics, which was sustained up to the final third visit (Fig. 2). Representative images of the treated eyelids and lashes from three patients across the three visits are shown in Fig. 3. Fluorescein staining severity score also improved with treatment from baseline, particularly when compared to the second visit ($p < 0.001$; Table 2).

4. Discussion

The findings of the current study demonstrated the efficacy of topical ivermectin 1.0 % cream in reducing the signs of demodicosis, sustained up to 1 year after the treatment was prescribed. This is evident through the improvement in the signs of ocular demodicosis, including reduction in collarettes at the base of lashes, number of Demodex tails observed and lash follicle pouting.

Collarettes are considered the pathognomonic sign of ocular demodicosis, with studies showing apparent ocular demodicosis diagnosis in patients showing signs of these solidified excretions at the base of their lashes [5,23]. These excretions are thought to be accumulations of undigested material, keratinized cells or encasing of dead mites or eggs [4,24]. Ivermectin effectively reduces the presence of such secretions through its antiparasitic action on the Demodex mites by binding to glutamate-gated chloride ion channels required for neurotransmission, leading to paralysis and death of the mites [25]. This is supported by several studies which showed reduction in cylindrical dandruffs or collarettes. Choi et al showed a reduction in eyelid debris grade from baseline to about 15 weeks after treatment when compared to a control group who only used eyelid hygiene [14]. While a recent study demonstrated reduction in Demodex mite counts with epilated lashes and observed under light microscopy with topical treatment for 30 days, the gel used also included 1.0 % metronidazole together with 0.1 % ivermectin [26]. The current study involves a longer follow-up period of up to a year, which provides insight into the safety and sustained improvements of topical ivermectin treatment on several indicators or signs of ocular demodicosis even without conventional lid wipes or foam. The treatment protocol in the current study also enables therapy to be conducted at home, reducing chair time compared to in-office application of cream. Notably, no serious side effects were observed in any of the patients with only mild irritation reported as has been reported previously [14]. However, clinicians should be cautious of the use of ivermectin in patients on anticoagulant therapy as there is a potential for ivermectin to interfere with these therapies [22].

The reduction in the observed Demodex tails shown in the current study also supports the efficacy of ivermectin in reducing the Demodex load at the base of the lashes. This impact on Demodex tail quantification may have been even more apparent with an additional diagnostic technique using eyelash manipulation by applying lateral tension with forceps without epilation [7], which could be a consideration for future studies. Lash follicle pouting, a sign that is not often reported, is thought to represent follicular hypertrophy due to inflammation in the underlying skin from Demodex mites impeding the normal growth of the eyelash [4]. This sign is also thought to be specific to ocular demodicosis and may provide an additional surrogate measure alongside the pathognomonic sign of collarettes when diagnosing or assessing the efficacy of treatments for this condition. A potential benefit of assessing lash pouting is that it is an assessable sign in patients who may still have high Demodex load but have low number of collarettes due to good lid hygiene.

By alleviating the Demodex load, ocular surface health has also been shown to improve with topical ivermectin treatment in this study. This is reflected by the improvement in fluorescein staining severity scores.

Table 2
Image analysis of lashes, ocular demodicosis characteristics and fluorescein staining severity scores across the three visits.

Measures	Visit			p-value		
	Visit 1	Visit 2	Visit 3	Visit 1 vs 2	Visit 1 vs 3	Visit 2 vs 3
Total number of lashes assessable	26 [20–33]	31 [22–37]	32.5 [23.5–39]	**0.003**	**< 0.001**	0.31
Number of lashes with collarettes	8 [4–13]	0 [0–1]	0 [0–2]	**< 0.001**	**< 0.001**	0.26
Percentage of lashes with collarettes (%)	28.6 [14.8–50.0]	0 [0–4.8]	0 [0–7.1]	**< 0.001**	**< 0.001**	0.41
Number of lashes with visible tails	0 [0–0]; 0 to 4	0 [0–0]; 0 to 1	0 [0–0]; 0 to 0	**0.001**	**0.004**	0.99
Percentage of lashes with visible tails (%)	0 [0–0]; 0 to 14.3	0 [0–0]; 0 to 3.3	0 [0–0]; 0 to 0	**0.001**	**0.008**	0.99
Number of lashes with follicle pouting	3 [1–5]	0 [0–1]	0 [0–1.8]	**< 0.001**	**< 0.001**	0.11
Percentage of lashes with follicle pouting (%)	10.5 [4.5–16.1]	0 [0–3.4]	0 [0–5.6]	**< 0.001**	**< 0.001**	0.26
Fluorescein staining severity score	1 [0–2]	0 [0–1]	0 [0–1]	**< 0.001**	0.017	0.20

Data reported as median [interquartile range] and/or range from minimum to maximum value. For Wilcoxon signed rank test with Bonferroni adjustment for ocular demodicosis characteristics and fluorescein staining severity scores, $p < (\frac{0.05}{3}$ or 0.017) was considered statistically significant.

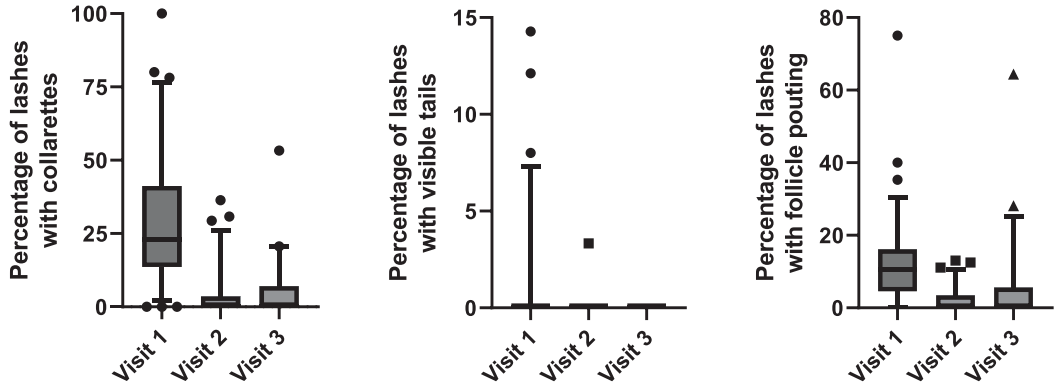

Fig. 2. The distribution of percentages of analysed blepharitis or Demodex characteristics across the three study visits: Visit 1 (baseline), Visit 2 (first follow-up), Visit 3 (second follow-up).

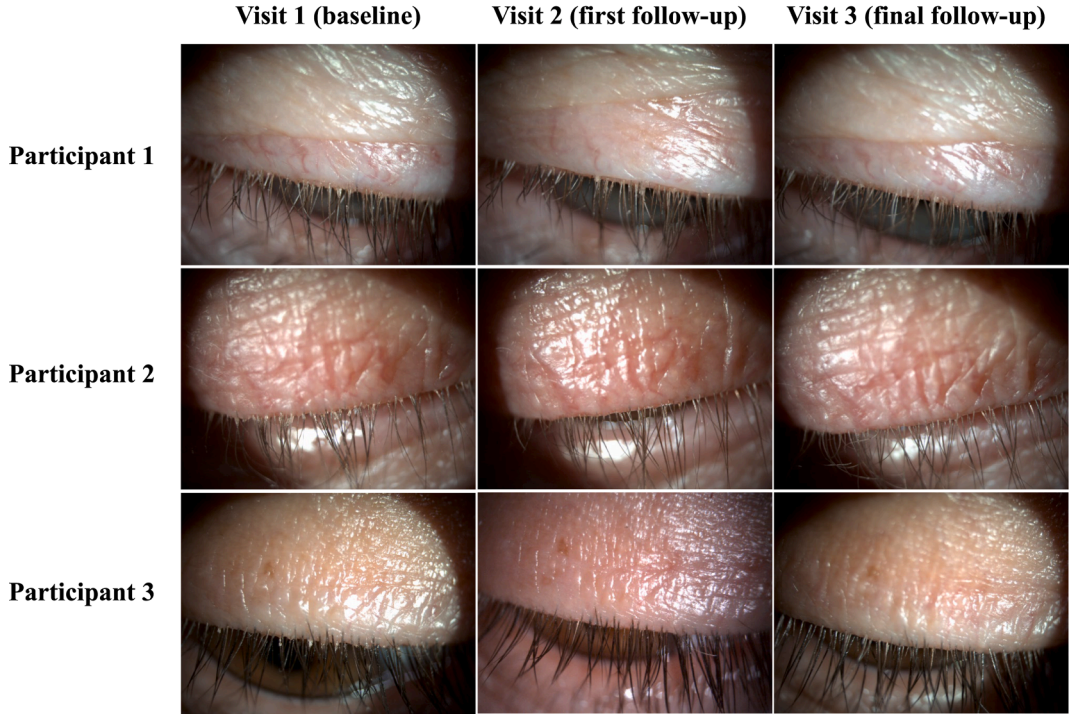

Fig. 3. Representative images of three patients treated with ivermectin cream from baseline to the final follow-up.

Other studies have also shown similar improvements in ocular surface health with the use of ivermectin, including symptomatology and corneal staining [14,27]. Ocular demodicosis is a known contributor of dry eye disease, potentially through the incitement of inflammation and the disruption of the intricate tear film structure [28]. Notably, it has been demonstrated that the proinflammatory cytokine, interleukin (IL)-17, is significantly elevated in the tear film of patients with Demodex proliferation [29]. In addition to its antiparasitic effect, ivermectin has been shown to reduce inflammation within the surface of the skin in cases of rosacea with Demodex proliferation [30]. The improvement in ocular surface damage as shown in the current study may indicate this dual impact of ivermectin on improving ocular surface health in patients with ocular demodicosis.

One of the limitations of the current investigation is the retrospective nature of the study. Randomised controlled trials involving careful quantification of the various signs of ocular demodicosis would be valuable in understanding the impact of ivermectin on this condition. Such prospective studies should also incorporate validated questionnaires to track patient-reported outcomes and symptomatology such as the Ocular Surface Disease Index (OSDI) or 5-Item Dry Eye Questionnaire (DEQ-5). Other indicators of ocular surface health such as measures of tear film inflammatory mediators and osmolarity may also provide further insight on the potential effects of Demodex proliferation and investigated therapies on the ocular surface. The optimal treatment duration is yet to be established, and the optimal dose may vary depending on the presenting severity of ocular demodicosis. Further investigations should also assess when treatment should be reinitiated and if additional treatments should be considered if there is a relapse in ocular demodicosis signs. Given that there was no evident relapse at the 12-month point in the current study, annual follow-ups for treated patients should be adequate. Comparisons with lotilaner ophthalmic solution (Tarsus Pharmaceuticals), an antiparasitic agent which inhibits chloride ion channels recently approved by the Food and Drug Administration in the United States of America for ocular demodicosis [31], would also be beneficial to identify potential differences in efficacy and usability between the two therapies. The potential differential impact of ivermectin treatment on different species of Demodex mites, including Demodex folliculorum generally found at the base of lashes and Demodex brevis inhabiting sebaceous or Meibomian glands would also be of interest. The consistency in eyelid imaging could also be improved by using instruments which could aid in precise localisation and focus of the base of the lashes to enable identical and larger areas of lash regions to be assessed across visits.

Given the ubiquitous presence of Demodex mites in humans, and the potential for proliferation of these mites in causing debilitating ocular surface disease, more research is warranted to improve the diagnosis and management of this condition which is often overlooked or misdiagnosed [32]. This study shows evidence of good efficacy and safety profile of topical ivermectin 1.0 % cream in alleviating signs of ocular demodicosis and improving ocular surface health in affected patients.

Funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Palopoli MF, Fergus DJ, Minot S, Pei DT, Simison WB, Fernandez-Silva I, et al. Global divergence of the human follicle mite Demodex folliculorum: Persistent associations between host ancestry and mite lineages. Proc Natl Acad Sci U S A 2015;112:15958–63.
[2] Thoemmes MS, Fergus DJ, Urban J, Trautwein M, Dunn RR. Ubiquity and diversity of human-associated Demodex mites. PLoS One 2014;9:e106265.
[3] Aktaş Karabay E, Aksu Çerman A. Demodex folliculorum infestations in common facial dermatoses: Acne vulgaris, rosacea, seborrheic dermatitis. An Bras Dermatol 2020;95:187–93.
[4] Nicholls SG, Oakley CL, Tan A, Vote BJ. Demodex species in human ocular disease: New clinicopathological aspects. Int Ophthalmol 2017;37:303–12.
[5] Gao YY, Di Pascuale MA, Li W, Liu DT, Baradaran-Rafii A, Elizondo A, et al. High prevalence of Demodex in eyelashes with cylindrical dandruff. Invest Ophthalmol vis Sci 2005;46:3089–94.
[6] Trattler W, Karpecki P, Rapoport Y, Sadri E, Schachter S, Whitley WO, et al. The prevalence of Demodex blepharitis in US eye care clinic patients as determined by collarettes: A pathognomonic sign. Clin Ophthalmol 2022;16:1153–64.
[7] Muntz A, Purslow C, Wolffsohn JS, Craig JP. Improved Demodex diagnosis in the clinical setting using a novel in situ technique. Cont Lens Anterior Eye 2020;43:345–9.
[8] Murphy O, Lloyd-McKernan A. The clinical use of eyelash manipulation in the diagnosis of Demodex folliculorum blepharitis. Eye Contact Lens 2020;46(Suppl 1):S33–8.
[9] Savla K, Le JT, Pucker AD. Tea tree oil for Demodex blepharitis. Cochrane Database Syst Rev 2020;6. Cd013333.
[10] Chen D, Wang J, Sullivan DA, Kam WR, Liu Y. Effects of terpinen-4-ol on meibomian gland epithelial cells in vitro. Cornea 2020;39:1541–6.
[11] Craig JP, Bitton E, Dantam J, Jones L, Ngo W, Wang MTM. Short-term tolerability of commercial eyelid cleansers: A randomised crossover study. Cont Lens Anterior Eye 2022;45:101733.
[12] Shah PP, Stein RL, Perry HD. Update on the management of demodex blepharitis. Cornea 2022;41:934–9.
[13] Raedler LA. Soolantra (Ivermectin) 1% cream: A novel, antibiotic-free agent approved for the treatment of patients with rosacea. Am Health Drug Benefits 2015;8:122–5.
[14] Choi Y, Eom Y, Yoon EG, Song JS, Kim IH, Kim HM. Efficacy of topical ivermectin 1% in the treatment of Demodex blepharitis. Cornea 2022;41:427–34.
[15] Helm CJ. Treatment of ocular Demodex infestation with topical ivermectin cream. Am J Ophthalmol Case Rep 2022;26:101551.
[16] Abokwidir M, Fleischer Jr AB. Additional evidence that rosacea pathogenesis may involve demodex: new information from the topical efficacy of ivermectin and praziquantel. Dermatol Online J 2015;21.
[17] Salem DA, El-Shazly A, Nabih N, El-Bayoumy Y, Saleh S. 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. Int J Infect Dis 2013;17:e343–7.
[18] Filho PA, Hazarbassanov RM, Grisolia AB, Pazos HB, Kaiserman I, Gomes J. The efficacy of oral ivermectin for the treatment of chronic blepharitis in patients tested positive for Demodex spp. Br J Ophthalmol 2011;95:893–5.
[19] Trave I, Merlo G, Cozzani E, Parodi A. Real-life experience on effectiveness and tolerability of topical ivermectin in papulopustular rosacea and antiparasitic effect on Demodex mites. Dermatol Ther 2019;32:e13093.
[20] Ebbelaar CCF, Venema AW, Van Dijk MR. Topical ivermectin in the treatment of papulopustular rosacea: A systematic review of evidence and clinical guideline recommendations. Dermatol Ther (heidelb) 2018;8:379–87.
[21] Efron N. Grading scales for contact lens complications. Ophthalmic Physiol Opt 1998;18:182–6.
[22] Gilbert BW, Slechta J. A case of ivermectin-induced warfarin toxicity: First published report. Hosp Pharm 2018;53:393–4.
[23] Kasetsuwan N, Kositphipat K, Busayarat M, Threekhan P, Preativatanyou K, Phumee A, et al. Prevalence of ocular demodicosis among patients at Tertiary Care Center, Bangkok. Thailand Int J Ophthalmol 2017;10:122–7.
[24] Rhee MK, Yeu E, Barnett M, Rapuano CJ, Dhaliwal DK, Nichols KK, et al. Demodex blepharitis: A comprehensive review of the disease, current management, and emerging therapies. Eye Contact Lens 2023;49:311–8.
[25] Wolstenholme AJ, Rogers AT. Glutamate-gated chloride channels and the mode of action of the avermectin/milbemycin anthelmintics. Parasitology 2005;131(Suppl):S85–95.
[26] Ávila MY, Martínez-Pulgarín DF, Rizo Madrid C. Topical ivermectin-metronidazole gel therapy in the treatment of blepharitis caused by Demodex spp.: A randomized clinical trial. Cont Lens Anterior Eye 2021;44:101326.
[27] Sobolewska B, Doycheva D, Deuter CM, Schaller M, Zierhut M. Efficacy of topical ivermectin for the treatment of cutaneous and ocular rosacea. Ocul Immunol Inflamm 2021;29:1137–41.
[28] Sędzikowska A, Tarkowski W, Moneta-Wielgoś J, Grzyliński K, Tarkowski G, Młocicki D. Effect of ocular demodicosis on the stability of the tear film and the tear break up time. Sci Rep 2021;11:24296.
[29] Kim JT, Lee SH, Chun YS, Kim JC. Tear cytokines and chemokines in patients with Demodex blepharitis. Cytokine 2011;53:94–9.
[30] Schaller M, Gonser L, Belge K, Braunsdorf C, Nordin R, Scheu A, et al. Dual anti-inflammatory and anti-parasitic action of topical ivermectin 1% in papulopustular rosacea. J Eur Acad Dermatol Venereol 2017;31:1907–11.
[31] Yeu E, Wirta DL, Karpecki P, Baba SN, Holdbrook M. Lotilaner ophthalmic solution, 0.25%, for the treatment of demodex blepharitis: Results of a prospective, randomized, vehicle-controlled, double-Masked, pivotal trial (Saturn-1). Cornea 2023;42:435–43.
[32] Luo X, Li J, Chen C, Tseng S, Liang L. Ocular demodicosis as a potential cause of ocular surface inflammation. Cornea 2017;36(Suppl 1):S9–s14.