CLINICAL AND EXPERIMENTAL
OPTOMETRY

RESEARCH PAPER

Efficacy of azithromycin 1% ophthalmic solution for treatment of ocular surface disease from posterior blepharitis

Clin Exp Optom 2011; 94: 2: 200–206 DOI:10.1111/j.1444-0938.2010.00540.x

Dominick L Opitz*† OD FAAO
Keith F Tyler* OD FAAO
* Illinois College of Optometry, Chicago, Illinois, USA and † Midwest Eye Professionals, Palos Heights, Illinois, USA
E-mail: dopitz@ico.edu

Background: Posterior blepharitis is an eyelid disease primarily of the meibomian glands. Bacteria and chronic inflammation are contributing factors for meibomian gland disease, which leads to ocular surface and tear film alterations and chronic patient symptoms. Azithromycin 1.0% ophthalmic solution is a broad spectrum topical antibiotic with anti-inflammatory properties. The present study evaluates the efficacy of azithromycin 1.0% ophthalmic solution in the treatment of the clinical signs and symptoms, including vision-related function, associated with meibomian gland dysfunction.

Methods: In an open label study, 33 patients with meibomian gland dysfunction were treated with azithromycin 1.0% ophthalmic solution twice a day for two days, then every evening for a total of 30 days. Tear break-up time, corneal staining, conjunctival staining, Schirmer scores with anaesthetic, meibomian gland score and patient's symptom scores were evaluated at baseline and after 30 days of treatment. The Ocular Surface Disease Index (OSDI) was administered at baseline, after two weeks of treatment and after 30 days of treatment.

Results: Twenty-six of 33 patients completed the study. Tear break-up time and Schirmer score increased by 52.7 per cent ($p < 0.0001$) and 24 per cent ($p < 0.05$), respectively. There was a reduction in corneal and conjunctival staining by 83.2 and 67.9 per cent, respectively ($p < 0.0001$). Lid margin scores were reduced by 33.9 per cent ($p < 0.0001$). The patient's symptom score improved from 2.73 at baseline to 2.21 after 30 days of treatment ($p < 0.01$). The mean OSDI at baseline was 34.44. After two weeks and 30 days of treatment, the ODSI was 14.51 and 13.15 respectively ($p < 0.0001$).

Conclusion: These results demonstrate clinically and statistically significant improvement in the signs and symptoms associated with posterior blepharitis. Based on these results, azithromycin 1% ophthalmic solution offers a viable option for the treatment of posterior blepharitis.

Submitted: 28 April 2010
Revised: 14 July 2010
Accepted for publication: 17 August 2010

Key words: azithromycin, blepharitis, dry eye syndrome, eyelid disease, meibomian glands

Blepharitis is a commonly-encountered ocular disease that is characterised by inflammation of the lid margin and is multifactorial in aetiology.[1–6] Posterior blepharitis, also known as meibomian gland dysfunction (MGD), is a specific type of blepharitis that afflicts the meibomian glands (MG), causing alterations to the anatomy of the meibomian glands and to their secretions. With meibomian gland dysfunction, the meibomian gland orifices can become obstructed.

There are several proposed theories on the aetiology of this obstruction. One theory suggests meibomian gland

dysfunction is the result of hyperkeratinisation of the epithelium lining the meibomian gland ducts[1,7–9] while another theory suggests the changes are occurring to the meibomian gland secretions or the meibum.[1,10,11] Once obstructed, the lipid composition of the meibum becomes altered.[1] Alterations include thickening of the secretions, increased melting point of the secretions, ductal stagnation and pouting of the meibomian gland orifices.[1,12] Bacterial colonisation and inflammatory mediators are released once the meibomian glands become obstructed.[1] The inflammatory mediators are formed when lipolytic enzymes are produced from bacteria, such as *Staphylococcal epidermidis*, *Staphylococcal aureus*, *Propionibacterium acnes* and *cornebacterium*.[13,14] The lipolytic enzymes released by the bacteria result in highly irritating free fatty acids that compromise the tear film integrity.[10,15,16] Both the structural changes to the meibomian glands and the secretions contribute to increased evaporation of the tear film, increased tear osmolarity and increased inflammatory cytokines that ultimately damage the ocular surface, resulting in patient symptoms.[16–20]

Although posterior blepharitis or meibomian gland dysfunction is common with a prevalence of 39 to 50 per cent,[21–23] there is no definitive or universally approved treatment regimen. Historically, treatments have included lid hygiene,[24] warm compresses,[25] topical and systemic antibiotics,[26,27] nutritional supplements[28,29] and topical cyclosporine A.[30,31] One such topical antibiotic, azithromycin 1% ophthalmic solution (Azasite Inspire Pharmaceuticals, Inc, Durham, NC, USA) is a macrolide antibiotic indicated for the treatment of bacterial conjunctivitis.[32] Azithromycin 1% ophthalmic solution is an effective microbial agent for CDC coryneform group C, *Haemophilus influenza*, *Staphylococcal aureus*, *Streptococcus pneumonia*, *Streptococcus mitis* group.[32,33] Like other macrolides, oral azithromycin has anti-inflammatory activities.[34–36] The mechanism for the potential ocular anti-inflammatory activity of azithromycin is not completely understood. Li and associates[37] demonstrated that azithromycin suppresses zymosan-induced production of pro-inflammatory mediators by human corneal epithelial cells by blocking NFkappaB activation in human corneal epithelial cells. Although Li's study examined the inhibition of pro-inflammatory mediators with fungal infections, topical azithromycin 1% was shown to be an effective treatment alternative for posterior blepharitis,[38] while another study demonstrated effectiveness for mixed anterior and posterior blepharitis.[39]

The present study was designed to further quantify and evaluate the effect of topical azithromycin 1% ophthalmic solution when applied to the eye and lid margin for the treatment of posterior blepharitis or meibomian gland dysfunction. Unlike previous evaluations, this study will evaluate vision-related function, ocular symptoms and environmental triggers as measured by the Ocular Surface Disease Index. Additionally, we will evaluate specific clinical signs commonly used to diagnose ocular surface disease caused by posterior blepharitis, including tear break-up time, Schirmer scores with anaesthetic, conjunctival and corneal staining and meibomian gland dysfunction.

METHODS

This research was conducted in strict accordance with the guidelines of the Illinois College of Optometry Institutional Review Board and in accordance with the Tenets of the Declaration of Helsinki. Written informed consent was obtained from each subject.

Thirty-three patients from the Illinois Eye Institute (Chicago, IL, USA) and Midwest Eye Professionals (Palos Heights, IL, USA) participated in this open label, prospective clinical study. Patients diagnosed with posterior blepharitis over the age of 18 years were included in the study. Patients with any of the following were excluded from study participation: younger than 18 years of age, ocular injury, ocular infection, non-dry eye ocular inflammation, ocular trauma or ocular surgery within the previous six months. Additionally, patients were excluded if they were using any topical and/or systemic medication that could be used for the treatment of meibomian gland dysfunction or dry eye, including topical or oral antibiotics, topical cyclosporine A, topical and/or oral steroids, topical non-steroidal anti-inflammatories, topical ocular allergy medications or artificial tear supplements. Patients were able to use only Optive (Allergan, Inc, Irvine, CA, USA) lubricating eye-drops for a maximum of three times daily two weeks prior to study enrolment. If patients were using any other artificial tear supplements or any other topical and/or systemic medication for the treatment of dry eye or meibomian gland dysfunction, the patient was instructed to discontinue them two weeks prior to study enrolment (wash-out). Patients who were pregnant, had uncontrolled systemic disease or significant illness that could hinder adherence to the study protocol were excluded from the study. Patients from whom written informed consent could not be obtained were excluded. Patients who could not adhere to the treatment protocol or who had a known allergy to the study medication were also excluded.

Following the appropriate two-week wash-out period, patients were examined for baseline measurements by one of two examiners. During the baseline visit, visual acuity (VA) was measured with a standard Snellen chart for each eye. Slit-lamp biomicroscopy was performed. The meibomian glands and its secretions were graded and recorded on a scale of 0 to 4 (Table 1).

Tear break-up time (TBUT) was measured using sterile sodium fluorescein strips (Ful-Glo, Akorn Inc, Buffalo Grove, IL, USA). TBUT was performed according to the following protocol: a fluorescein strip was moistened with non-preserved saline solution (Unisol, Alcon, Ft Worth, TX, USA), the fluorescein was instilled in each eye and the patient was asked to blink several times to ensure the fluorescein was evenly distributed across the cornea. While looking straight ahead, the tear film was evaluated using the cobalt blue filter during biomicroscopy. The time from the blink that evenly distributed the fluorescein to the appearance of

Meibomian gland score	Description of secretions	Digital pressure to express
0	Clear	Easily expressed
1	Cloudy fluid	Easily expressed
2	Cloudy fluid	Mild pressure
3	Cloudy, particulate fluid	Moderate pressure
4	Thick, toothpaste like secretions	Hard pressure

Table 1. Lid margin grading scale

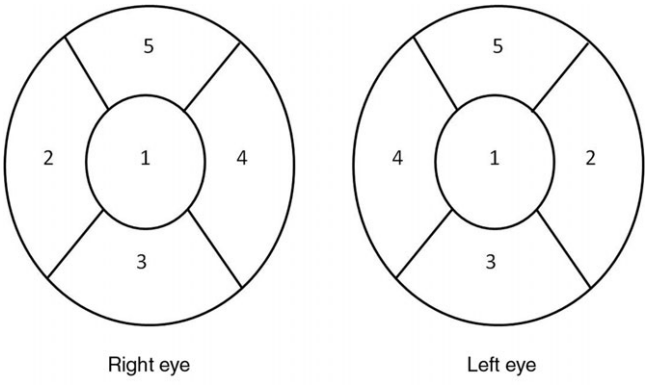

Figure 1. Diagram of the five areas assessed for corneal staining. Each area was graded on a scale of 0 to 4 at baseline and at one month.

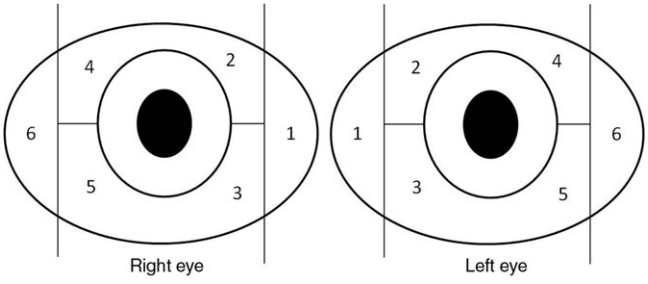

Figure 2. Diagram of the six areas assessed for conjunctival staining. Each area was graded on a scale of 0 to 4 at baseline and at one month.

the first tear break-up was recorded in seconds. The average of the three measurements was then recorded for each eye as the TBUT.

Following the TBUT measurements, corneal staining was measured using a cobalt blue filter and biomicroscope between one and three minutes after fluorescein was instilled in each eye. Five areas of the cornea (Figure 1)[40] were evaluated with each area graded on a scale of 0 to 4 (0 = no staining, 4 = severe/coalesced staining). The sum of the five areas was recorded as the corneal staining score for each eye.

Sterile lissamine green strips (Green Glo, HUB Pharmaceuticals, Rancho Cucamonga, CA) were used to measure conjunctival staining after TBUT and corneal staining measurements. Conjunctival staining assessments were taken between one and three minutes after a moistened lissamine green strip was applied to each eye. Six conjunctival areas were evaluated and scored on a scale of 0 to 4 (0 = no staining, 4 = severe staining) (Figure 2).[40] The sum of the six areas was recorded as the conjunctival staining score for each eye.

Following conjunctival staining, one drop of proparacaine 0.5% (Accu-Proparicaine, Bausch & Lomb, Tampa, FL) was instilled in each eye and the excess moisture was wiped from the eyes with a facial tissue. A sterile Schirmer strip (Tear Flo, Rose Stone Enterprises, Alta Loma, CA) was placed in the temporal one-third of the lower eyelid cul-de-sac in each eye one minute after instillation of proparacaine 0.5%. The eyes were closed, as if sleeping and after five minutes, the Schirmer score was recorded in millimetres for each eye.

The patients' symptoms were measured by two methods. First, patients were asked to grade the overall comfort of their eyes on a scale of 0 to 5 (0 = no symptoms, 5 = severe symptoms). This was recorded as the symptom score. Second, we administered the Ocular Surface Disease Index (OSDI), which is a survey reflecting disease severity that assesses vision-related function, ocular symptoms and environmental triggers.[41]

Clinical signs assessed	Mean at baseline	Mean at one month	*P* Value	% Change from baseline
TBUT (seconds)	4.37 ± 1.67	6.58 ± 2.84	<0.0001	52.7%
Corneal staining score	3.65 ± 3.06	0.62 ± 0.80	<0.0001	83.2%
Conjunctival staining score	5.38 ± 3.82	1.73 ± 2.29	<0.0001	67.9%
Meibomian gland score	2.44 ± 0.65	1.62 ± 0.57	<0.0001	33.8%
Schirmer II (mm)	11.54 ± 7.33	14.31 ± 9.53	<0.01	24.0%

Table 2. Comparison of parameters (mean ± SD) between baseline visit and 30 days after treatment (n = 26)

Symptoms assessed	Baseline	2 weeks	1 month	*P* Value	% Baseline change
OSDI	34.44 ± 20.31	14.51 ± 15.21	13.15 ± 16.80	<0.0001	61.8%
Symptom score	2.73 ± 0.89		2.21 ± 0.78	<0.01	19.0%

OSDI score = [(sum of scores on OSDI) × 25] / (# questions answered). The OSDI is scored on a scale of 0 to 100, with higher scores representing greater disability.

Table 3. Comparison of symptoms baseline and visit 2 (mean ± SD)

On completion of the baseline visit, patients were instructed to instil one drop of azithromycin 1% ophthalmic solution in each eye on waking and prior to bed for two days and then only before bed for a total of 30 days. Patients were further instructed to close the eyes gently for 30 seconds following instillation and to rub any spill-over medication into the lid margins and lashes. Following a demonstration of drop instillation, written instructions were provided to the patient. Optive lubricating drops were allowed as needed but no more than three times a day in each eye. Optive was not to be instilled 30 minutes before or after the topical azithromycin 1% ophthalmic solution.

After two weeks of using the topical azithromycin 1%, patients were interviewed either via telephone or in person to ensure adherence to the study protocol, to administer a two-week treatment OSDI and to monitor for any adverse reactions. Thirty days following treatment with topical azithromycin 1%, patients were re-evaluated by the same examiner and according to the same protocol as at the baseline examination. Visual acuity, TBUT, meibomian gland dysfunction scores, corneal staining scores, conjunctival staining scores, Schirmer II scores, symptom score and OSDI were measured and recorded.

Analysis was completed using a paired Student-t test to compare the baseline measurements and the one month measurements for the following tests: TBUT, Schirmer scores with anaesthetic, lid margin grading, conjunctival staining, corneal staining and symptom score. A general linear model was performed to compare the OSDI scorings at the baseline visit, the two-week interview and the final 30 day visit. The results of the right eye were used for all analyses, as there was no statistically significant difference between the results of the right and left eyes.

RESULTS

Thirty-three subjects were enrolled and 26 completed the study protocol. The mean age was 52.5 years with a range of 24 to 88 years; there were 14 males and 12 females. The results of the clinical characteristics are shown in Table 2.

Visual acuity remained unchanged. The mean tear break-up time for patients at baseline was found to be 4.31 seconds (range, zero to seven seconds). After treatment, the mean TBUT increased to 6.57 seconds (range, two to 12 seconds) demonstrating an increase in TBUT by 52.7 per cent ($p < 0.0001$) with no difference between TBUT in the right and left eyes ($r = 0.624$, $p < 0.01$). The mean corneal staining score at baseline was 3.65 (range, 0 to 12). After one month, the mean corneal staining score was reduced to 0.62 (range, 0 to 3) showing an 83.2 per cent reduction in mean corneal staining compared to baseline ($p < 0.0001$). The mean baseline lissamine green conjunctival staining score was 5.38 with a range of 0 to 15. After 30 days of treatment, the mean conjunctival score was 1.73 (range, 0 to 8), representing a reduction by 67.9 per cent ($p < 0.0001$). Both corneal ($r = 0.946$) and conjunctival staining showed no differences between eyes ($r = 0.774$).

The mean meibomian gland score (MGS) at baseline was 2.44 with a range of 1 to 4. At the one-month visit, the meibomian gland score was 1.62 (range, 1 to 3) showing a 33.8 per cent reduction ($p < 0.0001$). The mean Schirmer score with anaesthetic was 11.54 mm at baseline (range, one to 25 mm). At the one month visit, the mean Schirmer score increased by 24 per cent to 14.31 mm (range, three to 34 mm), ($p < 0.05$). Both meibomian gland score ($r = 0.955$) and Schirmer score ($r = 0.625$) showed no significant difference between the right and left eyes.

Subjective symptoms were analysed based on symptom scores and on the OSDI (Table 3). At baseline, the mean symptom score was 2.73 (range, 1 to 5). Symptom scores were reduced by 19 per cent to 2.21 ($p < 0.01$) at the one-month visit. The mean OSDI at baseline was 34.44 (range, 2.78 to 65.91). After two weeks of

treatment, the mean OSDI was 14.51 indicating a significant reduction in symptoms ($p < 0.0001$). At the one-month visit, the mean OSDI was 13.15 also indicating a significant decrease from baseline ($p < 0.0001$). From the two-week OSDI to visit 2, there was no statistically significant change (14.51 to 13.15, respectively). Overall, the OSDI improved by 57.9 per cent at two weeks and 61.8 per cent from baseline at visit 2. Statistical analysis was also performed to determine if the use of Optive affected the OSDI. Comparison of patients who used Optive more than once a day (n = 13) with patients who used Optive less than once a day (n = 13), showed that the Optive did not affect the OSDI ($p = 0.291$).

DISCUSSION

Our study demonstrated that azithromycin 1% ophthalmic solution is effective in reducing the signs and symptoms associated with meibomian gland dysfunction. Surprisingly, vision-related function, ocular symptoms and environmental triggers were significantly improved after two weeks ($p < 0.0001$) of treatment as evident by the reduction of OSDI. We found this relatively quick improvement to be especially interesting and may suggest that 30 days of treatment may not be necessary in all patients. This should be further investigated. The overall improvement of symptoms in our study is likely to be due to significant improvement in clinical signs from baseline, including conjunctival staining, corneal staining, TBUT, basic tear production as measured by Schirmer with anaesthetic and meibomian glands.

In normal meibomian glands, the lipid secretions consist of neutral sterols and wax esters, with a lesser amount of polar lipids (free fatty acids), diesters, triesters, triglycerides and free sterols.[16,19,42] These secretions have a variety of functions that allow for a smooth optical surface, inhibit tear evaporation and decrease the surface tension of the tear film.[11,17,43] The normal meibomian gland lipids also create a barrier to contaminants, prevent tear overflow, cause maceration of the lid margins and create a watertight seal during eyelid closure.[11,17,43] With meibomian gland dysfunction, obstruction of meibomian glands can occur.[1] This obstruction is caused by hyperkeratinisation of the epithelium lining the meibomian glands[1,7–9] and from alterations to the lipids of the meibum.[1,10,16,18,19] Specifically, alteration of the lipids in meibomian gland dysfunction may result from lipolitic exoenzymes produced by *S. epidermis* and *S. aureus*, including triglyceride lipase, cholesterol and wax esterases, hydrolyse wax and sterol esters with the release of highly irritating free fatty acids and other products affecting the tear film integrity. Tear film instability and thinning allow for increased evaporation of the tears. This increases the tear osmolarity and increases the level of inflammatory cytokines, further contributing to changes to the ocular surface.[10,16,18,19,44] Furthermore, the abnormal meibum has a higher melting point than normal meibum, leading to thickening of the meibum, ductal plugging, stagnation and pouting of the meibomian gland orifices.[1] All of these changes to the tissue and meibum contribute to further ductal obstruction, more inflammation and bacterial colonisation.[1,12,45]

Although the underlying mechanism for meibomian gland dysfunction is complex, both inflammation and bacterial colonisation are thought to contribute to the development of the disease.[1] In addition to the excellent microbial activity of azithromycin, it also has anti-inflammatory properties. While the mechanism for this anti-inflammatory activity is not completely understood, the oral formulation of azithromycin is thought to suppress the production of pro-inflammatory mediators such as cytokines (TNFα and IL-1β), chemokines and matrix metalloproteinases (MMP-1, MMP-3 and MMP-9).[34–36] Based on the work by Li and associates[37] demonstrating the anti-inflammatory effect of azithromycin on human corneal epithelial cells, we feel azithromycin 1% ophthalmic solution used in our study not only eradicated ocular surface bacteria but also quelled ocular surface inflammation. This presumed reduction of inflammation may explain the improvement in basic Schirmer scores whereby the accessory lacrimal glands produce more aqueous. The combination of the antimicrobial and anti-inflammatory effects coupled with the medication's long duration of action[32,33] make it a viable treatment option for meibomian gland dysfunction as demonstrated in our study and may explain why all parameters in this study were clinically and statistically significant.

The strengths of this study include that it is prospective and that both subjective and objective parameters were assessed. The limitations of this study include the open-label design, lack of a control group and the relatively small number of patients. Five patients failed to complete the required one-month visit. Of note, two of 26 patients suffered adverse reactions to the study medication. One developed an allergic conjunctivitis after three weeks and one developed burning after two days. Our adverse reaction rate (7.7 per cent) was higher than the one to two per cent reported by the phase 3 clinical trials on the safety of azithromycin ophthalmic solution 1% for the treatment of bacterial conjunctivitis.[46] It should also be noted that in the phase 3 clinical trials, azithromycin ophthalmic solution 1% was used twice daily for two days then once daily for the next five days.[46] Our study protocol was longer using azithromycin ophthalmic solution 1% twice daily for two days then once daily for a total of 30 days.

Given the lack of a control group, we were concerned that the use of Optive may affect the results. At the final 30-day visit, 50 per cent of the patients in the study used Optive more than once daily and 50 per cent used it less than once a day. Statistical analysis showed that the Optive had no significant effect ($p = 0.291$) on the outcomes that were analysed.

Our study specifically evaluated the efficacy of topical azithromycin 1% solution for the signs and symptoms associated with posterior blepharitis or meibomian gland dysfunction. We did not address the treatment of comorbid conditions such as atopy, acne rosacea and seborrhoeic dermatitis but these should be considered in conjunction with ocular treatment of meibomian gland dysfunction.[12] Posterior

blepharitis is a chronic condition and our study did not assess the length of the therapeutic effect of the medication for meibomian gland dysfunction. Additional studies should evaluate the duration of the therapeutic effects as well as the potential benefit of adjunctive maintenance therapies, such as cyclosporine A, omega-3 fatty acids, warm compresses or artificial tear supplementation.

CONCLUSION

Meibomian gland dysfunction is a common ocular disease in eye-care practices[47] and treatment options have met with variable success. The results of our study indicate that azithromycin 1% ophthalmic solution significantly improved not only the signs and symptoms of meibomian gland dysfunction in a relatively short time but also vision-related function resulting from meibomian gland disease.

ACKNOWLEDGEMENTS

The authors thank Lexi Surber for her assistance, Dr Yi Pang for her statistical analysis and review of the study and Dr Bruce Teitelbaum for his insightful comments and editing of the manuscript.

STATEMENT OF CONFLICT OF INTEREST

Dr Dominick Opitz is a member of the Educational Speakers Bureau and has stock ownership for Inspire Pharmaceuticals.

REFERENCES

1. Henriquez A, Korb DR. Meibomian glands and contact lens wear. *Br J Ophthalmol* 1981; 65: 108–111.
2. McCulley JP, Dougherty JM, Deneau DG. Chronic Blepharitis: Classification and mechanisms. *Immunol Abstsr* 1981; 55–72.
3. McCulley JP, Dougherty JM, Deneau DG. Classification of chronic blepharitis. *Ophthalmology* 1982; 89: 1173–1180.
4. Dougherty JM, McCulley JP. Tear lysozyme measurements in chronic blepharitis. *Ann Ophthalmol* 1985; 17: 53–57.
5. Dougherty JM, McCulley JP, Meyer DR. Keratoconjunctivitis sicca and tear lysozyme in chronic blepharitis. In: Holley FJ, ed. The Preocular Tear Film. Lubbock, Texas: Dry Eye Institute, 1984. pp. 176–181.
6. Bowman RW, Dougherty JM, and McCulley JP. Chronic blepharitis and dry eyes. *Int Ophthalmol Clin* 1987; 27: 27–35.
7. Jester JV, Nicolaides N, Smith RE. Meibomian gland dysfunction. I. Keratin protein expression in normal human and rabbit meibomian glands. *Invest Ophthalmol Vis Sci* 1989; 30: 927–935.
8. Jester JV, Nicolaides N, Kiss-Palvolgy I, Smith RE. Meibomian gland dysfunction. II. The role of keratinization in a rabbit model of MGD. *Invest Ophthalmol Vis Sci* 1989; 30: 936–945.
9. Nicolaides N, Santos EC, Smith RE, Jester JV. Meibomian gland dysfunction. III. Meibomian gland lipids. *Invest Ophthalmol Vis Sci* 1989; 30: 946–951.
10. Bron AJ, Tiffany JM. The contribution of meibomian disease to dry eye. *Ocul Surf* 2004; 2: 149–165.
11. Foulks GN, Bron AJ. Meibomian gland dysfunction: a clinical scheme for description, diagnosis, classification, and grading. *Ocul Surf* 2003; 1: 107–126.
12. Driver PJ, Lemp MA. Meibomian gland dysfunction. *Surv Ophthalmol* 1996; 40: 343–367.
13. Dougherty JM, McCulley JP. Comparative bacteriology of chronic blepharitis. *Br J Ophthalmol* 1984; 68: 524–528.
14. McCulley JP, Dougherty JM. Bacterial aspects of chronic blepharitis. *Trans Ophthalmol Soc* UK 1986; 105: 314–318.
15. Kellum RE. Acne vulgarus: Studies in pathogenesis: Relative irritancy of free fatty acids from C2 to CM. *Arch Dermatol* 1968; 97: 722–726.
16. Shine WE, McCulley JP. Role of wax ester fatty alcohols in chronic blepharitis. *Invest Ophthalmol Vis Sci* 1993; 34: 3515–3521.
17. McCulley JP, Shine WE. Meibomian gland function and the tear lipid layer. *Ocul Surf* 2003; 1: 97–106.
18. Jackson WB. Blepharitis: current strategies for diagnosis and management. *Can J Ophthalmol* 2008; 43: 170–179.
19. Shine WE, McCulley JP. Polar lipids in human meibomian gland secretions. *Curr Eye Res* 2003; 26: 89–94.
20. Shine WE, McCulley JP. Keratoconjunctivitis sicca associated with meibomian secretion polar lipid abnormality. *Arch Ophthalmol* 1998; 116: 849–852.
21. Hom MM, Martinson JR, Knapp LL, Paugh JR. Prevalence of meibomian gland dysfunction. *Optom Vis Sci* 1990; 67: 710–712.
22. Ong BL, Larake JR. Meibomian gland dysfunction: some clinical, biochemical and physical observations. *Ophthalmic Physiol Opt* 1990; 10: 144–148.
23. Ong BL. Relationship between contact lens wear and meibomian gland dysfunction. *Optom Vis Sci* 1996; 73: 208–210.
24. Romero JM, Biser SA, Perry HD, Levinson DH, Doshi SJ, Terraciano A, Donnenfeld ED. Conservative treatment of meibomian gland dysfunction. *Eye Contact Lens* 2004; 30: 14–19.
25. Olson MC, Korb DR, Greiner JV. Increase in tear film lipid layer thickness following treatment with warm compresses in patients with meibomian gland dysfunction. *Eye Contact Lens* 2003; 29: 96–99.
26. Frucht-Pery J, Sagi E, Hemo I, Ever-Hadani P. Efficacy of doxycycline and tetracyclines in ocular rosacea. *Am J Ophthalmol* 1993; 116: 88–92.
27. Dougherty JM, McCulley JP, Silvany RE, Meyer DR. The role of tetracycline in chronic blepharitis. Inhibition of lipase production in staphylococci. *Invest Ophthalmol Vis Sci* 1991; 32: 2970–2975.
28. Pinna A, Piccinini P, Carta F. Effect of oral linoleic and γ-linolenic acid on meibomian gland dysfunction. *Cornea* 2007; 26: 260–264.
29. Mascai MS. The role of omega-3 dietary supplementation in blepharitis and meibomian gland dysfunction. *Trans Am Ophthalmol Soc* 2008; 106: 336–356.
30. Perry HD, Doshi-Carnevale S, Donnenfeld ED, Solomon R, Biser SA, Bloom AH. Efficacy of commercially available topical cyclosporine A 0.05% in the treatment of meibomian gland dysfunction. *Cornea* 2006; 25: 71–175.
31. Rubin M, Rao SN. Efficacy of topical Cyclosporin 0.05% in the treatment of posterior blepharitis. *J Ocul Pharmacol Ther* 2006: 22: 47–53.
32. Fiedlaender MH, Protzko E. Clinical development of 1% azithromycin in durasite, a topical azalide anti-infective for ocular surface therapy. *Clin Ophthalmol* 2007; 1: 3–10.
33. Amar T, Caillaud T, Elena PP. Ocular pharmacokinetic study following single and multiple azithromycin administrations in pigmented rabbits. *Curr Eye Res* 2008; 33: 149–158.
34. Ianaro A, Ialenti A, Maffia P, Sautebin L, Rombolà L, Carnuccio R, Iuvone T et al. Anti-inflammatory activity of macrolide antibiotics. *J Pharmacol Exp Ther* 2000; 292: 156–163.
35. Scaglione F, Rossoni G. Comparative anti-inflammatory effects of roxithromycin, azithromycin and clarithromycin. *J Antimicrob Chemother* 1998; 41: 47–50.
36. Aghai ZH, Kode A, Saslow JG, Nakhla T, Farhath S, Stahl GE, Eydelman R et al. Azithromycin suppresses activation of nuclear factor-kappa B and synthesis of pro-inflammatory cytokines in tracheal aspirate cells from premature infants. *Pediatr Res* 2007; 62: 483–488.
37. Li DQ, Zhou N, Zhang L, Ma P, Pflugfelder SC. Azithromycin suppresses Zymosan-

induced production of pro-inflammatory mediators by human corneal epithelial cells. *Invest Ophthalmol Vis Sci* 2010 Jun 10. [Epub ahead of print]
38. Luchs J. Efficacy of topical azithromycin ophthalmic solution 1% in the treatment of posterior blepharitis. *Adv Ther* 2008; 25: 858–870.
39. John T, Shah AA. Use of azithromycin ophthalmic solution in the treatment of chronic mixed anterior blepharitis. *Ann Ophthalmol* (Skokie) 2008; 40: 68–74.
40. Perry HD, Solomon R, Donnenfeld ED, Perry AR, Wottpenn JR, Greenman HE, Savage HE. Evaluation of topical cyclosporine for the treatment of dry eye disease. *Arch Ophthalmol* 2008; 126: 1046–1050.
41. Schiffman RM, Christianson MD, Jacobsen G, Hirsch JD, Reis BL. Reliability and validity of the Ocular Surface Disease Index. *Arch Ophthalmol* 2000; 118: 615–621.
42. Nicolaides N, Kaitaranta JK, Rowdah TN, Macy JI, Boswell FM, Smith RE. Meibomian gland studies: Comparison of steer and human lipids. *Invest Ophthalmol Vis Sci* 1981; 20: 522–536.
43. Shine WE, McCulley JP. Keratoconjunctivitis sicca associated with meibomian secretion polar lipid abnormality. *Arch Ophthalmol* 1998; 116: 849–852.
44. McCulley JP, Shine WE. Changing concepts in the diagnosis and management of blepharitis. *Cornea* 2000; 19: 650–658.
45. Zengin N, Tol H, Gunduz K, Okudan S, Balevi S, Endogru H. Meibomian gland dysfunction and tear film abnormalities in rosacea. *Cornea* 1995; 14: 144–146.
46. Protzko E, Bowman L, Abelson M, Shapiro A, AzaSite Clinical Study Group. Phase 3 safety comparisons for 1.0% azithromycin in polymeric mucoadhesive eye drops versus 0.3% tobramycin eye drops for bacterial conjunctivitis. *Invest Ophthalmol Vis Sci* 2007; 48: 3425–3429.
47. Lemp MA, Nichols KK. Blepharitis in the United States 2009: a survey-based perspective on prevalence and treatment. *Ocul Surf* 2009 April 7; (2 Suppl): S1–S14.

Corresponding author:
Dr Dominick L Opitz
Illinois College of Optometry
3241 S, Michigan Avenue
Chicago IL 60616
USA
E-mail: dopitz@ico.edu