

# Use of Azithromycin Ophthalmic Solution in the Treatment of Chronic Mixed Anterior Blepharitis

THOMAS JOHN, MD,  
AMI A. SHAH, BS MBB

## ABSTRACT

We tested the efficacy of azithromycin ophthalmic solution for the treatment of chronic mixed anterior blepharitis. The findings suggest that patients with chronic mixed anterior blepharitis can be more effectively treated with azithromycin ophthalmic solution than erythromycin ophthalmic ointment. Patients treated with azithromycin ophthalmic solution show an extraordinary clinical response with shorter treatment duration.

## INTRODUCTION

Blepharitis refers to chronic inflammation of the eyelid margins (Figs. 1 and 2). It is often the source for ocular discomfort, redness, and tearing. Patients usually complain of irritation, burning, tearing, itching, foreign-body sand-like sensation, and redness; symptoms that are associated with dry eye (1–4). In addition, there may be misdirection and loss of eyelashes (5). It can be classified into distinct groups of: staphylococcal, seborrhoeic, seborrhoeic with staphylococcal superinfection (mixed), meibomian seborrhea, and meibomian keratoconjunctivitis (MKC) (1–4). Blepharitis can also be classified as anterior or posterior blepharitis. Anterior blepharitis is associated with staphylococcal, seborrhoeic, or mixed infections, while posterior blepharitis is associated with meibomian gland dysfunction (3). This study focused on eyes with clinical anterior blepharitis.

The most commonly isolated organisms in chronic blepharitis include: *Staphylococcus aureus*, coagulase-negative *Staphylococcus* spp., *Corynebacterium* spp., and *Propionibacterium acnes* (1, 4, 6–8). Chronic blepharitis is also associated with dry eyes, facial and ocular rosacea, and chalazia (3, 6). In particular, tear sufficient (evaporative) dry eyes due to a deficiency in the lipid layer of the tear film. The deficiency of the lipid layer is caused by a blockage of meibomian glands and leads to increased evaporation that is not followed by increased tear production by the lacrimal glands (9–11). Ocular rosacea in children has been shown to lead to corneal changes such as pannus, neovascularization,

## REPRINTS

Thomas John, MD, 16532 S. Oak Park Avenue, Tinley Park, IL 60477 E-mail: tjcornea@gmail.com

Dr. John is from the Department of Ophthalmology, Loyola University at Chicago, Maywood, IL, Thomas John Vision Institute, Tinley Park and Oak Lawn, IL, and the Chicago Cornea Research Center, Tinley Park, IL, USA. Dr. Shah is from The Chicago Medical School at Rosalind Franklin University of Medicine and Science, North Chicago, IL, USA.

## DISCLOSURE

Thomas John is on the speaker bureau of Inspire pharmaceuticals. Ami Shah has stated that she does not have a significant financial interest or other relationship with any product manufacturer or provider of services discussed in this article. Direct application of azithromycin ophthalmic solution to the eyelids is an off-label use of a FDA-approved medication. This is an independent study that was not funded by any corporate entity.

Submitted for publication: 05/09/08. Accepted: 06/19/08.

Annals of Ophthalmology, vol. 40, no. 2, Summer 2008

© Copyright 2008 by ASCMSO

All rights of any nature whatsoever reserved.

infiltrate, punctate epithelopathy, phlyctenules, and corneal scarring (12). These corneal changes can lead to visual loss. There has also been significant association with sebaceous gland dysfunction, plugging and inflammation of the meibomian glands, and an unstable tear film (13–15). Chronic blepharitis is known to predispose to external punctal stenosis perhaps via inflammatory changes (16).

Parasitic infection due to *Demodex* has been implicated in facial and ocular rosacea and is also a common cause of blepharitis. Treatments recommended for ocular rosacea include oral tetracycline and topical antibiotics, with or without the judicious use of topical steroids (17–18).

Current treatments for chronic blepharitis include: warm compresses, lid scrubs with baby shampoo, anti-inflammatories with omega 3 fatty acids, and antibiotics (erythromycin ophthalmic ointment, oral tetracyclines), steroid-antibiotic combinations, and more recently, the use of topical cyclosporin drops (2, 4, 8, 19–21). The role of tetracyclines does not include eradicating bacterial organisms but rather, inhibiting lipase production (especially in cases of MKC) (13, 22). This effect is significant when blepharitis is due to *P. acnes* or *S. epidermidis* but does not affect *S. aureus* blepharitis (13). Although vancomycin can be used to treat corneal infections caused by *S. aureus*, the potential ocular surface toxicity of vancomycin, keeps it from being commonly used to treat chronic blepharitis (23).

Azithromycin topical solution (AzaSite®; Inspire Pharmaceuticals, Durham, NC) is a newly approved drug (April 2007) indicated for the treatment of bacterial conjunctivitis caused by the following: *CDC coryneform group G*, *Haemophilus influenzae*, *Staphylococcus aureus*, *Streptococcus mitis* group, and *Streptococcus pneumoniae* (24). Azithromycin is a broad spectrum antibiotic used to treat bacterial infections of the throat, ears and skin, as well as tonsillitis, laryngitis, bronchitis, pneumonia, sinusitis, and certain sexually transmitted diseases (STDs). Unlike most other antibiotics, azithromycin remains in the body tissues for extended periods of time. Azithromycin was discovered in 1980, and it has been available as an oral suspension, tablet, or intravenous injection to treat various systemic infections. It had limitations and several formulation challenges as an ophthalmic drug for topical use, especially due to its instability in aqueous solutions and heat instability. However, combined with DuraSite® drug delivery technology, azithromycin has been successfully formulated for topical treatment of ocular infections, especially bacterial conjunctivitis (24). DuraSite® is a polymer of cross-linked polyacrylic acid that in the aqueous environment of the eye, expands its particles,

allowing for an increased viscosity (24). This results in the drug it is combined with, namely azithromycin, to remain stable and at therapeutic levels for at least 24 hours in the aqueous environment (24). This offers the advantages of longer drug residence time, less frequent dosing, and greater patient compliance.

In this present study, the efficacy of azithromycin ophthalmic solution (1%) in the treatment of chronic mixed anterior blepharitis was evaluated.

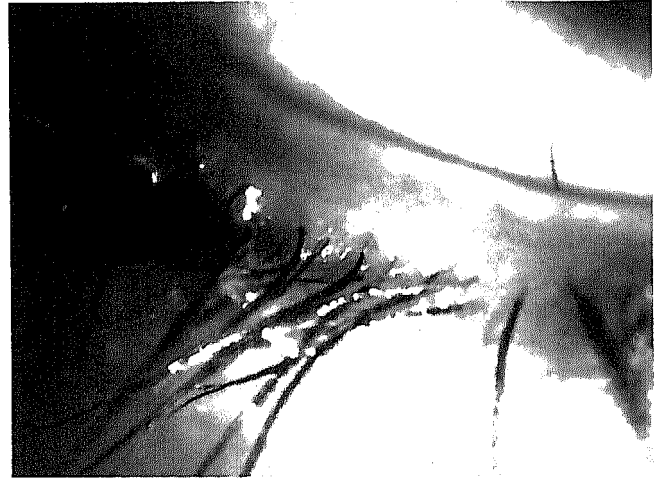


Fig. 1. Slit-lamp photograph showing anterior blepharitis with matting of the eyelashes, collarettes at the base of lashes and misdirection of lashes.

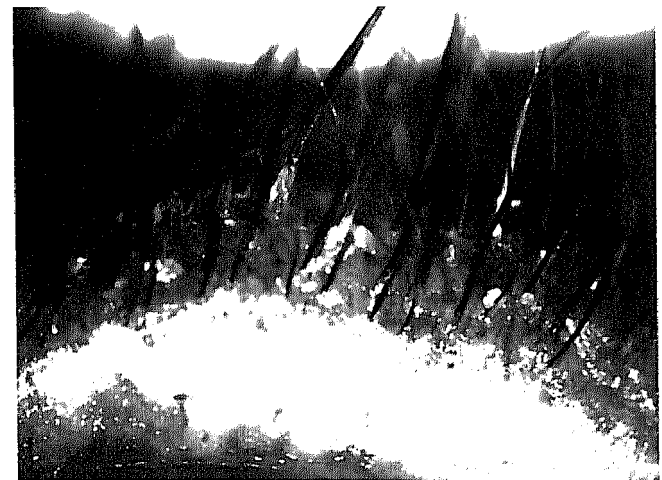


Fig. 2. High-power slit-lamp view of anterior blepharitis showing prominent collarettes, crusting of lashes, increased vascularity, ulceration and thickening of the eyelid margins.

## MATERIALS AND METHODS

This was a prospective, open-label study involving, 150 eyes of 75 patients with clinical chronic mixed anterior blepharitis. The average age of patients was 65.7 years ±

**TABLE 1**

**Patients treated with azithromycin 1% ophthalmic solution**

No	Treatment Date	Blepharitis Grade	KCS	AC Rosacea	No	Treatment Date	Blepharitis Grade	KCS	AC Rosacea	No	Treatment Date	Blepharitis Grade	KCS	AC Rosacea
1	02/19/08 03/11/08	3 2	N	N	24	10/16/07 11/05/07 12/11/07	3 0.5 0	N	N	47	11/06/07 11/27/07	3 0	Y	N
2	02/28/08 03/06/08	2 0	Y	N	25	02/01/08 02/22/08	2 0	Y	N	48	10/29/07 11/26/07 12/17/07	2 0.5 0	N	N
3	11/06/07 12/21/07 01/15/08	1 1 0	Y	Y	26	11/20/07 12/11/07	2 0	N	N	49	12/11/07 01/15/08	2 0	Y	N
4	10/19/07 11/20/07	2 0	N	N	27	11/19/07 12/10/07	3 0	Y	N	50	11/16/07 12/07/07	2 0	Y	N
5	02/12/08 03/04/08	3 0	N	N	28	10/23/07 11/27/07	2 0	Y	N	51	2/22/08 03/10/08	3 0	Y	N
6	01/14/08 02/18/08	2 0	Y	N	29	02/19/08 03/11/08	2 0	Y	N	52	10/16/07 11/16/07	3 0	Y	N
7	10/23/07 11/02/07	2 0	Y	N	30	12/21/07 02/01/08 03/07/08	2 1 0	Y	N	53	12/31/07 01/29/08	2 0	Y	N
8	12/17/07 01/14/08	1 0	Y	N	31	01/28/08 02/18/08	2 0	Y	N	54	01/18/08 02/19/08 03/04/08	2 2 0	Y	N
9	01/15/08 02/12/08	2 0	Y	N	32	01/28/08 03/03/08	2 0	Y	N	55	10/22/07 12/27/07	2 0	Y	N
10	02/19/08 03/11/08	2 0	Y	N	33	11/27/07 12/14/07	1 0	Y	N	56	02/18/08 02/28/08	2 0	Y	N
11	11/06/07 12/15/07	2 0	Y	N	34	02/11/08 03/03/08	2 0	Y	N	57	11/27/07 12/21/07	1 0	Y	N
12	10/16/07 11/20/07	3 0	Y	N	35	11/27/07 12/18/07	1 0	Y	N	58	02/18/08 03/10/08	1 0	Y	N
13	11/06/07 11/20/07	2 0	N	N	36	11/29/07 12/03/07 12/24/07	4 1 0	Y	N	59	12/21/07 02/22/08	2 0	Y	N
14	12/10/07 01/28/08	2 0	Y	N	37	01/25/07 02/07/08	1 0	Y	N	60	11/27/08 12/18/07	2 0	Y	N
15	11/27/07 12/18/07	2 0	Y	N	38	12/13/07 12/18/07	2 0	Y	N	61	02/08/08 02/28/08	3 0	Y	N
16	01/31/08 02/25/08	3 0	Y	N	39	12/11/07 01/15/08	2 0	Y	N	62	12/03/07 01/14/08	2 0	Y	N
17	02/12/08 03/11/08	1 0	Y	Y	40	12/11/07 01/15/08	2 0	Y	N	63	10/15/07 11/5/07	3 0	Y	N
18	02/11/08 03/03/08	1 0	Y	N	41	02/07/08 02/22/08	1 0	Y	N	64	12/24/07 01/14/08	1 0	Y	N
19	01/17/08 02/12/08	2 0	Y	N	42	12/31/07 02/01/08	3 0	N	N	65	11/19/07 12/10/97	2 0	Y	N
20	12/18/07 01/15/08	2 0	N	N	43	11/27/07 02/19/08	3 0	Y	N	66	11/19/07 12/10/07	3 0	N	N
21	12/03/07 12/17/07 12/31/07	3 0.5 0	Y	N	44	11/26/07 12/17/07	2 0	Y	N	67	02/19/08 03/11/08	3 0	Y	N
22	01/14/08 02/18/08 03/10/08	3 1 0	Y	N	45	10/15/07 11/05/07	2 0	Y	N					
23	12/14/04 02/8/08	2 0	Y	N	46	01/28/08 03/03/08	3 0	Y	N					

TABLE 2				
Patients treated with erythromycin ophthalmic ointment				
No	Treatment Date	Blepharitis Grade	KCS	ACR
1	11/06/07 01/15/08	3 1	Y	N
2	10/02/07 11/06/07 11/27/07	2 1 0	Y	N
3	02/18/08 03/10/08	1 0	Y	N
4	10/02/07 11/06/07	2 1	Y	N
5	10/02/07 11/06/07 02/19/08	2 1 0	Y	N
6	12/14/07 01/15/08	2 1	Y	Y
7	12/18/07 01/15/08	2 0	Y	Y
8	12/14/07 02/08/08	2 0	Y	Y

TABLE 3				
Grading of chronic mixed anterior blepharitis (Any three criteria/ upper or lower lid). Patients with clinical resolution were graded 0				
Grade	Collarettes (Height in mm)	Ulcerations (Percentage of Lid Margin)	Matting	Erythema (Percentage of Lid Margin)
1 (Trace)	< 1	10	0	< 25
2 (Mild)	1	30	0-5	25-50
3 (Moderate)	2	50	6-10	50-75
4 (Severe)	> 2	> 50	> 10	> 75

1.86. There were 33 males and 42 females. These patients were evaluated and treated with azithromycin (67 patients, n = 134 eyes) or erythromycin (8 patients, n = 16) (Tables 1 and 2). Both eyes of each patient were treated with azithromycin ophthalmic solution or erythromycin ophthalmic ointment. Eight of the 75 patients (16 eyes) were treated with erythromycin topical treatment (Table 2). At the initial visit, all patients underwent a complete slit-lamp examination and the eyelids were evaluated. Lids were evaluated for lid closure and blink patterns, apposition of eyelids, lid inflammation, and changes or disorders of the lid margin. Blepharitis was

graded according to the following: presence of collarettes, ulcerations at the base of eyelashes, matting of eyelashes, and lid margin erythema. Grades of 1 to 4 were assigned as per Table 3. Patients were also documented whether keratoconjunctivitis sicca (KCS) and/or acne rosacea (ACR) was present. Patients were instructed to apply azithromycin ophthalmic solution on to their washed, clean index finger or to a clean applicator and then to apply the medication directly to the eyelids of both eyes, rather than using eye drops directly onto the ocular surface. Patients returned to clinic in 1-month intervals for slit-lamp examinations and reevaluation of the eyelids. Data was evaluated using the Student's t-test.

## RESULTS

At initial visit, the blepharitis grade of 150 eyes was  $2.15 \pm 0.67$  (Tables 1 and 2, Fig. 3). The total duration of treatment for azithromycin ophthalmic solution was  $1.17 \pm 0.49$  months with 66 of the 67 patients (132 eyes) showing complete recovery (represented as Grade 0 blepharitis). One patient did not show complete recovery at the completion of this study, but showed an improvement in the blepharitis (Grade 3 to Grade 2) after one month of treatment, and at two months, the blepharitis grade decreased from Grade 2 to Grade 1, and subsequently resolved. The total clinical resolution after four weeks was 98.5% for the Azithromycin treated group and 37.5% for the erythromycin treated group (Fig. 6), and at eight weeks, it was 98.5% for the Azithromycin treated group and 50% for the erythromycin treated group (Fig. 7). It was found that 87% of patients with chronic blepharitis were simultaneously found to have KCS and 7% had ACR (Figs. 4 and 5). In the eight patients treated with topical erythromycin ophthalmic ointment, it was seen that five of the patients (10 eyes) had unresolved blepharitis with inadequate clinical improvement after 1 month of treatment (Table 2). Duration of treatment for erythromycin was  $1.75 \pm 1.39$  months. Treatment with azithromycin ophthalmic solution also results in a faster rate of improvement as compared to treatment with erythromycin. Fifty percent (8 of 16 eyes) of patients treated with erythromycin required 8 weeks of treatment as compared to 1.5% (2 of 134 eyes) of patients treated with azithromycin ophthalmic solution. The average initial blepharitis grade of patients and the average blepharitis grade taken at 4 and 8 week intervals of treatment showed that patients treated with azithromycin ophthalmic solution had a better clinical response during a shorter treatment duration as compared to patients treated with erythromycin ophthalmic ointment. The results at 4-week treatment duration is

statistically significant ( $t = 2.31$ ,  $df = 73$ ,  $p = 0.0237$ ). Patients treated with azithromycin ophthalmic solution showed clinically significant improvement with approximately 1-month of treatment.

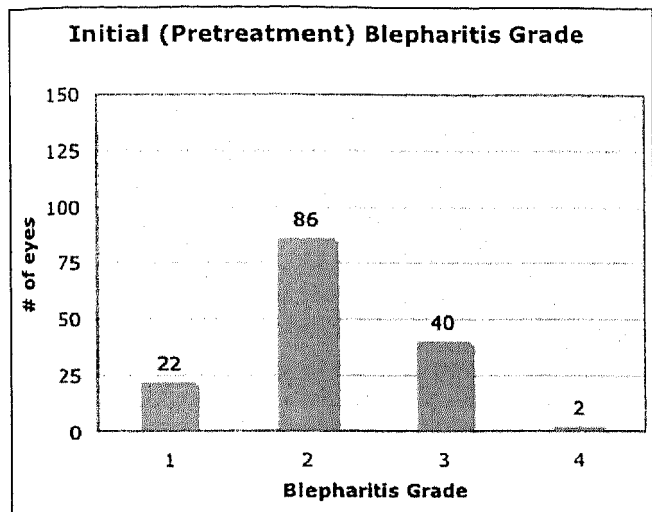


Fig. 3. Initial (Pretreatment) blepharitis grade in 150 eyes.

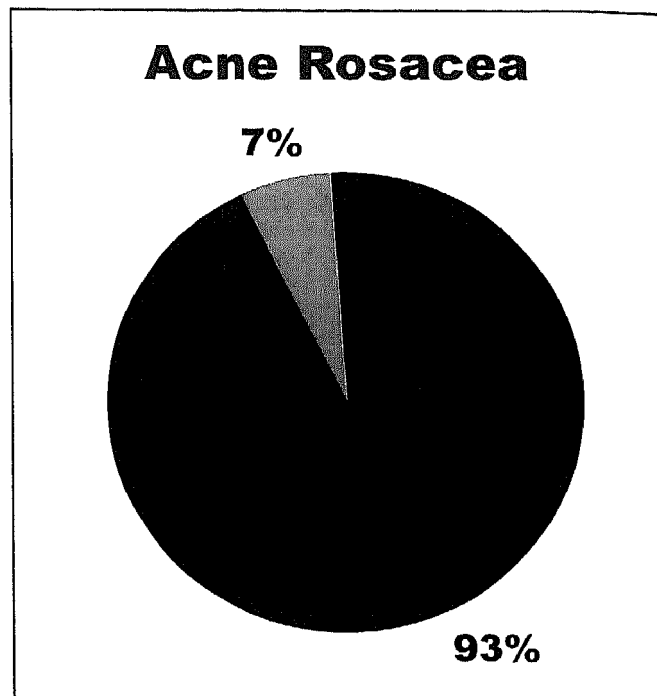


Fig. 5. The percent of patients in this study with acne rosacea.

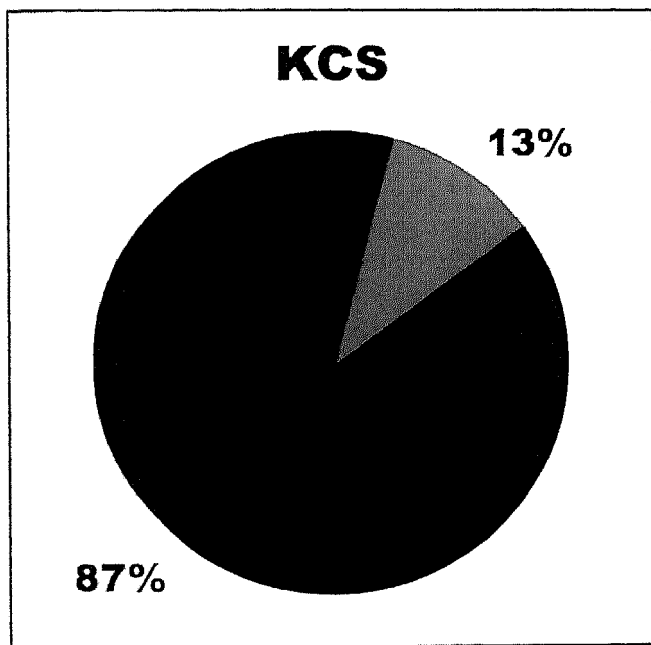


Fig. 4. The percent of patients in this study with keratoconjunctivitis sicca.

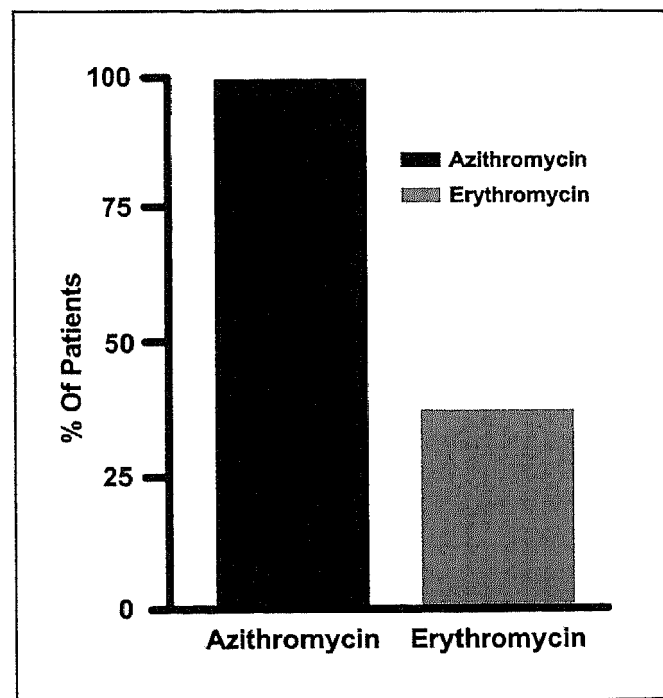


Fig. 6. The total clinical resolution after 4 weeks was 98.5% for the azithromycin treated group and 37.5% for the erythromycin treated group.

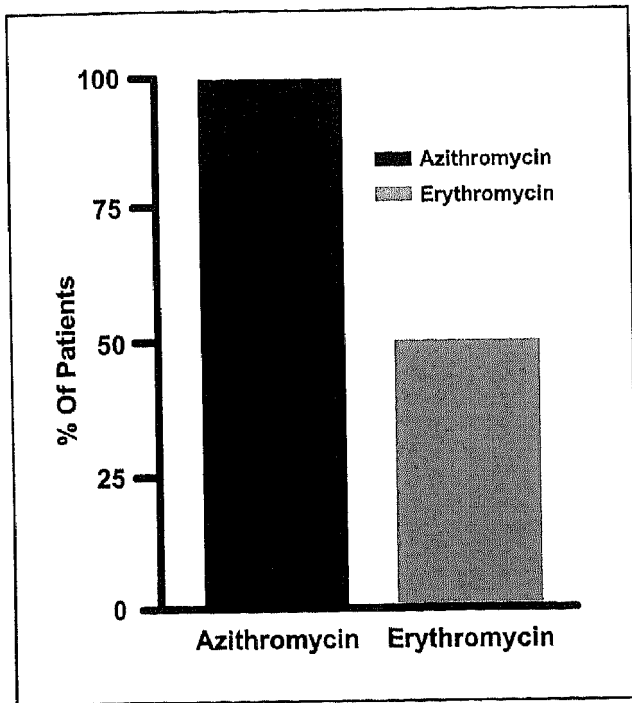


Fig. 7. The total clinical resolution after 8 weeks was 98.5% for the azithromycin treated group and 50% for the erythromycin treated group.

## DISCUSSION

Treatment of chronic mixed anterior blepharitis with azithromycin ophthalmic solution produced excellent results, especially in contrast to traditional treatment with erythromycin ophthalmic ointment. Of the patients treated with azithromycin, 98.5% showed complete resolution of the chronic anterior blepharitis after one or two month treatment regimens. This is an extraordinary clinical response as current treatment is usually not adequate, as it results in either unresolved blepharitis or frequent recurrence of the blepharitis. Mixed anterior blepharitis is a combination of seborrhoeic blepharitis with staphylococcal superinfection. Staphylococcal infection of the eyelids cause matted, hard scales on the eyelids and eyelid ulcerations that can be severe (2). With seborrhoeic infections deposits on the eyelids appear oily or greasy with no ulcerations (2). Additionally, there is an increased bacterial resistance to the current treatment modalities that are most commonly used for the treatment of blepharitis. The broad bacterial coverage of azithromycin ophthalmic solution is sufficient to treat the common bacterial organisms that cause chronic blepharitis.

Azithromycin is a member of the new generation macrolide antibiotics that have activity by binding to the 50S ribosomal subunit of bacteria and inhibiting RNA-dependent protein synthesis (25). Azithromycin has also

been shown to be very effective in treating *S. aureus* infections due to its high tissue penetration, and long elimination half-life, which enables it to maintain higher levels in tissue (26). Both azithromycin and erythromycin are macrolide antibiotics, however azithromycin is structurally different from erythromycin (26). As shown in this study, patients treated with azithromycin as compared to erythromycin demonstrated significant improvement with short treatment duration. In addition, due to the less frequent dosing of azithromycin, there was high patient compliance (100% patient compliance).

Meibomian gland dysfunction (MGD) has been associated with chronic blepharitis. On slit-lamp examination, meibomian glands may be evaluated for position, number, size, length, obstruction, and orifice condition. Normal glands are seen as yellow globular lines with small gray ring orifices on the posterior lid margin containing clear yellow lipid. When congested, meibomian glands appear as yellow globular lines with stenosed or closed orifices. Blepharitis, a lid margin disorder, is often classified with accompanying MGD (27). The preferred treatment for MGD is with oral tetracyclines. However, the present study was undertaken to evaluate the efficacy of azithromycin treatment alone, without other oral antibiotics such as tetracyclines, for chronic, mixed, anterior blepharitis.

Keratoconjunctivitis sicca (KCS) has previously been reported in 50% of patients with staphylococcal blepharitis (2). In this study, 87% of blepharitis patients had KCS. Whether, this increased association of KCS with blepharitis was due to the older age group of the patients evaluated within this study or due to the blepharitis alone is unknown. Previous study has shown an age-related association with dry eye syndrome with a possible explanation being a decrease in tear production (28). Given that the average age of patients in this study was  $65.7 \pm 1.86$  years, increased age could be a partial explanation of this increased association of KCS with chronic, mixed, anterior blepharitis.

Acne rosacea, a dermatologic condition of unknown etiology, results in hypertrophy and plugging of sebaceous glands without an increase in the excretion of sebum (27, 29). This condition can result in meibomian gland dysfunction by affecting the meibomian glands themselves, as these glands are modified sebaceous glands (27). This, in turn, may cause chronic blepharitis. This study included 7% of patients with acne rosacea, all of who benefited in their anterior mixed blepharitis from the topical azithromycin treatment.

Meibomian gland dysfunction and blepharitis have both been seen to have areas of hyperkeratinization

within the meibomian glands (30). This hyperkeratinization may interfere with gland function and cause obstruction; however, the exact relationship between hyperkeratinization and blepharitis remains unknown (30).

In summary, this is the first study showing the clinical efficacy of using azithromycin ophthalmic solution directly on the eyelids for the effective treatment of chronic, mixed, anterior blepharitis, with treatment times as short as four weeks.

## REFERENCES

- Dougherty JM, McCulley JP. Comparative bacteriology of chronic blepharitis. *Br J Ophthalmol* 1984;68:524-528.
- American Academy of Ophthalmology, Cornea/External Disease Panel; Preferred Practice Pattern, *Blepharitis*. 2003;1-17.
- Auw-Haedrich C, Reinhard T. Chronic Blepharitis: Diagnosis, Pathogenesis, and New Treatment Options. *Essentials in Ophthalmology: Cornea and External Eye Disease*. New York, NY: Springer Berlin Heidelberg. 2008; Ch. 10;185-199.
- Hussein N, Schwab IR, Ostler HB. Blepharitis. *Duane's Clinical Ophthalmology Vol. 4*. Philadelphia, PA: Lippincott Williams & Wilkins. 2005; Ch. 22:1-9
- Leibowitz HM. The Red Eye. *N Engl J Med* 2000;343:345-351.
- Baudouin C. The pathology of dry eye. *Surv Ophthalmol* 2001;45:211-220.
- Seal DV, McGill JI, Jacobs P, et al. Microbial and immunological investigations of chronic non-ulcerative blepharitis and meibomianitis. *Br J Ophthalmol* 1985;69:604-611.
- McCulley JP, Shine WE. Changing concepts in the diagnosis and management of blepharitis. *Cornea* 2000;19:650-658.
- Goto E, Endo K, Suzuki A, et al. Tear evaporation dynamics in normal subjects and subjects with obstructive meibomian gland dysfunction. *Invest Ophthalmol Vis Sci* 2003;44:533-539.
- McCulley JP, Shine WE. The lipid layer of tears: dependent on meibomian gland function. *Exp Eye Res* 2004;78:361-365.
- Yokoi N, Mossa F, Tiffany JM, et al. Assessment of meibomian gland function in dry eye using meibometry. *Arch Ophthalmol* 1999;117:723-729.
- Donaldson KE, Karp CL, Dunbar MT. External eye, cornea, and refractive surgery - evaluation and treatment of children with ocular rosacea. *Cornea* 2007;27:42-46.
- Dougherty JM, McCulley JP, Silvany RE, et al. The role of tetracycline in chronic blepharitis. *Invest Ophthalmol Vis Sci* 1991;32:2970-2975.
- Cohen, EJ. Punctal occlusion. *Arch Ophthalmol* 1999;117:389-390.
- Mathers WD, Choi D. Cluster analysis of patients with ocular surface disease, blepharitis, and dry eye. *Arch Ophthalmol* 2004;122:1700-1704.
- Kashkoui MB, Beigi B, Murphy R, et al. Acquired external punctal stenosis: etiology and associated findings. *Am J Ophthalmol* 2003;136:1079-1084.
- Kheirkhah A, Casas V, Li W, et al. Corneal manifestations of ocular *Demodex* infestation. *Am J Ophthalmol* 2007;143:743-749.
- Arici MK, Sumer Z, Toker MI, et al. The prevalence of *Demodex folliculorum* in blepharitis patients and the normal population. *Ophthalm Epidemiol* 2005;12:287-290.
- Goto E, Takano Y, Mori A, et al. Treatment of non-inflamed obstructive meibomian gland dysfunction by an infrared warm compression device. *Br J Ophthalmol* 2002;86:1403-1207.
- Shine WE, McCulley JP. The role of cholesterol in chronic blepharitis. *Invest Ophthalmol Vis Sci* 1991;32:2272-2280
- Rubin M, Rao SN. Efficacy of topical cyclosporin 0.05% in the treatment of posterior blepharitis. *J Ocul Pharmacol Ther* 2006;22:47-53.
- Dougherty JM, McCulley JP. Bacterial lipases and chronic blepharitis. *Invest Ophthalmol Vis Sci* 1986;27:486-491.
- Romanowski EG, Mah FS, Yates KA, et al. The successful treatment of gatifloxacin-resistant *Staphylococcus aureus* keratitis with Zymar® (Gatifloxacin 0.3%) in a NZW rabbit model. *Am J Ophthalmol* 2005;139:867-877.
- InSpire Pharmaceuticals. AzaSite package insert. Durham, NC. 2007
- Champney WS, Burdine R. Macrolide Antibiotics inhibit 50S ribosomal subunit assembly in *Bacillus subtilis* and *Staphylococcus aureus*. *Antimicrob Agents Chemotherapy* 1995;39:2141-2144.
- Girard AE, Girard D, English AR, et al. Pharmacokinetic and in vivo studies with azithromycin (CP-62,993), a new macrolide with an extended half-life and excellent tissue distribution. *Antimicrob Agents Chemotherapy* 1987;31:1948-1954.
- Schaumberg DA, Sullivan DA, Dana MR. The epidemiology of dry eye syndrome. *Adv Exp Med Biol* 2002;506:989-998.
- Driver PJ, Lemp MA. Meibomian gland dysfunction. *Surv Ophthalmol* 1995;40:343-367.
- Ghanem VC, Mehra N, Wong S, et al. The prevalence of ocular signs in acne rosacea. *Cornea* 2003;22:230-233.
- Jester JV, Nicolaidis N, Kiss-Palvolgyi I, et al. Meibomian gland dysfunction. *Invest Ophthalmol Vis Sci* 1989;30:936-945.