



Systematic review and meta-analysis of treating meibomian gland dysfunction with azithromycin

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Abstract

To systematically review studies of managing meibomian gland dysfunction (MGD) with azithromycin and pool clinical outcomes to show its effectiveness. Eligible studies were retrieved from five main electronic databases. Symptom score was the primary outcome, while clinical signs and objective measurements were secondary outcomes. Pooled rates for adverse events were also calculated. Improvements in each outcome after administering either oral azithromycin (OA) or topical azithromycin (TA) were pooled and measured by standard mean difference (SMD) to show the overall effectiveness. Then the effectiveness was sub-grouped by TA and OA. In addition, pooled outcomes after administering TA and oral doxycycline (OD) were compared with assess their effectiveness. Finally, 18 eligible studies were included. The overall pooled symptom scores were significantly reduced after administering both TA and OA [$P < 0.0001$; SMD = 1.54 (95% CI: 1.15–1.92)]. Similarly, the overall combined eyelid signs, plugging of the meibomian gland, meibum quality, and tear secretion were also distinctly improved. However, significant improvements for tear break-up time (TBUT) and corneal staining (CS) were achieved by TA (TBUT: $P = 0.02$; CS: $P = 0.02$) but not by OA (TBUT: $P = 0.08$; CS: $P = 0.14$). The pooled adverse event rates for TA and OA were 25% and 7%, respectively. Moreover, TA was comparable to OD to treat MGD regarding symptom score, TBUT and tear secretion. This study showed that MGD could be treated effectively with oral or topical azithromycin by improving symptoms, clinical signs, and stabilization of tear film. Topical azithromycin seemed to be superior over oral azithromycin or doxycycline in improving the quality of tear film in the short term.

Introduction

Meibomian gland dysfunction (MGD) is a very common ocular surface disease with a prevalence of 39–50% and almost encountered every day by ophthalmologists in their outpatient departments [1]. The disease is a chronic and diffuse abnormality of the meibomian gland that is always accompanied by subsequent blepharitis, chalazion, and meibomitis and is the most common cause for evaporative dry eye syndrome [2]. People who suffer from acne rosacea

or seborrheic dermatitis or psoriasis are more prone to have MGD than the general population [3]. Complicated pathogenesis of the disease combined with the cutaneous conditions makes it hard to manage, while the current means of therapy are limited [4].

To achieve better therapeutic effects, combined means are always employed to treat the disease because both inflammatory and bacterial elements are involved in the development of MGD [5]. To date, eyelid hygiene, lid massage, warm compresses, artificial tears, and topical antibiotics are routine ways to treat the disease [4]. In addition, topical steroids and/or immunosuppressive agents (e.g., cyclosporine A, Cs A) have been used in some cases and gained satisfactory outcomes, but the complications from steroids and high cost of Cs A cannot be ignored for long-term use [6, 7]. Considering the pathogenesis of MGD, medications that have dual effects targeting the two elements should be the optimal choice for treatment.

Macrolide antibiotics, which have dual effects, have been indicated to be effective in treating MGD and have been

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the traditional systemic management for acne rosacea and posterior blepharitis, but the severe side effects of first-generation macrolides limit their clinical use [8]. Compared with former macrolides, azithromycin is a semi-synthetic macrolide antibiotic of the second generation, which is characterized by a long half-life, good intraocular penetration, and broad antibacterial scope [9–11]. Previous studies have verified prolonged high-level ocular concentrations could be achieved after administering either oral azithromycin (OA) or topical azithromycin (TA); even after discontinuing the medication, relatively high concentrations still can be maintained in the conjunctiva [8, 9]. Based on these advantages, azithromycin, either topical, or oral formulations, has been employed to treat MGD in recent years. Although the efficacy of treating MGD with azithromycin has been testified in several clinical studies, contrary results were found when comparing some outcomes (e.g., tear secretion, corneal staining, and Schirmer test) among these studies [1, 4, 8, 12–26]. In addition, comparisons of managing MGD with different azithromycin formulations and the effectiveness between azithromycin and other macrolides are still not confirmative due to the small sample sizes of the studies. Thus, pooling the data of the current studies by means of meta-analysis seems to be an ideal way to draw relatively reliable conclusions.

The aim of this study is to systematically review the clinical trials on treating MGD with either TA or OA and combine the outcomes by pooling data regarding symptom scores, clinical signs, and objective measurements. In addition, the effectiveness of managing MGD between TA and oral doxycycline (OD) will be compared.

Materials and methods

Strategy for literature retrieval

Two independent reviewers searched five electronic databases, PUBMED, EMBASE, OVID Medline, the Cochrane Library, and ClinicalTrials.gov, to retrieve literature on treating MGD with azithromycin. Synonyms for MGD, such as posterior blepharitis, chronic blepharitis, meibomianitis, meibomitis, and ocular rosacea, were also used to expand the search scope, although these terms seem not to be interchangeable [4]. Moreover, alternative terms or acronyms of azithromycin (e.g., macrolide antibiotic, AMZ, and AZI) were employed to avoid missing any related citations. After database searching, the two reviewers also indexed the references of the retrieved literature manually in order to find other related literature or conference proceedings. Finally, the reviewers compared their search results and solved discrepancies with discussion.

Study selection

The two independent reviewers selected target literature mainly based on participants (patients with MGD) and interventions (oral and/or topical azithromycin). Briefly, they excluded obvious unrelated literature by scanning titles. Then, eligible literature was selected through browsing abstracts and full-text versions of articles. The reviewers compared and discussed the selected results until a consensus was achieved.

Studies, participants, and interventions

All studies about treating MGD with azithromycin were included without considering what the study design or azithromycin formulation was. Patients with MGD combined with posterior blepharitis, ocular rosacea, or seborrheic dermatitis were the participants. According to the definition of MGD proposed by the international workshop, the disease was defined as a diffuse and chronic abnormality of the meibomian gland and characterized by terminal duct obstruction and/or qualitative or quantitative changes in meibum [2]. Patients <18 years or women of child-bearing age or who were breastfeeding were excluded due to the possible side effects of azithromycin.

Clinical outcomes

Improvement in symptom score at the end of follow-up was chosen as the primary outcome in the present study because most patients with MGD complain of symptoms linked to the ocular surface which affect their daily life severely, including foreign body sensation, ocular itching, eye redness, dry eye intolerance, etc. In addition, clinical signs that occurred frequently and objective measurements were set as the secondary outcomes. Clinical signs included eyelid signs (lid debris, lid swelling, and lid redness), plugging of the meibomian gland, meibum quality, and conjunctival injection. Objective measurements encompassed in this study were corneal staining, tear break-up time (TBUT), lissamine green staining, and tear secretion (Schirmer test I/II). In addition, adverse events were also recorded.

Data extraction and management

Study characteristics of each eligible study, including study design, region, sample size, demographics of the participants (age and gender ratio), interventions (formulation, dose, frequency, and duration), supplemental treatments, follow-up, and the clinical outcomes were all extracted and managed by the two reviewers independently. The extracted data were compared between the reviewers, and discrepancies were solved by discussion or by consulting a third reviewer.

Study quality assessment

The included studies were assessed by a 14-item checklist (<http://links.lww.com/ICO/A265>) developed by the Review Body for Interventional Procedures. The checklist could be used for evaluating either prospective or retrospective studies, and these 14 items cover the main elements of an interventional study. Each item is an assessment question that could be answered by three options: “Yes” (Y), “No” (N), and “Unclear” (U). One study could be deemed as high-quality when at least 8–9 “Yes” responses were obtained. According to the checklist, important prognostic factors (Item 5) defined in this study included participant gender and age, disease severity, combined conditions (e.g., posterior blepharitis, rosacea, and seborrheic dermatitis), disease course and previous treatments (e.g., lid hygiene, lid massage or topical administrations), and important outcomes (Item 11) were symptom scores, eyelid signs and/or one of the objective measurements. Moreover, a long follow-up period (Item 12) was defined as >1 month.

Effect size and statistical analyses

In this study, all the statistical analyses, including random-effects model and fixed-effects model, were performed by using Stata 14.0 (Stata Corp LLC, College Station, TX, USA). The outcomes were assessed by standard mean difference (SMD) rather than mean difference (MD) for reducing the heterogeneity generated from different grading systems adopted in each study. Improvements in each outcome after administering either OA or TA were pooled together to evaluate the overall effectiveness. Then, the effectiveness for some important outcomes (e.g., symptom score, TBUT, and corneal staining) was sub-grouped by TA and OA to demonstrate the influences of the different formulations on the effectiveness. To compare the effectiveness between TA and OD, the outcomes extracted from the comparative studies were combined. In addition, occurrence rates of adverse events for either TA or OA were calculated, respectively. All the effect size values were expressed as a mean and 95% confidence interval (CI). When distinct heterogeneity (P value for Chi^2 test <0.1 or $I^2 > 50\%$) existed, the random-effects model was used, but when distinct heterogeneity was not present, the fixed-effects model was employed. $P < 0.05$ was considered as the significant threshold.

Results

Study selection

Figure 1 shows the diagram of screening eligible studies. A total of 169 records were harvested after searching the

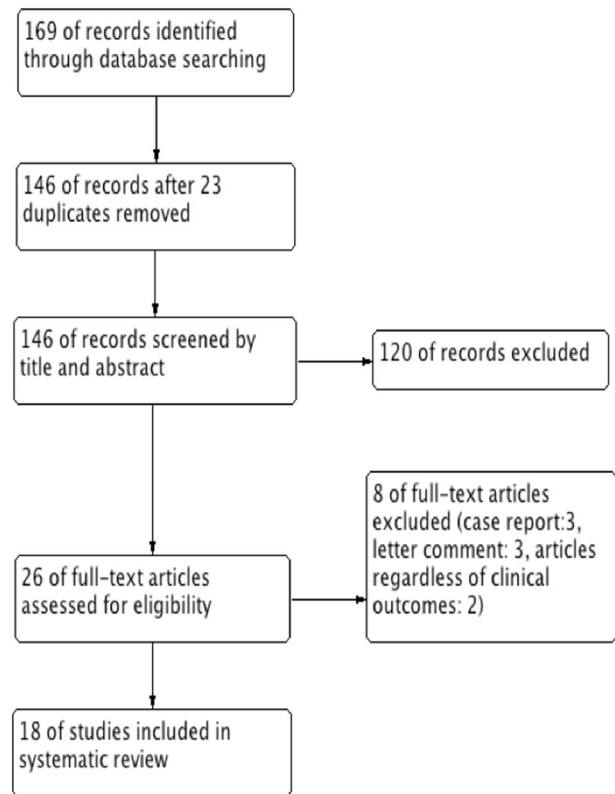


Fig. 1 Flow diagram showing study inclusion and exclusion. Eighteen eligible studies were selected for systematic review and meta-analysis.

databases and indexing the references of the searched literature. After 23 duplicates were removed, 146 records were screened by browsing titles and abstracts. Afterward, 26 records remained. Then, the remaining records were evaluated by their full-text versions, and 18 final studies were included for systematic review and meta-analysis.

Characteristics of included studies

Table 1 presents the characteristics of the included studies. The publication year of these studies spanned from 2008 to 2018. The regions covered nine countries with different races. Among the 18 studies, seven studies (38.9%) were random clinical trials (RCTs), while the others (61.1%) were non-randomized studies (seven were prospective studies and four were retrospective studies). Referring to the presence of a control group, nine (50.0%) were non-comparative studies; the others (50.0%) were comparative studies, including topical azithromycin versus oral doxycycline/azithromycin ($n = 5$, 27.8%), oral azithromycin versus oral doxycycline ($n = 2$, 11.1%), and topical azithromycin versus warm compress or placebo ($n = 2$, 11.1%). All the patients in the 18 studies suffered from MGD with or without other combined conditions (posterior blepharitis and acne rosacea), but the severity of

Table 1 Characteristics of the included studies.

Author	Year	Region	Study design	No. participant group	Combined condition	F/M	Age (mean ± SD)	Intervention	Dose/frequency/duration	Supplemental treatment	Follow-up
Oral Azithromycin (OA)											
Bakar et al.	2009	Turkey	PS	n = 18	OR	12/6	51.39 ± 15.70	OA	500 mg × 3 days, then weekly for 4 weeks	None	4 weeks
Igami et al.	2010	Brazil	PS	n = 13	PB	7/6	53.15 ± 13.18	OA	500 mg × 3 days in 3 cycles with 7-day intervals	LH + AT	1 month
Greene et al.	2013	USA	PS	n = 32	Meibomitis	19/13	60	OA	1 g/week × 3 weeks	NA	5.6 weeks
Al-Hity et al.	2015	UK	RS	n = 11	NA	4/7	51.39 ± 15.70	OA	500 mg × 3 days	AT + TS + LH	2–3 months
*Yildiz et al.	2018	Turkey	RCT	n = 19	PB	7/8	59.33 ± 6.78	OA	(500 mg for 1 day, 250 mg for 4 days) × 3 cycles	WLC	5 weeks
Topical Azithromycin (TA)											
Haque et al.	2010	USA	PS	n = 26	CB	17/9	64.2 ± 11.58	TA	1% ZAI bid for 2 days, qn for 1 month	None	2 months
Opitz et al.	2011	USA	PS	n = 26	PB	12/14	52.5	TA	1% AZI bid × 2 days, then qn for 1 month	AT	1 month
Doan et al.	2013	France	RS	n = 16	OR & BKC	10/6	9.3 ± 4.0	TA	1.5% AZI tid × 2 months, bid × 2 months, qd × 2 months	NA	11 months
Lazreg et al.	2014	Algeria	PS	n = 85	NA	NA	1.5–16	TA	ZAI bid × 5 days repeated each month for 3 months	TS + LH	3 months
Balci et al.	2017	Turkey	RS	n = 35	NA	17/18	40.5 ± 13.2	TA	1.5% azithromycin bid × 2 days, then qn for 1 month	LH	3 months
*Yildiz et al.	2018	Turkey	RCT	n = 15	PB	6/9	57.73 ± 13.19	TA	1.5% azithromycin bid × 3 days, then qd for 1 month	WLC	5 weeks
Topical Azithromycin (TA) VS Oral doxycycline (OD)											
Mantelli et al.	2013	Italy	RS	TA (n = 16) OD (n = 12) AT (n = 9)	OR	21/16	46.5 ± 9.5	TA OD AT	1.5% ZAI bid × 6 days 100 mg for 1 month Artificial tears	LH	3 months
Foulks et al.	2013	USA	PS	TA (n = 22)	PB	10/12	64 ± 3	TA	1% ZAI bid × 2 days, qd for 4 weeks	None	4 weeks
Zandian et al.	2015	Iran	RCT	OD (n = 9) TA (n = 25)	CB	0/9 24/26	68 ± 4 33.88 ± 9.03	OD TA	100 mg bid × 2 months 1% ZAI bid × 1 week, then qd for 2 weeks	WLC	8 weeks 3 weeks
Oral Azithromycin (OA) vs Oral doxycycline (OD)											
Kashkouli et al.	2014	Iran	RCT	OA (n = 50) OD (n = 50)	PB	26/24 24/26	42 ± 16.3 38.5 ± 14.6	OA OD	500 mg on the first day, then 250 mg/d for 4 days 100 mg bid for 1 month	NA	2 months

Table 1 (continued)

Author	Year	Region	Study design	No. participant group	Combined condition	F/M	Age (mean ± SD)	Intervention	Dose/frequency/duration	Supplemental treatment	Follow-up
Heitz et al.	2014	France	RCT	OA (n = 49) OD (n = 46)	NA	NA	NA	OA	500 mg three times 1 week tapered for 3 months 100 mg/d for 3 months	NA	3 months
Topical azithromycin (TA) vs Warm compress or Placebo											
Luchs et al.	2008	USA	RCT	TA (n = 9)	PB	4/5	58.7 ± 20.12	TA	1% AZI bid × 2 days, then once for 12 days	WLC	2 weeks
Fadlalah et al.	2012	Lebanon	RCT	WLC (n = 11) TA (n = 33) TA (n = 34)	CB	7/4 16/17 19/15	67.7 ± 11.38 52.0 ± 14.7 58.0 ± 15.2	WLC TA TA	WLC 1.5% AZI bid for 3 days 1.5% AZI bid × 3 days, then qn for 1 month	NA WLC + LH	3 months
Dona et al.	2014	France	RCT	TA	CB	NA	NA	TA	(1.5% AZI bid for 1 day, then daily for 6 days, followed by a 2 weeks interval) × 2 cycles (1.5% AZI bid for one day, then daily for 6 days, followed by a 2 weeks interval) × 2 cycles	NA	63 days
				PL				PL			

PS Prospective study, RS Retrospective study, RCT Random clinical study, TA Topical azithromycin, OD Oral doxycycline, AT Artificial tears, OA Oral azithromycin, AZI azithromycin, WLC Warm lid compress, PL Placebo, OR Ocular rosacea, PB Posterior blepharitis, MGD Meibomian gland dysfunction, BKC Blepharokeratoconjunctivitis, CB Chronic blepharitis, LH Lid hygiene, TS Topical steroids, NA Not available, * the same study.

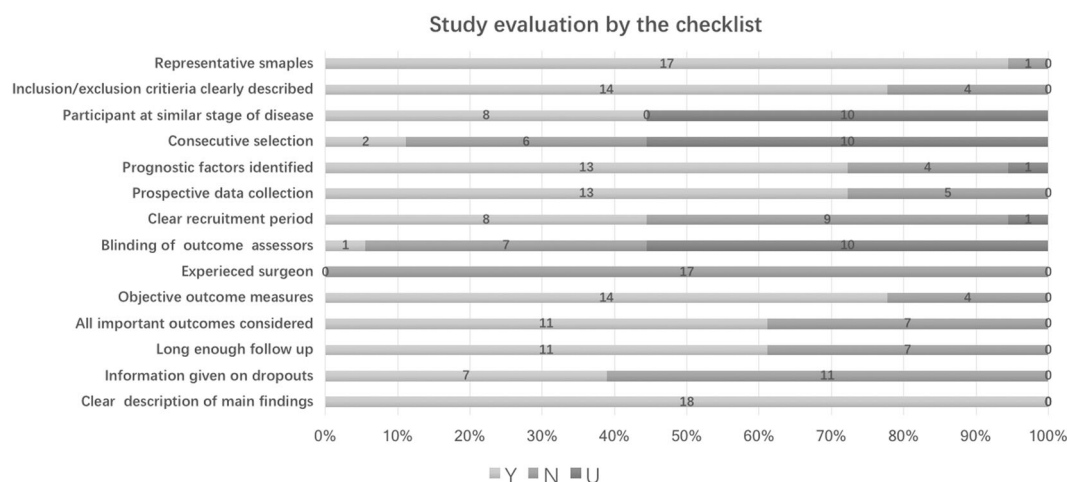


Fig. 2 Evaluation of studies based on the checklist. Most studies were deemed as high-quality.

MGD varied within these studies. Moreover, azithromycin regimens in the studies varied to some extent. Specifically, TA concentrations applied in these studies were 1.0% or 1.5%, while single doses of oral azithromycin varied from 250 to 1000 mg. Accordingly, the administration frequencies and durations also varied among these studies, and the follow-up durations ranged from 2 weeks to 3 months.

Study assessment

Figure 2 shows the results of assessing the studies based on the checklist. Among the 18 studies, thirteen (72.2%) obtained more than 8 “Yes” responses and were deemed as high-quality.

Effectiveness of treating MGD with azithromycin

Figure 3 shows the overall pooled symptom scores at the end of follow-up were significantly reduced compared with the baseline scores ($Z = 7.89$, $P < 0.0001$; $SMD = 1.54$, 95% CI: 1.15–1.92). As Fig. 4 shows, when the scores were sub-grouped by the different formulations, the pooled scores also showed significant reductions from the baseline scores either after administering OA ($Z = 4.15$, $P < 0.0001$; $SMD = 1.64$, 95% CI: 0.87–2.42) or TA ($Z = 6.24$, $P < 0.0001$, $SMD = 1.49$, 95% CI: 1.02–1.96).

Table 2 shows the pooled secondary outcomes after administering azithromycin. Regarding the eyelid signs, the pooled lid debris ($Z = 3.56$, $P < 0.0001$; $SMD = 1.53$, 95% CI: 0.69–2.37), lid swelling ($Z = 2.84$, $P < 0.0001$; $SMD = 1.67$, 95% CI: 0.52–2.82) and lid redness ($Z = 3.06$, $P = 0.002$; $SMD = 1.52$, 95% CI: 0.55–2.50) improved distinctly by applying azithromycin. As Fig. 5 shows, plugging of the meibomian gland also significantly improved after using either TA ($Z = 3.69$, $P < 0.0001$; $SMD = 1.64$, 95%

CI: 0.77–2.51) or OA ($Z = 3.40$, $P = 0.001$; $SMD = 1.88$, 95% CI: 0.80–2.96). In addition, both meibum quality ($Z = 2.91$, $P = 0.004$; $SMD = 2.15$, 95% CI: 0.70–3.60) and conjunctival injection ($Z = 3.88$, $P < 0.0001$; $SMD = 0.97$, 95% CI: 0.48–1.46) were also improved substantially by administering azithromycin.

As for objective measurements, the combined scores of lissamine green staining for both formulations were also significantly reduced by administering azithromycin ($Z = 1.96$, $P = 0.05$; $SMD = 0.92$, 95% CI: 0.00–1.85). The combined corneal staining after applying TA significantly improved compared with the baseline values ($Z = 2.36$, $P = 0.02$; $SMD = 0.69$, 95% CI: 0.12–1.27), but no significant improvements after administering OA were found ($Z = 1.47$, $P = 0.14$; $SMD = 0.57$, 95% CI: –0.19–1.33) (Fig. 6). As another measurement for evaluating the quality of tear film, the pooled TBUT also increased distinctly from baseline values after applying TA ($Z = 2.41$, $P = 0.02$; $SMD = -1.20$, 95% CI: –2.17 to –0.22) but not after administering OA ($Z = 1.74$, $P = 0.08$; $SMD = -0.35$, 95% CI: –0.75–0.04) (Fig. 7). However, tear secretion distinctly increased after applying both TA ($Z = 2.56$, $P = 0.01$; $SMD = -0.34$, 95% CI: –0.60 to –0.08) and OA ($Z = 2.52$, $P = 0.01$; $SMD = -0.44$, 95% CI: –0.79 to –0.10) (Fig. 8).

Comparison between topical azithromycin and oral doxycycline

The combined improvements in symptom scores between TA and OD showed a significant difference ($Z = 0.24$, $P = 0.81$; $SMD = -0.08$, 95% CI: –0.76–0.59). Similarly, no distinct differences were found after administering the two medications regarding TBUT ($Z = 0.42$, $P = 0.68$; $SMD = 0.11$, 95% CI: –0.43–0.65) and tear secretion ($Z = 0.00$, $P = 1.00$; $SMD = 0.00$, 95% CI: –0.45–0.45).

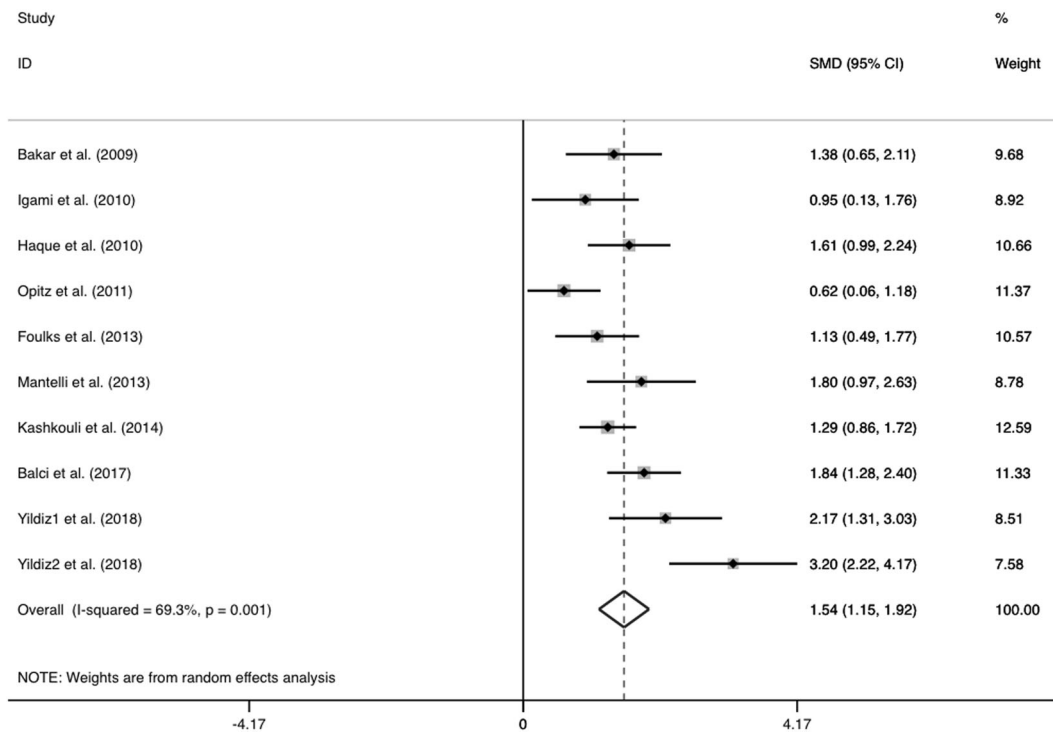


Fig. 3 Forest plot showing the effect of Azithromycin on symptom scores in MGD patients, ordered by date of publication. The overall pooled symptom scores at the end of follow-up were significantly reduced compared with the baseline.

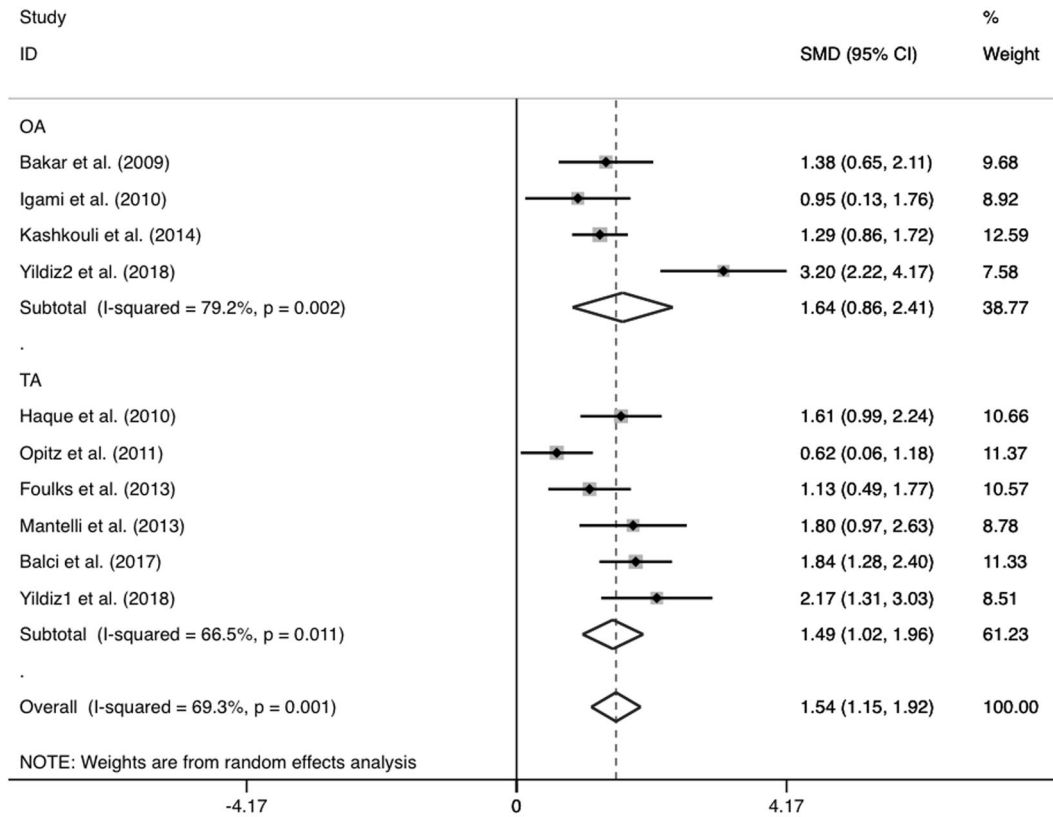


Fig. 4 Forest plot of subgroups showing the effect of Azithromycin on symptom scores in MGD patients (OA or TA), ordered by date of publication. The pooled scores significantly reduced from the baseline after administering either OA or TA.

Table 2 Pooled secondary outcomes after administering azithromycin.

Outcomes	SMD (95%CI)	Heterogeneity (I^2)	Z	P	Effects model
Lid Deris	1.53 (0.69–2.37)	82.0%	3.56	<0.0001*	Random
Lid swelling	1.67 (0.52–2.82)	88.7%	2.84	0.005*	Random
Lid redness	1.52 (0.55–2.50)	76.6%	3.06	0.002*	Random
Plugging of MG	1.71 (1.05–2.37)	87.8%	5.10	<0.0001*	Random
	1.64 (0.77–2.51)	89.0%	3.69	<0.0001***	Random
	1.88 (0.80–2.96)	84.7%	3.40	0.001***	Random
Meibum quality	2.15 (0.70–3.60)	89.4%	2.91	0.004*	Random
Conjunctival injection	0.97 (0.48–1.46)	61.9%	3.88	<0.0001*	Random
Corneal staining	0.64 (0.20–1.08)	77.1%	2.87	0.004*	Random
	0.69 (0.12–1.27)	74.3%	2.36	0.02**	Random
	0.57 (–0.19–1.33)	83.4%	1.47	0.14***	Random
Tear break-up time	–0.90 (–1.56 to –0.25)	88.5%	2.71	0.007*	Random
	–1.20 (–2.17 to –0.22)	92.4%	2.41	0.02**	Random
	–0.35 (–0.75–0.04)	0%	1.74	0.08***	Random
Lissamine green	0.92 (0.00–1.85)	83.1%	1.96	0.05*	Random
Tear secretion	–0.38 (–0.58 to –0.17)	6.3%	3.56	<0.0001*	Fixed
	–0.34 (–0.60 to –0.08)	10.1%	2.56	0.01**	Fixed
	–0.44 (–0.79 to –0.10)	22.5%	2.52	0.01***	Fixed

*Overall *P* value; **sub-grouped *P* value of topical azithromycin; ***sub-grouped *P* value of oral azithromycin.

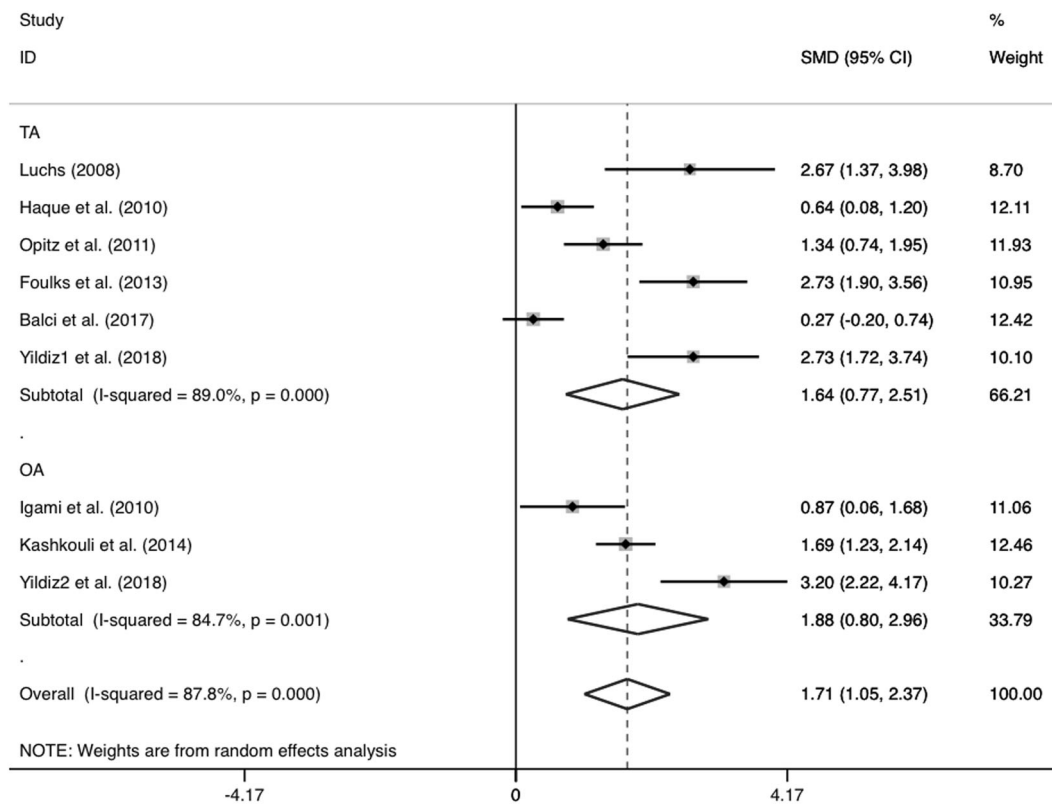


Fig. 5 Forest plot of subgroups showing the effect of Azithromycin on plugging of the meibomian gland in MGD patients (TA or OA), ordered by date of publication. Plugging of the meibomian gland significantly improved after administering either TA or OA.

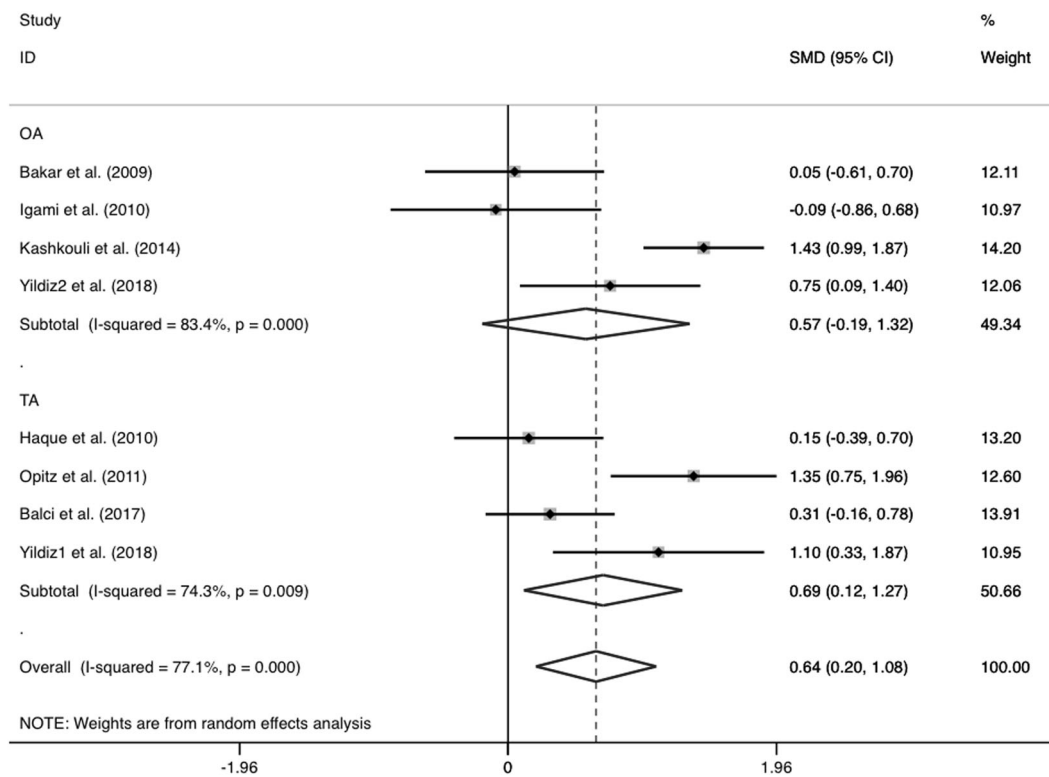


Fig. 6 Forest plot of subgroups showing the effect of Azithromycin on corneal staining in MGD patients (OA or TA), ordered by date of publication. The combined corneal staining after applying TA significantly improved compared with the baseline, but not after administering OA.

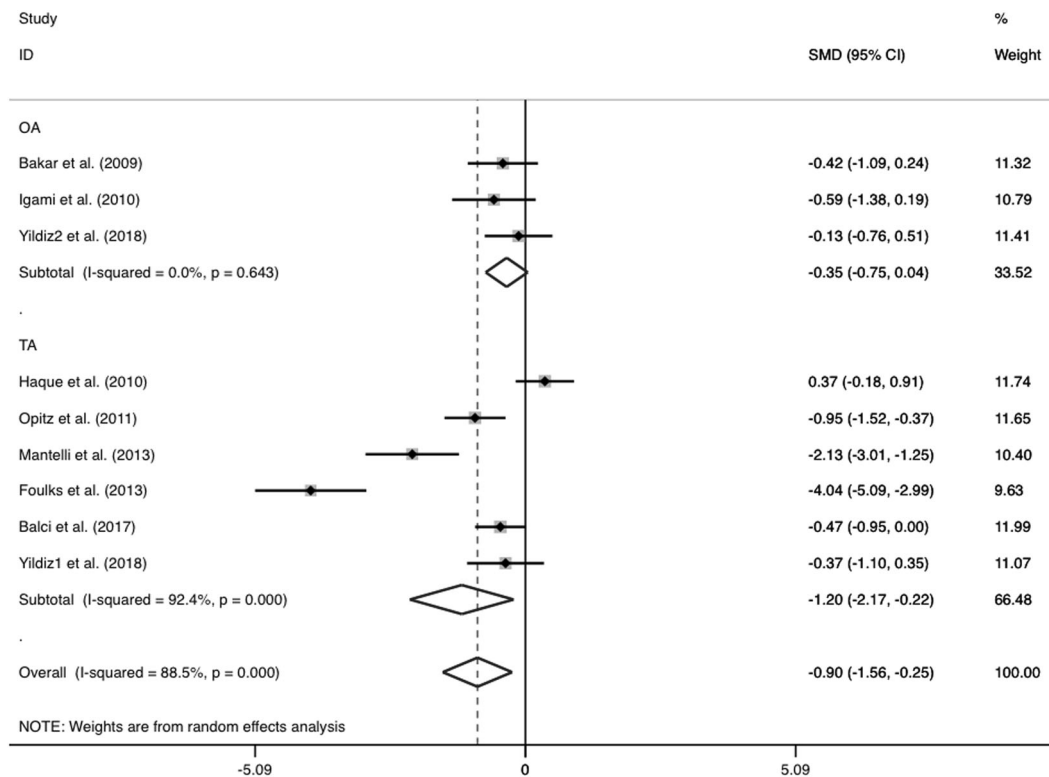


Fig. 7 Forest plot of subgroups showing the effect of Azithromycin on the quality of tear film in MGD patients (OA or TA), ordered by date of publication. The pooled TBUT increased distinctly from the baseline after applying TA but not after administering OA.

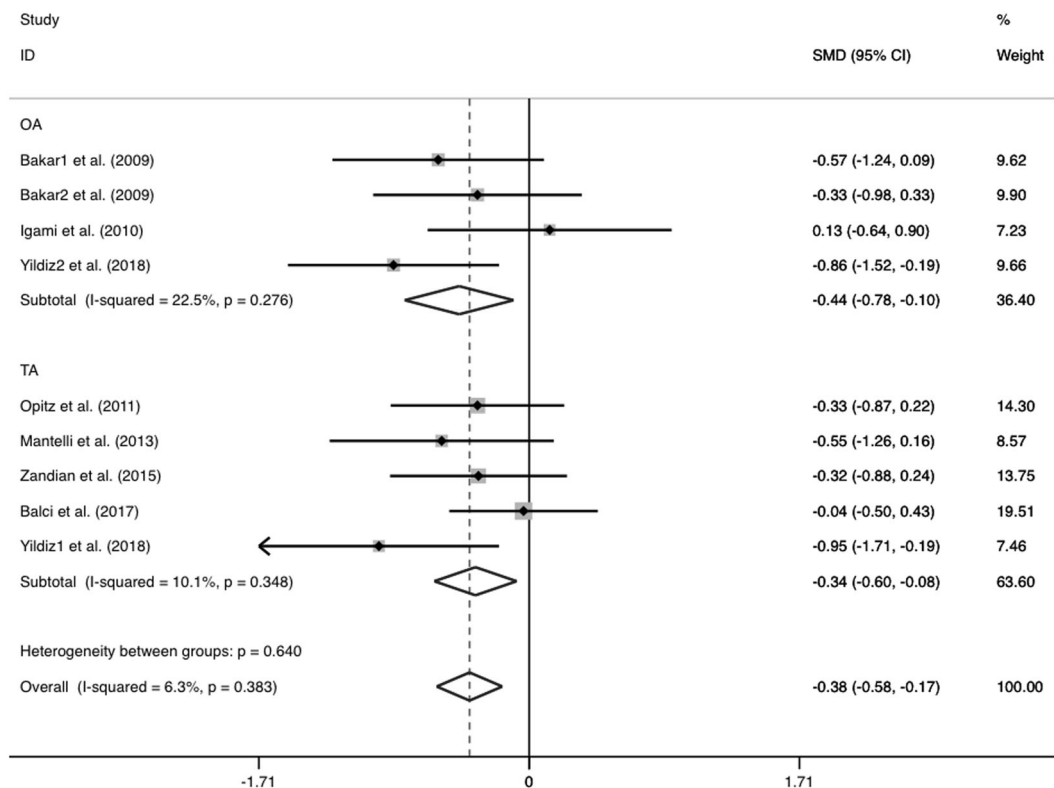


Fig. 8 Forest plot of subgroups showing the effect of Azithromycin on tear secretion in MGD patients (OA or TA), ordered by date of publication. Tear secretion distinctly increased after applying both TA and OA.

Occurrence rate of adverse events after administering azithromycin

The combined rate of adverse events after applying TA was 25% (95% CI: 0.19–0.31). The common adverse events reported in these studies were all related to ocular discomfort, including irrigation sensation, ocular redness, and blurred vision [4, 17, 24]. No systemic complications were reported after TA treatment. In addition, the pooled rate was 7% (95% CI: 0.02–0.13) after OA administration. Gastro-intestinal upset and decreased appetite were common complaints, but severe systemic complications were not reported in these studies [14, 19, 22].

Discussion

In this meta-analysis, the studies of treating MGD with azithromycin were systematically reviewed, and the clinical outcomes were pooled to demonstrate the effectiveness of azithromycin to manage MGD with respect to symptom scores, eyelid signs, and objective measurements. The pooled results showed that either OA or TA could significantly alleviate subjective symptoms and improve eyelid signs, plugging of the meibomian gland, meibum quality, and conjunctival injection. These

results proved the effectiveness of treating MGD with azithromycin.

Previous studies have demonstrated that an anti-inflammatory property was one aspect of azithromycin to treat MGD [27]. The antibiotic could eliminate inflammation at different levels. On the cellular level, the antibiotic could mediate neutrophil apoptosis and suppress their migration and phagocytic function [28]. An experimental study also showed it had the effects of inhibiting macrophage and dendritic cell migration in a mouse model of a cornea burn [29]. On the molecular level, azithromycin has effects on reducing pro-inflammatory cytokines/chemokines and metalloproteinases, such as IL-8, IL-1, TNF- α , nitric oxide, prostaglandin E2, MMP-1, and MMP-9, via its anti-oxidative and antibacterial properties (reducing exotoxin-induced cytokines) [9–11, 28, 30]. In addition, it may downregulate growth-related oncogene- α and suppress nuclear transcription factor NF κ B and Toll-like receptors in vitro [27, 31].

Bacterial colonization also plays an important role in the development of MGD [32]. Some authors revealed *S. aureus*, *Staphylococcus epidermidis*, *Propionibacterium acnes*, and *Corynebacterium* were more frequently isolated from patients with posterior blepharitis than from healthy patients [33]. In addition, these bacteria can aggravate the inflammation of the posterior eyelid margin and change the meibum properties by

releasing lipolytic enzymes, which could change the lipids to free fatty acids to irritate the ocular surface [34]. Azithromycin is a broad-spectrum antibiotic that can suppress bacteria effectively through binding to the 50 S subunit of the bacterial ribosome and inhibiting RNA synthesis [25]. Given that mechanism, the antibacterial effects exerted by azithromycin is the other aspect to managing MGD.

Although symptom scores and eyelid signs could be improved significantly after administering either OA or TA, the combined data in this study representing corneal staining and TBUT were improved distinctly by applying TA but not by administering OA. The results suggested that different formulations of azithromycin have varied abilities to improve the quality of tear film. Theoretically, the therapeutic effects after applying TA should be more direct, and the time to demonstrate the effects should also be less than the time for OA. This hypothesis was proven by Yildiz et al., who found that longer cytological improvements and better stabilization of tear film occurred after applying TA instead of administering OA [1]. However, another study demonstrated administering OD for 2 months could achieve comparable effects of applying TA for 1 month with respect to TBUT and corneal staining [20], suggesting prolonged therapy of OA/OD should be adopted to improve the quality of tear film distinctly. Moreover, our pooled results showed tear production was increased significantly by either OA or TA. Some authors assumed that the anti-inflammatory effects of azithromycin on accessory lacrimal glands could increase the aqueous secretion [16].

In this meta-analysis, we also combined the studies on treating MGD using both TA and OD to compare the effectiveness when considering the latter is also a potent agent to treat MGD and ocular rosacea. Interestingly, our pooled results showed that there were no significant differences between the two therapies regarding symptom score, tear secretion and TBUT, but the therapeutic courses of OD were obviously longer than those of TA in these studies. Foulks et al. investigated the changes in meibum composition through spectroscopic analysis after applying the two agents and found they had different mechanisms of managing MGD [20]. Although the pooled results showed OD was not inferior to TA to treat MGD, only prolonged therapy of OD could achieve comparable improvement in the quality of tear film [20]. Similarly, Zandian et al. proved OD was superior to TA in reducing eye redness and plugging of the meibomian gland in the same course (3 weeks) [21]. Given that result, TA appeared to reach therapeutic effects more rapidly, but the costs for TA are higher than the costs of OD in the US market [21]. Occurrence rates of adverse events after administering TA and OA were also pooled in this study. Although the rate seemed to be higher for TA (25%) than for OA (7%), no systemic adverse events were reported after using TA [4, 17, 24], which suggests TA

may be safer and more suitable for children or child-bearing women. Systemic adverse events caused by OA were mainly related to gastro-intestinal upset, which was tolerable by most of the patients [14, 19, 22]. Considering that result, OA is cheaper and more convenient to obtain for most adult patients with MGD who have no special restraints.

To be honest, differences among these studies regarding therapeutic regimens (dose, frequency, and course), supplemental management, and follow-up periods may bias the pooled results, which was reflected by the distinct heterogeneities. One inevitable factor to invalidate the conclusion drawn from this meta-analysis is most of the participants also employed artificial tears, lid hygiene, and warm compresses as the routine treatment when they were administered azithromycin, which might confound the effects of the medication to treat MGD. To some extent, the supplemental treatment may also improve the stability of tear film, eyelid swelling, plugging of the meibomian gland, meibum quality, and corneal staining. Considering these positive effects yielded by the supplemental treatment, further studies should avoid these confounding factors in order to make a confirmative conclusion. Small sample sizes, different study designs and variance of severities of the studies might also influence the validity of this meta-analysis. In addition, we were unable to conduct further comparisons between OA and TA and investigate the relationship between effectiveness and doses further because of the nature of the data. However, based on the current evidence provided by this study, the effectiveness of treating MGD with either TA or OA was basically confirmed. Randomized, multiple centered and large sample size studies should be carried out to explore the best regimens to treat MGD, and the safety of azithromycin for the long term should also be observed.

In conclusion, meibomian gland dysfunction could be treated effectively with oral or topical azithromycin by improving symptoms, clinical signs, and stabilization of the tear film. Topical azithromycin seemed to be superior over oral azithromycin or doxycycline in improving the quality of tear film in the short term.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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