Special Issue

The International Workshop on Meibomian Gland Dysfunction: Report of the Clinical Trials Subcommittee

Penny A. Asbell,[1] *Fiona J. Stapleton,*[2] *Kerstin Wickström,*[3] *Esen K. Akpek,*[4] *Pasquale Aragona,*[5] *Reza Dana,*[6] *Michael A. Lemp,*[7] *and Kelly K. Nichols*[8]

The objective of this subcommittee was to summarize the evidence in clinical trials on meibomian gland dysfunction (MGD) and to use this information to make recommendations for best-practice clinical trial design for this condition.

We conducted a PubMed and Medline literature review (through the end of 2009) to identify treatment or observational trials. Our search terms were those commonly used interchangeably with MGD, including (in addition to MGD) posterior blepharitis, meibomian gland disease, and tarsal gland disease. The level of evidence for each study was classified (Table 1) according to American Academy of Ophthalmology (AAO) Classification Scheme. In short, level I evidence includes evidence obtained from at least one properly conducted, well-designed randomized controlled trial. It could include meta-analyses of randomized controlled trials. Level II includes evidence obtained from well-designed controlled trials without randomization, well-designed cohort or case–control analytic studies, preferably from more than one clinical center or from multiple-time series with or without the intervention. Level III includes evidence obtained from descriptive studies, case reports, or reports of expert committees/organizations (e.g., panel consensus with external peer review). Additional information on levels of evidence is found in Table 1 of The Report on Management and Therapy. In some cases, the trial designs were not sufficiently described to have more than a tentative grading. Further, recent publications (August 2009 and later) were purposely excluded from Table 1.

Articles were reviewed according to the key components that are necessary for protocol design in determining safety and efficacy of a new treatment: *objectives*, *trial design and methodology*, *patient group*, *inclusion criteria*, *exclusion criteria*, *outcome measures*, *treatment*, and *statistical considerations*. We also evaluated clinical trials that had been registered at ClinicalTrials.gov if they included a summary of key trial design features. Further, a summary of key design features of the registered trials plus recommendations for future trials are suggested.

The review and summary were also based on the committee's personal expertise, including experience in clinical trials in ocular disease and in MGD. The initial search was performed in March 2009 and updated in July 2009. Twenty-six eligible papers[1–26] were identified and reviewed.

During the review, committee members found that the study investigators in the published papers often had not been explicit in describing their methods. As a result, the members, who conducted their reviews independently of one another, often interpreted the available data differently. The various interpretations are included in this summary.

Few publications qualify as well-designed randomized controlled trials. Aside from the three studies graded level I, there are additional trials that were randomized and controlled. Some were open-label with very small sample sizes and seemed to be lacking information on the statistical planning of the study. We expect that these smaller open-label studies will continue to provide information that will lead to larger placebo-controlled double-masked randomized clinical trials.

Key Topics to Be Addressed

Trial Objectives

Overview and Results. A summary of key trial objectives and design for the 26 studies[1–26] reviewed is detailed in Table 2. Of the 26 published articles, 25 reported the use of a treatment for MGD. Of those 25, 24 were considered interventional studies. Twenty-two (84.6%) of the 26 studies had as their objective the assessment of efficacy of a therapeutic approach. Of the 26, 9 (34.6%) were noncomparative. Of the remaining studies, most compared the treatment approach of interest with a traditional or palliative treatment, such as use of hot compresses or artificial tears, whereas several studies used a nontreatment control group for comparison.

Trial Design and Methodology

Overview and Results. The MGD clinical studies primarily comprised trials with fewer than 40 participants and were of short (<3 months) duration. Although most were prospective, fewer than half used a randomized controlled design, and only three were double-masked.

Twenty-four (92.3%) of the reviewed studies were interventional. Only one of those evaluated a surgical intervention, two evaluated a medical device, and the remainder assessed the efficacy of a supplement, drug intervention, or warm-compress therapy.

The majority of the trials (21/26, 80.8%) had a prospective component; some of the studies also reported a preliminary retrospective evaluation. Of the 26 studies reviewed, 16 used either a control group (e.g., normal/healthy group) or a pla-

From the [1]Department of Ophthalmology, Mount Sinai Medical Center, New York, New York; the [2]School of Optometry and Vision Science, University of New South Wales, Sydney, New South Wales, Australia; [3]Läkemedelsverket, Medical Products Agency, Uppsala, Sweden; [4]The Wilmer Eye Institute, Johns Hopkins Hospital, Baltimore, Maryland; the [5]Department of Surgical Specialties, Section of Opthalmology, University of Messina, Messina, Italy; [6]Schepens Eye Research Institute, Boston, Massachusetts; [7]Georgetown University, Washington, DC; and the [8]School of Optometry, Ohio State University, Columbus, Ohio.

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Corresponding author: Kelly K. Nichols, College of Optometry, 338 W. 10th Avenue, Ohio State University, Columbus, OH 43210-1280; knichols@optometry.osu.edu.

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TABLE 1. Evidence Levels of Eligible Trials (in Chronological Order)

Evidence Level*	Publications (*n*)	References†
I	3	Yoo et al.[26] Perry et al.[17] Schechter et al.[21]
I–II	2	Goto et al.[8] Rubin and Rao[20]
II	8	Paugh et al.[16] Yalcin et al.[25] Olson et al.[15] Romero et al.[19] Pinna et al.[18] Luchs[10] Souchier et al.[24] Matsumoto et al.[12]
II–III	1	Mori et al.[14]
III	12	Dougherty et al.[4] Epstein and Putterman[5] Song et al.[23] Meisler et al.[13] Goto et al.[6] Goto et al.[7] Shine et al.[22] Albietz and Lenton[1] Cetinkaya et al.[3] Matsumoto et al.[11] Blackie et al.[2] Ishida et al.[9]

* Additional information on levels of evidence is found in Table 1 of The Report on Management and Therapy.

† In many of the papers, the trial design was not sufficiently described to accurately grade the publication and the grading is therefore tentative.

cebo group, whereas 7 were controlled but the control groups were not uniformly well defined. Important design factors such as washout periods and management of concurrent treatments were often not mentioned or clearly detailed. Ten (38.5%) of the studies were classified as randomized: Seven were randomized between groups and three by eye (contralateral eye receiving a different therapy). Descriptions of the method of randomization were omitted in all but one study. For example, it was unclear who performed the randomization or how randomization was performed. Only three (11.5%) of the studies were double-masked, whereas examiner or photography/interferometry grading masking was used in an additional five studies.

Comments. In general, although a significant majority of the studies included herein were prospective, there has been a dearth of prospective, randomized double-masked trials in the area of MGD. The studies have tended to be small and of short duration. Randomization techniques, inclusion and exclusion criteria, and clear choices for allowed or disallowed concurrent treatments have been mostly lacking. Adoption of more rigorous approaches to study design and biostatistical methods (including a clear approach on how to handle various endpoints) is a requirement for more definitive trial results in this area.

Patient Group

Overview and Results. Various definitions of MGD have been used in past clinical trials or observational studies, but such trials typically discuss selection of patients with chronic lid disease and use the terms posterior blepharitis or MGD, sometimes in association with anterior lid disease, including seborrhea. A concise description of definitions can be found in the Report on Definition and Classification.

Most of the studies evaluated herein included adults older than 18 years, with the average age of the subjects approximately 50 to 60 years. Two studies evaluated children (4–12 years old), and the age of the sample was not reported in two studies (Table 2). Clinical testing for entry in the study or as an outcome was described in 23 of the 26 studies reviewed (Table 3). Of the 26 studies, 13 (50.0%) included symptoms as an entry criterion, diagnostic criterion, or an outcome. The symptoms described are those primarily associated with dry eye disease; only one (3.8%) study specifically examined MGD symptoms in the presence and absence of dry eye disease.

MGD was clinically defined most frequently through the evaluation of meibomian gland obstruction and/or gland dropout and abnormal gland secretions. Of the 26 papers, 12 (46.2%) reported meibomian gland obstruction, 14 (53.8%) contained assessments of secretions, and 8 (30.8%) involved transillumination of the glands or meibography. Descriptions of lid abnormalities including erythema, irregularity of lid margins, lid margin thickening, and/or telangiectasia were included in 10 (38.5%) studies. Four (15.3%) papers specifically eliminated patients with evidence of lid inflammation, but did not define the symptom further.

It was of interest to note that tests typically performed in dry eye clinical trials, such as fluorescein tear break-up time (FTBUT), conjunctival and corneal staining, and Schirmer's test, were included in only approximately 5% of the studies in defining the MGD subjects. Most studies, however, did evaluate these signs at baseline and in follow-up visits, and such signs were often used as outcome measures (Table 3). FTBUT was the most frequently reported clinical test in the studies evaluated (14/26, 53.8%).

Nearly all studies excluded subjects who had recent eye surgery or were current contact lens (CL) wearers, except for one study on MGD in association with CL intolerance and one study in which contact lens wear was allowed. Three studies specifically targeted MGD with concurrent skin disease, such as acne rosacea.

Comments. In summary, past MGD clinical trials did not have a uniform way of defining the study population, although symptoms and changes in the lid, especially plugging and abnormal secretions, were the most common clinical characteristics used to define the clinical sample of patients. Of note, dry eye disease was not typically either specifically included or excluded in selecting patients other than in selecting subjects with symptoms. Signs of dry eye disease were not generally used as selection criteria, although they were frequently included in the study design as outcome measures.

Inclusion Criteria

Overview. In approximately half of the identified studies, adult patients with a known history of MGD (12/26, 46.1%) or chronic blepharitis were enrolled, whereas specific eyelid findings were reported as entry qualifications for others. In three of the studies, the patients had to have clinical evidence of facial acne rosacea to be included. A previously established classification system was used in three studies,[27] whereas in the remaining studies, no specific published criteria were routinely used. Several studies reported no specific inclusion criteria other than a diagnosis of MGD or posterior blepharitis. How these diagnoses were determined was not disclosed. A list of the details related to inclusion in the 26 studies can be seen in Tables 4 and 5.

Results. In most of the studies, adult patients between 18 and 70 years of age with chronic signs and symptoms of blepharitis or MGD were enrolled. In three of the studies (two prospective and one retrospective case series), children were included. The age of the participants was not mentioned in two studies. In three studies, treatment with warm compresses and lid scrubbing had to fail for the patient to be included.

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TABLE 2. Study Design and Descriptive Features

Ref.	First Author	Evidence Level	Title	Journal/Year
17	Perry HD	I	Efficacy of commercially available topical cyclosporine A 0.05% in the treatment of meibomian gland dysfunction	*Cornea.* 2006 Feb;25(2):171–175
21	Schechter BA	I	Efficacy of topical cyclosporine for the treatment of ocular rosacea	*Adv Ther.* 2009;26(6):651–659
26	Yoo SE	I	The effect of low-dose doxycycline therapy in chronic meibomian gland dysfunction	*Korean J Ophthalmol.* 2005;19(4):258–263
8	Goto E	I–II	Low-concentration homogenized castor oil eye drops for noninflamed obstructive meibomian gland dysfunction	*Ophthalmology.* 2002;109(11):2030–2035
20	Rubin M	I–II	Efficacy of topical cyclosporin 0.05% in the treatment of posterior blepharitis	*J Ocul Pharmacol Ther* 2006;22:47–53
10	Luchs J	II	Efficacy of topical azithromycin ophthalmic solution 1% in the treatment of posterior blepharitis.	*Adv Ther.* 2008;25:858–870
12	Matsumoto Y	II	The evaluation of the treatment response in obstructive meibomian gland disease by in vivo laser confocal microscopy	*Graefes Arch Clin Exp Ophthalmol.* 2009;247(6): 821–829
15	Olson MC	II	Increase in tear film lipid layer thickness following treatment with warm compresses in patients with meibomian gland dysfunction	*Eye Contact Lens.* 2003;29(2):96–99
16	Paugh JR	II	Meibomian therapy in problematic contact lens wear	*Optom Vis Sci.* 1990;67(11):803–806
18	Pinna A	II	Effect of oral linoleic and gamma-linolenic acid on meibomian gland dysfunction	*Cornea.* 2007;26(3):260–264
19	Romero JM	II	Conservative treatment of meibomian gland dysfunction	*Eye Contact Lens.* 2004;30(1):14–19
24	Souchier M	II	Changes in meibomian fatty acids and clinical signs in patients with meibomian gland dysfunction after minocycline treatment	*Br J Ophthalmol.* 92(6):819–822
25	Yalcin E	II	N-acetylcysteine in chronic blepharitis	*Cornea.* 2002;21:164–168
14	Mori A	II–III	Disposable eyelid-warming device for the treatment of meibomian gland dysfunction	*Jpn J Ophthalmol.* 203;47(6):578–586
1	Albietz JM	III	Effect of antibacterial honey on the ocular flora in tear deficiency and meibomian gland disease	*Cornea.* 2006;25:1012–1019
2	Blackie CA	III	Inner eyelid surface temperature as a function of warm compress methodology	*Optom Vis Sci.* 2008;85(8):675–683
3	Cetinkaya A	III	Pediatric ocular acne rosacea: long-term treatment with systemic antibiotics	*Am J Ophthalmol.* 2006;142(5):816–821
4	Dougherty JM	III	The role of tetracycline in chronic blepharitis. Inhibition of lipase production in staphylococci	*Invest Ophthalmol Vis Sci.* 1991;32(11):2970–2975
5	Epstein GA	III	Combined excision and drainage with intralesional corticosteroid injection in the treatment of chronic chalazia	*Arch Ophthalmol.* 1988;106(4):514–516
6	Goto E	III	Improvement of tear stability following warm compression in patients with meibomian gland dysfunction	*Adv Exp Med Biol.* 2002;506:1149–1152
7	Goto E	III	Treatment of non-inflamed obstructive meibomian gland dysfunction by an infrared warm compression device	*Br J Ophthalmol,* 2002;86(12):1403–1407
9	Ishida R	III	Tear film with "Orgahexa EyeMasks" in patients with meibomian gland dysfunction	*Optom Vis Sci.* 2008;85(8):684–691
11	Matsumoto Y	III	Efficacy of a new warm moist air device on tear functions of patients with simple meibomian gland dysfunction	*Cornea.* 200625(6):644–650
13	Meisler DM	III	Oral erythromycin treatment for childhood blepharokeratitis	*J AAPOS.* 2000;4(6):379–380
22	Shine WE	III	Minocycline effect on meibomian gland lipids in meibomianitis patients	*Exp Eye Res.* 2003;76(4):417–420
23	Song CH	III	Enhanced secretory group II PLA2 activity in the tears of chronic blepharitis patients	*Invest Ophthalmol Vis Sci.* 1999;40(11):2744–2748

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TABLE 2 (*continued*). Study Design and Descriptive Features

Ref.	Treatment	Interventional	Efficacy Assessed?	Comparative?	Treatment Protocol
17	Y	Y	Y	Y	Topical 0.05% cyclosporin versus artificial tears
21	Y	Y	Y	Y	Topical 0.05% cyclosporine versus artificial tears
26	Y	Y	Y	Y	Systemic doxycycline 200 or 20 mg twice a day or placebo
8	Y	Y	Y	Y	Castor oil eye drop versus artificial tears
20	Y	Y	Y	Y	Topical 0.05% cyclosporin versus topical 0.3% tobramycin/0.1% dexamethasone
10	Y	Y	Y	Y	Topical azithromycin 1% and hot compresses versus hot compresses alone
12	Y	Y	Y	Y	Lid hygiene, topical nonpreserved artificial tears, and 0.1% sodium hyaluronate eye drops, topical 0.5% levofloxacin, topical 0.1% fluorometholone, oral minocycline 100 mg twice a day versus lid hygiene, topical nonpreserved artificial tears and 0.1% sodium hyaluronate drops
15	Y	Y	Y	Y	Heated compress over experimental eye versus room temperature compress over control eye
16	Y	Y	Y	Y	Lid hygiene, warm compresses twice daily for 2 weeks in one eye
18	Y	Y	Y	Y	Oral linoleic acid and γ-linolenic acid once daily versus eyelid hygiene (warm eyelid compresses, eyelid massage, and eyelid margin scrubbing) versus both treatments
19	Y	Y	Y	Y	Lid hygiene, warm saline soaks, and non-preserved AT four times per day for 2 weeks and then twice per day for 4 weeks
24	Y	Y	Y	Y	Lid hygiene versus oral minocycline 50 mg (patients nonresponsive to compress therapy received minocycline)
25	Y	Y	Y	Y	Topical steroid, topical antibiotic, artificial tears, warm compress, and oral *n*-acetylcysteine versus topical steroid, topical antibiotic, artificial tears, warm compress
14	Y	Y	Y	Y	Application of Eye Warmer lid warming device versus untreated control
1	Y	Y	N	N	Topical antibacterial honey
2	Y	Y	N	Y	External heat (warm compresses in several different ways)
3	Y (case series)	Y	Y	N	Four pediatric cases: oral erythromycin or oral doxycycline in combination with topical methyl prednisolone and tobramycin
4	Y (clinical samples, no direct patient treatment)	N	N	N	Tetracycline solution incubated with tetracycline-sensitive strains (*Staphylococcus epidermidis* and *Staphylococcus Aureus*) and tetracycline-resistant strains (*S. Epidermidis* and *S. Aureus*)
5	Y	Y	Y	Y	Initial warm eyelid soaks for chronic chalazia, eyelid cleaning, topical antibiotic-steroid combination. If no improvement within 2 weeks, surgical excision versus surgical excision and intratarsal injection of triamcinolone
6	Y	Y	Y	N	Warm compress therapy with a warm steam eye cup device applied for 5 minutes
7	Y	Y	Y	N	Infrared warm compression device
9	Y	Y	Y	N	Orgahexa EyeMask eye warmer mask
11	Y	Y	Y	Y	Steam warmer four times daily versus traditional warm compresses twice daily
13	Y (case series)	Y	Y	N	Oral erythromycin, varying dose starting at 30 to 250 mg twice daily, depending on severity of disease, lid scrubbing twice a day
22	Y	Y	Y	N	Oral minocycline 50 mg/daily for 2 weeks followed by 100 mg/daily
23	7N	N	N	N	No treatment, normal tear PLA2 compared with blepharitis including MGD

(*continues*)

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TABLE 2 (*continued*). Study Design and Descriptive Features

Ref.	Duration	Prospective/Retrospective	Randomized	Masked
17	3 months	Prospective	Y	Y-double
21	3 months	Prospective	Y	Y-double
26	1 month	Prospective	Y	Y-patient
8	2 week washout, 1 month	Prospective, cross-over	Y	Y-double
20	3 months	Prospective	Y	N
10	2 weeks	Prospective	Y	N
12	12 weeks	Prospective	N	N
15	5, 15, 30 minutes following application (same day)	Prospective	Y (contralateral eye)	N
16	2 weeks	Prospective	Y (contralateral eye)	Y-examiner
18	6 months	Prospective	Y	Y-examiner
19	6 weeks	Prospective	N	Y-photo grader
24	8 weeks	Prospective	N	N
25	3 months	Prospective	N	N
14	2 weeks	Prospective	N	N (only interferometry grader was masked)
1	3 months	Prospective	N	N
2	Same day study	Same day study	Y (contralateral eye)	N
3	12–36 months	Retrospective case series	N	N
4	24 hours	Retrospective, sample collection	N	N
5	6 weeks	Initially retrospective, second part prospective	N	N
6	Same day study	Same day study	N	N
7	2 weeks	Prospective	N	N
9	2 weeks	Prospective	N	N
11	2 weeks	Prospective	N	N
13	Up to 12 months	Prospective case series	N	N
22	3 months on Tx, 3 months off Tx	Prospective	N	N
23	Same day study	Same day study	N	N

(*continues*)

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TABLE 2 (*continued*). Study Design and Descriptive Features

Ref.	Placebo or Control	Subject Group (*n*, Group)	Age Range
17	Y	n = 33 enrolled, n = 16 (12 completed) treatment (Tx), n = 17 (14 completed) placebo	18 and older, average age, not given
21	Y	n = 37, n = 21 Tx, n = 16 placebo	18 and older, average age, ~72.6 y
26	Y	n = 150 enrolled (n = 139 completed), n = 50 high dose, n = 50 low dose, n = 50 placebo	18 and older, average age, ~47.2 y
8	Y	n = 20, 10 per group	18 and older, average age, 52.1 y
20	N	n = 30, 15 per group	18 and older, average age, ~51 y
10	Y	n = 21, n = 11 Tx and n = 10 placebo	18 and older, average age, 63.7 y
12	Y	n = 27, n = 16 Tx, n = 11 control	18 and older, average age, ~65 y
15	Y	n = 20	range, 26–59 y
16	Y	n = 21	range, 22–33 y
18	Y	n = 57 (49 completed), 19 per group	18 and older, average age, 50 y
19	N	n = 37 enrolled (26 completed)	18 and older, average age, 57 y
24	Y	n = 20 patients, 10 per group	18 and older, average age, 66 y
25	Y	n = 40, n = 22 Tx, n = 18 control	18 and older, average age, ~43 y
14	Y	n = 25 (17 treated, 8 untreated)	18 and older, average age, 53.6 y
1	Y	n = 84 (49 completed), of those enrolled 15 MGD and 20 MGD with tear deficiency	18 and older, average age, ~59 y
2	Y	n = 32 normal patients, group A (n = 10), B (n = 10) and C (n = 12)	18 and older, average age, 34.7 y
3	N	n = 4	range, 4–12 y
4	N	MKC n = 2 samples (isolates), *Staphylococcus* blepharitis, 2 samples (isolates)	Not defined
5	N	n = 298, first 146 patients: 88 surgery only, 58 surgery and steroids in combination. Additionally 152 patients with combined treatment.	range, 6–88 y, most >50 y
6	N	n = 6	18 and older, average age, 45.8 y
7	N	n = 37	18 and older, average age, ~55 y
9	Y	n = 42, n = 20 Tx, n = 22 control	18 and older, average age, 54.5 y
11	Y	n = 35, n = 15 MGD, n = 20 control	18 and older, average age, ~58.8 y
13	N	n = 5	range, 4–9 y
22	N	n = 10	N/A
23	N	n = 46, chronic blepharitis n = 36, controls n = 10	range, 30–40 y

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TABLE 3. Clinical Characteristics and Symptoms Assessed as Either Entry Criteria or Outcomes

Ref.	First Author	Evidence Level	Title	Clinical Testing Described/ Performed	Symptoms
17	Perry HD	I	Efficacy of commercially available topical cyclosporine A 0.05% in the treatment of meibomian gland dysfunction	Yes	Yes
21	Schechter BA	I	Efficacy of topical cyclosporine for the treatment of ocular rosacea	Yes	Yes
26	Yoo SE	I	The effect of low-dose doxycycline therapy in chronic meibomian gland dysfunction	Yes	Yes
8	Goto E	I–II	Low-concentration homogenized castor oil eye drops for noninflamed obstructive meibomian gland dysfunction	Yes	Yes
20	Rubin M	I–II	Efficacy of topical cyclosporin 0.05% in the treatment of posterior blepharitis	Yes	
10	Luchs J	II	Efficacy of topical azithromycin ophthalmic solution 1% in the treatment of posterior blepharitis.	Yes	Yes
12	Matsumoto Y	II	The evaluation of the treatment response in obstructive meibomian gland disease by in vivo laser confocal microscopy	Yes	
15	Olson MC	II	Increase in tear film lipid layer thickness following treatment with warm compresses in patients with meibomian gland dysfunction	Yes	Yes
16	Paugh JR	II	Meibomian therapy in problematic contact lens wear	Yes	Yes
18	Pinna A	II	Effect of oral linoleic and gamma-linolenic acid on meibomian gland dysfunction	Yes	Yes
19	Romero JM	II	Conservative treatment of meibomian gland dysfunction	Yes	Yes
24	Souchier M	II	Changes in meibomian fatty acids and clinical signs in patients with meibomian gland dysfunction after minocycline treatment	Yes	
25	Yalcin E	II	N-acetylcysteine in chronic blepharitis	Yes	
14	Mori A	II–III	Disposable eyelid-warming device for the treatment of meibomian gland dysfunction	Yes	Yes
1	Albietz JM	III	Effect of antibacterial honey on the ocular flora in tear deficiency and meibomian gland disease	Yes	Yes
2	Blackie CA	III	Inner eyelid surface temperature as a function of warm compress methodology		
3	Cetinkaya A	III	Pediatric ocular acne rosacea: long-term treatment with systemic antibiotics	Yes	Yes
4	Dougherty JM	III	The role of tetracycline in chronic blepharitis. Inhibition of lipase production in staphylococci	No	
5	Epstein GA	III	Combined excision and drainage with intralesional corticosteroid injection in the treatment of chronic chalazia		
6	Goto E	III	Improvement of tear stability following warm compression in patients with meibomian gland dysfunction	Yes	
7	Goto E	III	Treatment of non-inflamed obstructive meibomian gland dysfunction by an infrared warm compression device	Yes	Yes
9	Ishida R	III	Tear film with "Orgahexa EyeMasks" in patients with meibomian gland dysfunction	Yes	
11	Matsumoto Y	III	Efficacy of a new warm moist air device on tear functions of patients with simple meibomian gland dysfunction	Yes	
13	Meisler DM	III	Oral erythromycin treatment for childhood blepharokeratitis	Yes	
22	Shine WE	III	Minocycline effect on meibomian gland lipids in meibomianitis patients	Yes	
23	Song CH	III	Enhanced secretory group II PLA2 activity in the tears of chronic blepharitis patients	No	
	Total (*n*)			24	13
	% (of 26)			92.3%	50.0%

(*continues*)

Several parameters were used, including symptomatology, lid margin, and ocular surface findings by slit lamp examination and dry eye findings, as follows:

- Symptomatology. No specific MGD questionnaire has been developed or validated to date. Only seven studies (7/26, 26.9%) used single or multiple patient symptoms or questionnaires specifically as inclusion factors, whereas three studies cited failure of conventional therapy. (It is unclear how failure was assessed; some examples of therapy were provided.) Published studies generally report on main symptom types: discomfort, visual disturbance, and ocular appearance. The main symptoms reported by patients in questionnaires or interviews in the studies assessed included dryness (6/26, 23.1%) and discomfort or foreign body sensation (6/26, 23.1%). These symptoms were usually graded subjectively as mild, moderate, or severe. Few studies applied questionnaires (mostly questionnaires used in dry eye studies) at entry into as well as exit from the study, but in general they did not require a certain level of symptomatology as a specific entry criterion.
- Lid margin findings. Lid margin signs are the most frequently reported inclusion criteria. Signs included posterior lid margin erythema/hyperemia, lid margin thickening/irregularity, meibomian gland orifice plugging, turbidity of meibomian gland secretions, lid margin telangiectasia, and meibomian gland plugging. Signs were mainly graded as mild, moderate, or severe. Meibomian gland plugging was the single most common lid margin finding to be used as an inclusion criterion (8/26, 30.8%).
- Ocular surface findings. Findings included, but were not limited to, corneal infiltrates, neovascularization, bulbar con-

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TABLE 3 (*continued*). Clinical Characteristics and Symptoms Assessed as Either Entry Criteria or Outcomes

Ref.	Transillumination (Obstruction and Dropout)	MG Obstruction	MG Secretions	Interferometry	Eyelid Temperature	Lid Debris	Lid Edema/ Thickening	Irregular Lid
17		Yes (plugging)						Yes
21		Yes	Yes					
26	Yes	Yes						
8	Yes	Yes	Yes	Yes			Yes	
20			Yes					
10		Yes	Yes			Yes	Yes	
12	Yes	Yes	Yes					
15		Yes		Yes				
16			Yes					
18		Yes	Yes				Yes	
19			Yes				Yes	Yes
24		Yes	Yes					Yes
25								
14			Yes	Yes				
1	Yes	Yes	Yes				Yes	Yes
2					Yes			
3								
4								
5								
6	Yes	Yes	Yes					
7	Yes	Yes	Yes				Yes	
9	Yes			Yes	Yes			
11	Yes			Yes	Yes			
13							Yes	
22			Yes					
23								
	8 30.8%	12 46.2%	14 53.8%	5 19.2%	3 11.5%	1 3.8%	7 26.9%	4 14.4%

(*continues*)

junctival hyperemia, and tarsal conjunctival papillae. Studies that involved patients with ocular rosacea listed ocular surface findings as inclusion criteria.

• Dry eye findings. It is notable that dry eye signs were inclusion criteria in several of the papers. They were used either to define groups or as an indicator of tear film stability. Dry eye signs included a low tear film breakup time (TFBUT), presence and degree of corneal staining using fluorescein, presence and degree of conjunctival staining as determined with rose bengal or lissamine green, and Schirmer's test for measuring aqueous tear production and flow.

Comments. Except for the lid margin findings determined by slit lamp examination, there seemed to be no specific and consistent inclusion criteria for blepharitis or MGD, which are different from the criteria commonly used in dry eye studies. This deficiency is perhaps not unexpected, as the overlap between MGD and dry eye has yet to be fully understood. In general, symptoms associated with MGD may be related to altered tear film stability and evaporative dry eye. The most commonly used inclusion criteria in MGD studies to date are symptoms of discomfort/foreign body sensation and signs of meibomian gland plugging, expressibility of the meibomian glands, and quality of gland secretions.

Exclusion Criteria

Overview. The exclusion criteria are reported in 17 (65.4%) studies (Tables 4, 5B). The exclusion criteria varied according to the objectives of each trial and the sample of patients included. It is therefore possible to classify the papers in four different types, divided according to the purpose of the trial, the terminology used by the authors, and the patients included:

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TABLE 3 (*continued*). Clinical Characteristics and Symptoms Assessed as Either Entry Criteria or Outcomes

Ref.	Lid Hyperemia/ Erythema	Lid Telangiectasia	Conjunctival Papillae/ Hyperemia	TFBUT	Corneal Staining	Schirmer's Test	Contact Lens Wear	Acne Rosacea
17	Yes	Yes	Yes					
21				Yes	Yes	Yes		Yes
26								
8				Yes	Yes			
20	Yes	Yes		Yes	Yes	Yes		
10	Yes							
12				Yes	Yes	Yes		
15				Yes		Yes		
16				Yes	Yes		Yes	
18	Yes		Yes		Yes		Yes	
19	Yes	Yes		Yes		Yes		
24		Yes		Yes	Yes			
25					Yes	Yes		
14				Yes				
1		Yes		Yes	Yes	Yes		
2								
3		Yes	Yes		Yes			Yes
4								
5								
6				Yes	Yes	Yes		
7	Yes			Yes	Yes	Yes		
9				Yes	Yes	Yes		
11				Yes	Yes	Yes		
13	Yes				Yes			
22								Yes
23								
	7 26.9%	6 23.1%	3 11.5%	14 53.8%	15 57.7%	11 42.3%	2 7.7%	3 11.5%

1. Obstructive meibomian gland dysfunction (nine papers)
2. Posterior blepharitis (six papers)
3. Seborrhea with secondary meibomianitis (one paper)
4. Meibomian therapy in CL wearers (one paper).

Furthermore, it is possible to classify the exclusion criteria reported into three different categories: (1) ocular disease-related, (2) iatrogenic, and (3) systemic disease-related.

Results. The 26 papers were reviewed for exclusion criteria, and in the 17 papers that included a description of exclusion criteria, 39 distinct criteria were reported. The most frequently were CL use (10/17, 58.8%), history of ocular surgery (7/17, 41.2%), and eye disorders affecting the ocular surface (6/17, 35.3%). The entire list of exclusion criteria and their frequency of citation is shown in Table 5B.

Considering the different goals of the studies included and the terminology used by the authors the exclusion criteria can be grouped as follows:

1. Papers about obstructive MGD treatment. In this group, three studies included patients with noninflamed obstructive MGD, one included patients with obstructive MGD and lid inflammation, three included MGD patients, and two described "simple" MGD. Seven studies evaluated different types of warm compress and lid hygiene for treatment of MGD. In these, the exclusion criteria were anterior blepharitis of more than moderate severity; infectious conjunctivitis; meibomitis; seborrheic MGD, and excessive meibomian lipid secretion; ocular adnexal pathology interfering with warm compress application; CL use; diabetes; current use of treatments for blepharitis; eyelid surgery; presence

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TABLE 4. Inclusion and Exclusion Criteria

Ref.	First Author	Evidence Level	Title	Inclusion Criteria
17	Perry HD	I	Efficacy of Commercially Available Topical Cyclosporine A 0.05% in the Treatment of Meibomian Gland Dysfunction	Adult patients with slit lamp diagnosis of meibomian gland dysfunction, with an OSDI score of >12.
21	Schechter BA	I	Efficacy of Topical Cyclosporine for the Treatment of Ocular Rosacea	Adult patients with rosacea-associated eyelid and corneal changes.
26	Yoo SE	I	The Effect of Low-Dose Doxycycline Therapy in Chronic Meibomian Gland Dysfunction	Adult patients with newly diagnosed chronic meibomian gland dysfunction with grade 2 or worse meibomian gland destruction or meibomian gland orifice obstruction, and whose symptoms failed to improve despite warm compression, lid massage, lid scrub, and topical eye drops or ointment therapy for more than 2 months.
8	Goto E	I–II	Low-Concentration Homogenized Castor Oil Eye Drops for Noninflamed Obstructive Meibomian Gland Dysfunction	Consecutive series of adult MGD patients nonresponsive to conventional therapy, which could include lid hygiene and topical artificial tears, antibiotics (oral/topical), and/or corticosteroids.
20	Rubin M	I–II	Efficacy of Topical Cyclosporin 0.05% in the Treatment of Posterior Blepharitis	Consecutive adult patients presenting with posterior blepharitis defined as lid erythema and MG telangiectasia.
10	Luchs J	II	Efficacy of Topical Azithromycin Ophthalmic Solution 1% in the Treatment of Posterior Blepharitis	Adult patients with a diagnosis of poster blepharitis by a qualified ophthalmologist; patients must have a grade of at least 2 of lid redness/swelling and gland plugging.
12	Matsumoto Y	II	The Evaluation of the Treatment Response in Obstructive Meibomian Gland Disease by in Vivo Laser Confocal Microscopy	Consecutive adult patients with severe obstructive MGD associated with lid inflammation.
15	Olson MC	II	Increase in Tear Film Lipid Layer Thickness Following Treatment with Warm Compresses in Patients with Meibomian Gland Dysfunction	Consecutive adult patients with symptoms of ocular dryness were enrolled with the following criteria: (1) subjective dry eye status determined by a score of ≥6 on dry eye symptoms questionnaire; (2) meibomian gland obstruction determined by SLE; (3) TFLLT baseline of ≤90 nm; as well as fluorescein tear breakup time and Schirmer results of ≤10 mm/5 min.
16	Paugh JR	II	Meibomian Therapy in Problematic Contact Lens Wear	Consecutive adult contact lens wearers with (1) minimal or transient symptoms of dryness, (2) cloudy or absent MG secretions, and (3) CL intolerance not related to lens or solution parameters.
18	Pinna A	II	Effect of Oral Linoleic and Gamma-Linolenic Acid on Meibomian Gland Dysfunction	Group 4 and 5 of McCulley Classification system for MGD (McCulley et al. Classification of chronic blepharitis.[27]
19	Romero JM	II	Conservative Treatment of Meibomian Gland Dysfunction	Adult patients with (1) a chief complaint of MGD (ocular discomfort assessed by questionnaire) and (2) diagnosis of MGD with two or more of the following: redness or thickening of the lid margin, telangiectasia, reduced or no secretions, poor quality secretions, gland capping.
24	Souchier M	II	Changes in Meibomian Fatty Acids and Clinical Signs in Patients with Meibomian Gland Dysfunction after Minocycline Treatment	Adult patients with chronic posterior blepharitis defined by redness, thickening, or irregularity of the lid margin, telangiectasia, reduced or no secretions, poor-quality secretions, gland capping, and/or MG metaplasia.
25	Yalcin E	II	*N*-Acetylcysteine in Chronic Blepharitis	Adult clinic patients with chronic posterior blepharitis.
14	Mori A	II–III	Disposable Eyelid-Warming Device for the Treatment of Meibomian Gland Dysfunction	Short term efficacy study: adult patients with TBUT ≤5 s and dry eye symptoms. Therapeutic study: adult patients with TBUT ≤5 s, MGD (not defined), and dry eye symptoms.
1	Albietz JM	III	Effect of Antibacterial Honey on the Ocular Flora in Tear Deficiency and Meibomian Gland Disease	Consecutive adult dry eye patients subsequently classified into four groups: non-Sjögren's tear deficienc y, Sjögren's tear deficiency, MGD (posterior lid margin thickening, irregularity, telangiectasia, gland loss, plugging and capping, and abnormal MG secretions), and MGD plus tear deficiency.
2	Blackie CA	III	Inner Eyelid Surface Temperature as a Function of Warm Compress Methodology	Healthy adult individuals.
3	Cetinkaya A	III	Pediatric Ocular Acne Rosacea: Long-Term Treatment with Systemic Antibiotics	Rosacea patients younger than 12 years of age, with or without obvious skin involvement, who were having active inflammation with ocular discomfort, photophobia, and red eyes, despite topical steroid, antibiotic or
4	Dougherty JM	III	The Role of Tetracycline in Chronic Blepharitis: Inhibition of Lipase Production in Staphylococci	Isolates from patients with meibomian keratoconjunctivitis and staphylococcal blepharitis; patients not clinically defined.
5	Epstein GA	III	Combined Excision and Drainage with Intralesional Corticosteroid Injection in the Treatment of Chronic Chalazia	Adult and pediatric patients undergoing surgical excision of chronic chalazia; patients not clinically defined.
6	Goto E	III	Improvement of Tear Stability Following Warm Compression in Patients with Meibomian Gland Dysfunction	Consecutive adult patients with noninflamed obstructive MGD.
7	Goto E	III	Treatment of Non-Inflamed Obstructive Meibomian Gland Dysfunction by an Infrared Warm Compression Device	Consecutive adult patients with MGD unresponsive to conventional treatment, which could include lid hygiene and topical artificial tears, antibiotics (oral/topical) and/or corticosteroids.
9	Ishida R	III	Tear Film with "Orgahexa EyeMasks" in Patients with Meibomian Gland Dysfunction	Adult patients with simple MGD defined as (1) occluded MG orifices, (2) cloudy secretions, (3) keratinization and/or mucocutaneous junction displacement, and (4) noninflamed lid margins.
11	Matsumoto Y	III	Efficacy of a New Warm Moist Air Device on Tear Functions of Patients with Simple Meibomian Gland Dysfunction	Adult patients with simple MGD defined as (1) occluded MG orifices, (2) cloudy secretions, (3) keratinization and/or mucocutaneous junction displacement, and (4) noninflamed lid margins.
13	Meisler DM	III	Oral Erythromycin Treatment For Childhood Blepharokeratitis	Children with chronic lid margin inflammation (lid redness and thickening).
22	Shine WE	III	Minocycline Effect on Meibomian Gland Lipids in Meibomianitis Patients	Patients were selected based on clinical appearance and categorized as having acne rosacea with or without meibomianitis, or seborrheic blepharitis alone.[27]
23	Song CH	III	Enhanced Secretory Group II PLA2 Activity in the Tears of Chronic Blepharitis Patients	Adult patients with the presence of one or more of the signs and symptoms of blepharitis for more than 6 months, categorized into six blepharitis groups.[27]

(*continues*)

of dry eye conditions other than MGD; history of Stevens-Johnson syndrome; chemical, thermal and radiation injury; topical drugs; and surgery or procedures that might create ocular surface problems.

2. Papers about posterior blepharitis (a term often used synonymously with MGD in the literature). This group included six studies that evaluated the effect of different types of antibiotic and anti-inflammatory pharmacologic treatment of posterior blepharitis. All patients had, to some extent, an inflammatory condition. The exclusion criteria in this group of studies were topical therapy within 2 weeks before the beginning of the study, systemic treatments with other antibiotic or anti-inflammatory agents, plugs, CL wear, active ocular diseases other than blepharitis, lid abnormalities, fungal or viral infections, ocular surface surgery or other inflammatory ocular surface diseases such as Sjögren's syndrome and Steven-Johnson syndrome, and thermal, chemical, or radiation injury.
3. Seborrhea with secondary meibomianitis. One study is included in this group, a trial studying the effect of the ω-6 fatty acid γ-linolenic acid on MGD patients. The reported exclusion criteria were infectious keratoconjunctivitis; in-

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TABLE 4 (*continued*). Inclusion and Exclusion Criteria

Ref.	Exclusion Criteria
17	Contact lens wear, active ocular disease other than blepharitis, surgery within past 3 months, active ocular allergy, used isotretinoin within the past 6 months, or have autoimmune disease requiring treatment.
21	Eyelid defects, lagophthalmos, active ingredient sensitivity, pregnant/nursing mothers.
26	Topical therapy within 2 weeks before the beginning of the study.
8	Anterior blepharitis of more than moderate severity, infectious conjunctivitis, MGD with acute inflammation, seborrheic MGD. No patients wore CLs; unclear if this was an exclusion criterion.
20	Current punctal plugs, doxycycline, steroids, women of childbearing age with no contraception.
10	Eyelid structural abnormalities, active inflammation, fungal or viral infection, ocular surgery in the past 90 days, including LASIK or glaucoma surgery.
12	History of Sjögren's syndrome; Stevens-Johnson syndrome; chemical, thermal, or radiation injury; or any ocular surgery or procedure that would create an ocular surface problem. History of contact lens use.
15	Exclusions were not defined other than evidence of ocular disease.
16	History of ocular trauma or surgery, use of tear-influencing medications, systemic connective tissue disease, ocular conditions (blepharitis, meibomitis, or any anterior segment disease), contact lens intolerance due to poor lens fit, deposits, care system hypersensitivity.
18	Infectious keratoconjunctivitis, inflammatory disease unrelated to MGD, Schirmer I test result <10 mm/5 min, concomitant ocular disease, previous ocular surgery, alterations of the lacrimal drainage system, concomitant topical ophthalmic medic ations, topical ophthalmic steroids taken during the 4 weeks before the study; treatment with systemic drugs affecting.
19	Current use of treatments for blepharitis, current use of topical or systemic steroids, topical or systemic antibiotics, or topical or systemic antimetabolites, history of contact lens wear, history of eyelid surgery, presence of any ocular disease provoking dry eye syndrome and
24	Smokers, contact lens wearers, and diabetic patients.
14	Exclusions were not defined.
25	Eye disorders that could affect the ocular surface (e.g. infectious conjunctivitis), excessive meibomian lipid secretion, ≤10 mm by Schirmer II, and contact lens use.
1	Contact lens wear, eye surgery, punctal occlusion, and use of eye drops other than artificial tears within the past 3 months, ocular infection, pregnancy/nursing, changes in systemic medications altering the tear film, uncontrolled systemic disease.
2	Ocular adnexal disease that would interfere with warm compress application.
3	Exclusions were not defined.
4	Exclusions were not defined.
5	Exclusions were not defined.
6	Anterior blepharitis of more than moderate severity, infectious conjunctivitis, MGD with acute inflammation, meibomitis, seborrheic MGD.
7	Anterior blepharitis of moderate or greater severity, infectious conjunctivitis, occluded punctum, contact lens wear, best corrected acuity <1.0 logMAR, "obvious" eyelid skin abnormalities (atopic dermatitis).
9	Exclusions were not defined.
11	Exclusions were not defined.
13	Exclusions were not defined.
22	Exclusions were not defined.
23	Exclusions were not defined.

flammatory disease unrelated to MGD; Schirmer I test <10 mm/5 minutes; concomitant ocular pathologies; a history of ocular surgery; alterations of the lacrimal drainage system; concomitant topical ophthalmic medications; topical ophthalmic steroids taken during the 4 weeks before the study; treatment with systemic drugs affecting tearing, pregnancy, or diabetes; and other systemic, neurologic, or dermatologic disorders affecting the health of the ocular surface.

4. Meibomian therapy in CL wearers. The single paper in this group discussed the treatment of MGD in CL wearers. The exclusion criteria in this article were a history of ocular trauma or surgery; use of tear-influencing medication (e.g., antihistamine, antianxiety, anticholinergic); systemic connective tissue disease; ocular conditions such as blepharitis, meibomianitis, and any anterior segment disease; CL intolerance related to lens fit; the presence of deposits; and known care system hypersensitivity or toxicity.

The 39 exclusion criteria can be divided into three categories: (1) ocular disease–related, (2) iatrogenic, or (3) systemic

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TABLE 5. List and Frequency of Reported Criteria (All Studies Represented)

A. Inclusion Criteria	Frequency (%)
Age of Participants	
Adult patients	22/26 (84.6)
Pediatric patients	2/26 (2.7)
Adult and pediatric patients	1/26 (3.8)
Not mentioned	1/26 (3.8)
Symptomatology	
Ocular Surface Disease Index questionnaire	1/26 (3.8)
Symptoms fail to improve with conventional therapy	3/26 (11.5)
Discomfort or foreign body sensation	2/26 (7.7)
Eye redness	1/26 (3.8)
Photophobia	1/26 (3.8)
Ocular dryness	3/26 (11.5)
Contact lens intolerance	1/26 (3.8)
Ocular Symptoms Scale	1/26 (3.8)
Lid Margin Findings	
Previous or current diagnosis of MGD or posterior blepharitis	12/26 (46.1)
Posterior lid margin erythema or hyperemia	5/26 (19.2)
Eyelid edema	1/26 (3.8)
Lid margin thickening or irregularity	4/26 (15.4)
Meibomian gland orifice plugging	8/26 (30.8)
Cloudy, yellow, or frothy meibomian gland secretions	5/26 (19.2)
Lid margin telangiectasia	4/26 (15.4)
Meibomian gland capping	3/26 (11.5)
Meibomian gland loss/destruction	5/26 (19.2)
Chalazia	1/26 (3.8)
Eyelid inflammation (not defined)	2/26 (7.7)
Eyelid noninflammation	2/26 (7.7)
Ocular Surface Findings	
Rosacea-associated eyelid and corneal changes	3/26 (11.5)
Tear Film Findings	
Tear interferometry	1/26 (3.8)
TBUT<10 seconds	1/26 (3.8)
TBUT<5 seconds	1/26 (3.8)
Schirmer's test <10 seconds	1/26 (3.8)
Existing Classification Scheme	
McCulley Classification system for MGD[27]	2/26 (7.7)

B. Exclusion criteria[1,2,6–8,10,12,14–21,24,26]	Frequency (%)
Contact lenses use	10/17 (58.8)
History of ocular surgery	7/17 (41.2)
Eye disorders affecting the ocular surface	6/17 (35.3)
Meibomitis, seborrheic MGD, and excessive meibomian lipid secretion	4/17 (27.5)
Topical medical therapy (of any kind)	4/17 (27.5)
Infectious conjunctivitis	4/17 (27.5)
Systemic diseases affecting the ocular surface	4/17 (27.5)
Topical or systemic steroids use	3/17 (17.6)
Active ocular disease	3/17 (17.6)
Pregnancy or childbearing age without contraception	3/17 (17.6)
Stevens-Johnson syndrome	3/17 (17.6)
Chemical, thermal, or radiation injury	3/17 (17.6)
Decreased reflex tearing (<10 mm/5 min Schirmer test result)	2/17 (11.8)
Diabetes	2/17 (11.8)
Current treatment for blepharitis	2/17 (11.8)
Topical or systemic antibiotics	2/17 (11.8)
Alteration of lacrimal drainage system	2/17 (11.8)
Drugs affecting tearing	2/17 (11.8)
Sjögren's syndrome	2/17 (11.8)
MGD with acute inflammation	2/17 (11.8)
Anterior blepharitis with more than moderate severity	2/17 (11.8)
Active ocular allergy	2/17 (11.8)
Inflammatory diseases unrelated to MGD	2/17 (11.8)
Ocular adnexal pathology interfering with warm compress application	2/17 (11.8)
Lid structural abnormality	2/17 (11.8)
Topical or systemic antimetabolites	1/17 (5.9)
Eyelid surgery	1/17 (5.9)
Use of isotretinoin within the past 6 months	1/17 (5.9)
Autoimmune disease requiring treatment	1/17 (5.9)
Smokers	1/17 (5.9)
Punctal plugs	1/17 (5.9)
Anterior chamber inflammation	1/17 (5.9)
Glaucoma	1/17 (5.9)
Anterior segment diseases	1/17 (5.9)
Best corrected visual acuity <1.0 logMAR	1/17 (5.9)
Lid skin disease	1/17 (5.9)
Cicatricial conjunctival diseases	1/17 (5.9)
Sensitivity to study medication	1/17 (5.9)

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TABLE 6. Categories of 39 Exclusion Criteria in 17 Studies*

	Frequency (%)
Ocular Diseases (20/39; 51.3%)	
Eye disorders that affect the ocular surface	6/17 (35.3)
Meibomitis, seborrheic MGD, and excessive meibomian lipid secretion*	4/17 (23.5)
Infectious conjunctivitis	4/17 (23.5)
Active ocular disease	3/17 (17.6)
Stevens-Johnson syndrome	3/17 (17.6)
Meibomitis and seborrheic MGD†	3/17 (17.6)
Highly decreased reflex tearing <10 mm	2/17 (11.8)
MGD with acute inflammation†	2/17 (11.8)
Anterior blepharitis of more than moderate severity	2/17 (11.8)
Active ocular allergy	2/17 (11.8)
Inflammatory diseases unrelated to MGD	2/17 (11.8)
Ocular adnexal pathology interfering with warm compress application	2/17 (11.8)
Lid structural abnormality	2/17 (11.8)
Alteration of lacrimal drainage system	2/17 (11.8)
Anterior chamber inflammation	1/17 (5.9)
Glaucoma	1/17 (5.9)
Anterior segment diseases	1/17 (5.9)
Best corrected visual acuity <1.0 logMAR	1/17 (5.9)
Cicatricial conjunctival diseases	1/17 (5.9)
Lid skin disease	1/17 (5.9)
Iatrogenic (13/39; 33.3%)	
Contact lens use	10/17 (58.8)
Ocular surgery	7/17 (41.2)
Topical medical therapy (of any kind)	4/17 (23.5)
Topical or systemic steroids	3/17 (17.6)
Chemical, thermal, radiation injury	3/17 (17.6)
Current treatment for blepharitis	2/17 (11.8)
Topical or systemic antibiotics	2/17 (11.8)
Drugs affecting tearing	2/17 (11.8)
Topical OD systemic antimetabolites	1/17 (5.9)
Eyelid surgery	1/17 (5.9)
Use of isotretinoin within the past 6 month	1/17 (5.9)
Smoking	1/17 (5.9)
Plugs	1/17 (5.9)
Systemic Diseases (6/39; 15.4%)	
Systemic, neurologic, dermatologic diseases affecting ocular surface	4/17 (23.5)
Pregnancy/child bearing age without contraception	3/17 (17.6)
Diabetes	2/17 (11.8)
Sjögren's syndrome	2/17 (11.8)
Autoimmune disease requiring treatment	1/17 (5.9)
Sensitivity to study medication	1/17 (5.9)

* Refs. 1, 2, 6–8, 10, 12, 14–21, 24, and 26.
† Exclusion criteria directly addressing the lid margins and meibomian glands (3/39; 7.7%).

disease-related. Table 6 describes the systemic disease–related exclusion criteria.

1. Exclusion criteria concerning the presence or history of ocular disease was the most frequently reported (20/39 criteria; 51.3%). Among these, three (7.7%) criteria described the presence of meibomian gland dysfunction, defined by the authors as seborrhea and/or acute or chronic meibomitis. These three exclusion criteria were reported in four papers regarding the treatment of obstructive MGD and in one paper about MGD therapy in CL wearers.
2. Exclusion criteria related to iatrogenic events was the second most common category, with 13 of 39 exclusion criteria (33.3%) falling in this category. Among these, medical therapy, surgical therapy, use of CLs or punctal plugs, and smoking are included.
3. The last group of exclusion criteria refers to the presence of systemic diseases, pregnancy or being of childbearing age without contraception, and known sensitivity to study drugs. This group of exclusion criteria included 6 of the 39 criteria identified (15.4%).

Comments. Inclusion and exclusion criteria define the patient sample of all types of studies. In studies of MGD, it is crucial to state how MGD is diagnosed, use consistent terminology, and carefully define clinical characteristics. Dividing exclusion criteria into three categories (ocular disease-related, iatrogenic, and systemic disease-related) can help in producing a logical list of eligible and ineligible subjects, suitable for each trial. Further consistency in entry and exclusion criteria in clinical trials related to MGD is needed.

Outcome Measures (Endpoints): Primary and Secondary

Overview. Many of the studies we evaluated were relatively small in sample size and were exploratory in nature. Therefore, several clinical variables were regarded as outcome variables, without identifying specific primary and

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TABLE 7. Clinical and Symptom Outcomes

		Eyelids						
Ref.	First Author	Lid Margin Appearance	Lid Margin Injection/ Erythema/Redness	Tarsal Telangiectasia	Edema	Debris	Inflammatory Cell Density	Temperature
17	Perry HD		Yes	Yes				
21	Schechter BA							
26	Yoo SE							
8	Goto E							
20	Rubin M		Yes	Yes				
10	Luchs J		Yes		Yes	Yes		
12	Matsumoto Y		Yes			Yes	Yes	
15	Olson MC							
16	Paugh JR							
18	Pinna A		Yes		Yes			
19	Romero JM	Yes						
24	Souchier M							
25	Yalcin E							
14	Mori A							
1	Albietz JM							
2	Blackie CA							Yes
3	Cetinkaya A							
4	Dougherty JM							
5	Epstein GA				Yes			
6	Goto E							
7	Goto E							
9	Ishida R							Yes
11	Matsumoto Y							Yes
13	Meisler DM							
22	Shine WE							
23	Song CH							

(*continues*)

secondary outcomes. The outcomes, therefore, can be grouped on the basis of clinical appearance. The main clinical characteristics can be categorized as follows:

- Symptoms (dry eye or blepharitis) and visual disturbance (fluctuation)
- Eyelid assessment (lid margin injection/hyperemia, blocked meibomian glands, debris on lashes, tarsal and lid margin telangiectasia, and edema)
- Tear film parameters (TFBUT, interferometry, aqueous production, and osmolarity)
- Ocular surface involvement (corneal and conjunctival staining)
- Inflammation of the ocular surface (injection)
- Abnormal meibum (expressibility, quantity, and quality)
- Bacterial involvement.

Defining the characteristics in this manner allows the outcome measures to be better contextualized, given the diversity of the disease. The individual papers were categorized according to the characteristics, and the main outcome measures are described in Table 7. All relevant studies independent of their level of evidence were included.

In these studies, it can be assumed that all types of MGD are more or less chronic, although chronicity was not explicitly described in all cases (none were described as acute). Future studies may include more specific terminology on the basis of the terminology proposed in the Report on Definition and Classification.

Results. While several outcome measures were used, a likely reflection of the diversity of the disease, the methods used to grade change varied. In general, there appeared to be no distinction between primary and secondary endpoints. In studies in which scales were defined, categorical or ordinal scales were often used (e.g., yes/no; graded 0–4; or none, mild, moderate, or severe).

The changes in outcome measures can be summarized as follows:

- Symptoms (improvement in total ocular symptom score, specific dry eye symptoms, reduction of visual fluctuation, and increase in comfortable CL wearing time)
- Eyelid assessment (reduction in graded severity)
- Tear film parameters (increased aqueous production TBUT and improvement in tear lipid layer interference)
- Ocular surface involvement (reduction in graded severity of staining)
- Inflammation of the ocular surface (reduction in graded severity injection)
- Abnormal meibum (improved expressibility, quantity, and quality)
- Bacterial involvement (reduction of bacterial load)
- Improvement/reduction of the recurrence of inflammation (chronic lid margin, corneal, and chronic granulomatous disease).

The most frequently reported outcome measures in the 26 papers included ocular symptoms (14, 53.8%), TBUT (14, 53.8%), meibomian gland secretion and expression (9, 34.6%), Schirmer I (10, 38.5%), corneal staining (8, 30.8%), meibomian gland obstruction (6, 23.1%), eyelids (5, 19.2%), and lipid layer interference (5, 19.2%).

Outcome measures associated with signs and symptoms of dry eye and not necessarily specific to MGD were used in most of the publications. Parameters related to evaluation of the eyelids have been more frequently used in recent years, and direct assessments of the glands have increasingly been used as outcome measures in the more recent papers.

There were no major differences in the choice of outcome measures when the evaluation was limited to papers of evidence level I or II.

Comment. The importance of signs and symptoms of dry eye appears evident in the outcome measures described in the literature. Specific symptom surveys for MGD as well as uniform grading of eyelid margin findings are needed. It is somewhat surprising that the different outcome measures selected in different trials appeared not to be associated with the different manifestations of MGD, but instead were

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TABLE 7 (*continued*). Clinical and Symptom Outcomes

	Meibomian Glands					Inflammation		Ocular Surface				
Ref.	Papillary Hypertrophy	Expression/ Secretion	Destruction (Meibography)	Obstruction/ Plugging	Meibum Composition	Improvement	Recurrence	Conjunctival Hyperemia	Conjunctival Papillae	Conjunctival Staining	Corneal Staining	Corneal Neovascularization
17	Yes			Yes				Yes		Yes	Yes	Yes
21		Yes									Yes	
26			Yes	Yes								
8				Yes		Yes	Yes					
20		Yes										
10		Yes		Yes								
12		Yes	Yes							Yes	Yes	
15												
16												
18		Yes		Yes				Yes	Yes		Yes	
19												
24		Yes			Yes						Yes	
25												
14		Yes										
1												
2												
3						Yes	Yes					
4												
5		Yes				Yes	Yes					
6												
7		Yes	Yes	Yes						Yes	Yes	
9										Yes	Yes	
11										Yes	Yes	
13						Yes						
22					Yes							
23												

(*continues*)

evenly distributed, independent of how the disease was expressed.

Treatment

Overview. Twenty-three of the 26 eligible studies had sufficient information to be assessed under the following categories (Table 2):

- Treatment type (pharmacological, homeopathic, surgical, and external)
- Dose regimen
- Concurrent treatment
- Control treatment
- Duration
- Washout
- Follow-up.

Results. Pharmacologic test treatments used in 11 (42.3%) of the 26 studies included systemic or topical macrolide antibiotics (3, 11.5%), systemic tetracyclines (4, 15.4%, in one case with topical prednisolone and tobramycin), and topical anti-inflammatory/immunosuppressive drugs (4, 15.4%). Homeopathic test treatments were used in three (11.5%) of the studies, including two with topical agents (honey or oil drop) and one with a systemic agent (linoleic acid). External treatments were reported in nine (34.6%) studies, including heat (warm compresses or a warming device) in seven (26.9%), lid hygiene in one (3.8%), and both treatments in one (3.8%).

Systemic treatments were almost invariably used twice daily. Dose regimens for tetracyclines ranged from 20 to 200 mg of doxycycline twice daily, 50 mg daily or 50 mg twice daily of minocycline, or 30 to 350 mg of erythromycin twice daily.

Concurrent treatment was continued or instituted in 10 trials. Artificial tears were used in nine trials and lid therapy in five, of which four used only lid hygiene. One study allowed whatever treatment in use 1 month before the trial to continue to be used throughout the trial. Most did not disclose whether concurrent treatment was continued.

Nine studies used some form of treatment in the control group. Lid hygiene was the most frequent treatment in the control group (three studies); one study used heat, one used conventional eye masks, and one used warm towels. Control groups were assigned to artificial tears in three studies; one of those studies also used lid hygiene. One study involved a placebo control for systemic doxycycline.

A single application was used in four eyelid heat trials. Three devices were tested using one 10-minute application and then a 2-week trial. Including this trial, there were seven trials involving 2-week treatments. The other most common length for a trial was 3 months (six studies). There were four trials of treatments lasting 2 weeks to 3 months and three trials with treatment lasting longer than 3 months.

No washout period (run-in period) was observed in the majority ($n = 17$) of the trials. Artificial tears were prescribed for the washout in two trials (specified for 2 weeks in one of these). One study discontinued the use of systemic doxycycline for 2 weeks before the study's start. No topical therapy was specified before two of the trials, with trial duration of 2 weeks one and of 3 months in the other. In the 3-month washout trial, artificial tears were allowed to be used, but no punctual occlusion or CL use was permitted.

To standardize treatment, some studies required all subjects to use lid scrubbing and artificial tears at entry. Standardizing treatment for lid disease may help decrease confounding variables when evaluating a new treatment. Using standard treatment for 2 to 4 weeks before randomizing subjects may help eliminate the placebo responders and provide better baseline information.

Five studies included a follow-up (to rule out relapse) after 2 to 3 months.

Comment. Most trials lacked a washout period and did not check for relapse; half allowed concurrent use of other treatments and a third allowed treatment in the control group. There was a large variability between duration of studies, but pharmacological trials tended to be of longer duration and were more likely to have a follow-up period than those using external factors and were more likely to have a follow-up period.

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TABLE 7 (*continued*). Clinical and Symptom Outcomes

	Microbial			Tear						
Ref.	Change In Flora	Lipase Production (In Vitro)	Bacterial Growth Inhibition (In Vitro)	TBUT	Schirmer I (w/wo Anesthesia)	Mucous Fern Test	Evaporation Rate	Lipid Layer Interference Pattern/ Thickness	Lysozyme Levels or PLA2 Type Activity	Foam (Tear Meniscus)
17				Yes	Yes w a					
21					Yes	Yes w a				
26				Yes	Yes wo a					
8				Yes			Yes	Yes		
20				Yes	Yes				Yes	
10										
12				Yes	Yes wo a					
15								Yes		
16				Yes						
18					Yes					Yes
19				Yes						
24				Yes						
25				Yes	Yes	Yes				
14				Yes				Yes		
1	Yes									
2										
3										
4		Yes	Yes						Yes	
5										
6										
7				Yes	Yes		Yes			
9				Yes	Yes wo a			Yes		
11				Yes	Yes wo a			Yes		
13										
22										
23									Yes	

(*continues*)

Statistical Considerations

Overview and Results. There were a limited number of well-conducted, randomized controlled trials available for statistical review. None of these studies gave much detail related to the calculation of effect size, power, or required sample size. There was limited information on how missing data—for example, loss to follow-up and exclusion due to noncompliance—were handled.

ADDITIONAL CLINICAL TRIALS

Additional ongoing clinical trials from ClinicalTrials.gov were retrieved with the search term *meibomian*. The relevant ones are listed in Table 8.

Comments. Several of the ongoing clinical trials are randomized double-masked placebo-controlled studies with well-defined primary and secondary outcome measures. Results from these trials may add to the list of clinical trials on MGD with a high evidence grades. At the time of this compilation, however, none of those studies had published results.

NECESSARY MGD TRIAL DESIGN IMPROVEMENTS

Decisions concerning the design of future trials should be based on available data from reliable studies published in peer-reviewed journals. Such studies should be prospective randomized double-masked (when possible) and controlled with a sufficiently large MGD sample.

To date, very few trials have met those stringent criteria, although as already noted, several are under way. It is unknown when, if ever, the results of those ongoing trials will be published.

Objectives

Although generic clinical trial design recommendations are available, design recommendations specific to MGD should include trials with well-defined objectives. Those objectives should be clearly stated and allow for concise and specific questions to be answered. Important and basic questions to address in MGD are:

- Is there an association between MGD and dry eye disease? Can we distinguish between MGD and dry eye disease? How? Our review of past clinical trials of MGD suggests that there is no clear consensus. Some researchers include subjects with dry eyes, others exclude them, and still others fail to evaluate dry eye status altogether. Given the current lack of sufficient reliable data, answers to this question can only be tentative; no conclusive recommendations are possible. MGD appears to be clinically associated with alterations in the quality and quantity of lipids secreted by the meibomian glands, which contribute to the preocular tear film. Many clinicians believe MGD is the most common cause of evaporative dry eye and that there is considerable overlap in the occurrence of MGD and aqueous-deficient dry eye states, both demonstrating typical signs and symptoms suggestive of dry eye disease. Studies that evaluate the possible role of MGD in aqueous deficiency, possibly through creating an inflammatory state on the ocular surface, would also be welcome.
- Given that there is considerable uncertainty between MGD and dry eye disease, trials that evaluate the association between MGD and dry eye would be beneficial, as would observational trials that assess the natural history of MGD. Of special value would be a standardized symptom questionnaire that could distinguish MGD lid disease from dry eye disease.
- Developing alternative or indirect ways of assessing and testing MGD would also be desirable. Accurate, repeatable measures of symptoms are of obvious value as outcome measures and are directly relevant to the patient's health. Quantitative measures of disease may also be useful, especially if it can be shown that reversal improves long-term health. Examples include osmolarity, interferometry, high resolution OCT, tests that can measure visual function and interblink visual acuity decay, and techniques that identify differences in the meibum. To learn how to use such tools, researchers need standardized video and/or web-based training. Clinical studies demonstrat-

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TABLE 7 (*continued*). Clinical and Symptom Outcomes

	Symptoms		Other		
Ref.	General Ocular	Face Scores	Progression of Post-Surgical Healing	Overall Disease Improvement	Safety
17	Yes				
21	Yes				
26	Yes				
8		Yes			
20	Yes				
10	Yes				Yes
12	Yes				
15					
16					
18	Yes (OSDI)				
19	Yes				
24					
25					
14	Yes				
1					
2					
3	Yes				
4					
5	Yes		Yes		
6					
7	Yes	Yes			
9	Yes				
11	Yes				
13				Yes	
22					
23					

ing the correlation between the results of these tests and clinical findings, such as symptoms or signs, should be executed first.

Design

The most desirable clinical trials would be prospective, randomized, controlled, and double-masked, if possible. Considerations important in good clinical trial design should be incorporated into any MGD trial (e.g., Guidelines from International Conference on Harmonization [ICH] E6 Good Clinical Practice: Consolidated Guidance,[28] ICH topic E8 General Consideration of Clinical Trials;[29] ICH topic E9 Statistical Principles for Clinical Trials[30]; and E10 topic Choice of Control Group and Related Issues in Clinical Trials,[31] see www.ich.org). Other types of designs, such as epidemiologic or registry studies, entail other considerations.

Selection of Subjects and Inclusion/Exclusion Criteria

Past MGD clinical trials did not have a uniform way of defining the study population, although symptoms and changes in the lid, especially plugging and abnormal secretions, were the most common clinical characteristics that were selected. Of note, dry eye disease was not usually specifically included or excluded in selecting patients, other than in subject recruitment based on symptoms. Signs of dry eye disease were uncommonly used as selection criteria but were often assessed to determine improvement. Future studies should carefully consider inclusion of tests for dry eye disease.

Clearly, the clinical trial study population must be rigorously defined. A robust classification system for MGD is important; however, in an interventional clinical trial, a system should be based on accessible and validated objective and/or subjective clinical signs and symptoms that are relevant to ocular surface health and are responsive to intervention. Noninterventional, exploratory therapeutic, or mechanistic studies may involve additional measurements (biomarkers or clinical signs) not feasible in a large population, according to the trial objective. Such studies may involve testing procedures that do not translate to a multicenter clinical trial or to more generalized patient care.

A consistent, standardized classification system is important in measuring the effects of intervention, in establishing natural history, and in defining inclusion and exclusion criteria. Two approaches can be taken when grading or classifying patients: grading of individual clinical characteristics or classification based on global severity. Individual grading is discussed in the Report on Diagnosis, whereas the Report on Management and Therapy utilizes a clinical-staging approach to determining disease according to a uniform grading methodology and not exclusively by tear and ocular surface characteristics. Development of such a consistent grading and evaluation methodology across all research in MGD would facilitate comparisons between studies.

To emphasize continuity between graders and examiners, a training program for researchers both for diagnosis and grading could be developed, perhaps using web-based delivery. Such a training program may assist in ensuring concordance between investigators and improve data quality. It might also include reading centers such as those used in other vision-related studies (i.e., those of the retina, glaucoma, and keratoconus).

An important aspect in MGD may be ethnicity. Ethnic differences may influence the choice of study population, as it may affect the study medication's safety, efficacy, dosage and dose regimen. Since epidemiologic data indicate a substantially higher prevalence of MGD in people of Asian descent, one must consider that both extrinsic (e.g., culture, including diet and medical practice) and intrinsic (e.g., genetic polymorphism; ICH E5: Ethnic Factors in the Acceptability of Foreign Clinical Data)[32] factors have a potential to influence the outcome of a clinical trial. The ability to generalize results will also reflect the homogeneity (or lack thereof) of the study population.

Appropriate inclusion and exclusion criteria are essential to ensuring the integrity of the trial. Previously published clinical studies have not adequately identified clinically relevant and specific inclusion criteria for MGD that differ from

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TABLE 8. Relevant Registered Clinical Trials

Condition	Title	Interventions	Status	Outcome	Comment
MGD	A Single-Center, Double-Masked, Randomized, Vehicle Controlled Study to Evaluate the Safety and Efficacy of Testosterone 0.03% Ophthalmic Solution Compared to Vehicle for the Treatment of MGD	Testosterone ophthalmic solution vs. vehicle	R	Primary: MG secretion (128 days) Secondary: comfort (128 days)	Phase II, enrollment by invitation only
MGD	Efficacy of 0.05% Cyclosporine Ophthalmic Emulsion Compare with Tear in MGD	0.05% cyclosporine eye drop	R	Primary: NTBUT (0,1,2,3 month) Secondary: OSDI score, TBUT, fluorescein/rose bengal staining, MG (0,1,2,3 month)	Phase IV
Blepharitis	Lipids of the Human Tear Film and Their Effect on Tear Stability	Doxycycline; essential fatty acid; azithromycin	R	Primary: inflammation of eyelid (2 months) Secondary: character of MG secretion (2 months)	Phase IV
Dry eye syndrome	A Prospective Clinical Study Assessing the Effects of Tetracycline Antibiotic on Tear Film and Tear Lipid Composition within a Population of Patients Diagnosed with Blepharitis and Dry Eye Disease Condition	Tetracycline: doxycycl ine analog	T	Primary: evaporimetry; fluorophotometry; MG expression and lipid analysis Secondary: Schirmer's, TBUT, bacteriology, transillumination and meibography	
Blepharitis	A Placebo-Controlled Double-Masked Clinical Assessment Study of Essential Fatty Acid Supplement and Its Effect on Patients with Apparent Aqueous-Deficient Dry Eye Syndrome Condition	Essential fatty acid supplement	R	Primary: lipid bio chemistry changes Secondary: evaporimetry and fluorophotometry	Phase IV
Posterior blepharitis	Topical IL-1-Ra for Treatment of Posterior Blepharitis	2.5% IL-1Ra, Placebo; 5% IL-1Ra	R	Primary: MG secretion/quality, TBUT, cornea and conjunctival staining, and OSDI questionnaire (12 weeks) Secondary: MG occlusion, Schirmer with and without anesthesia. (12 weeks)	Phase I/II
KCS	Efficacy and Safety Study of Nutritional Supplements for Treatments of Dry Eye Condition	Dietary supplement: Hydroeye; vs. inactive capsule	R	Primary: Schirmer, OSDI, TBUT, corneal staining (screening at weeks 4, 12, and 24) Secondary: Corneal topography, MGD, facial expression subjective scale, artificial tear usage, HLA-DR staining of impression cytology (screening, at weeks 12 and 24)	Signs of MGD were inclusion criteria
Blepharitis meibomitis; dry eye	Treatment of Patients With Blepharitis and Facial Rosacea	Doxycycline vs. placebo	R	Primary: Change in OSDI, bulbar conjunctival hyperemia (baseline to end of study) Secondary: Change in Schirmer result, TBUT, meibum character/fluidity, MG inspissation (baseline to end of study)	Phase II

Source: Clinicaltrials.gov, accessed March 2010. R, recruiting; T, terminated; OSDI, Ocular Surface Disease Index; KCS, keratoconjunctivitis sicca.

those for dry eye disease. In general, the use of CLs has been a major reason for excluding subjects from trials, followed by exclusion criteria related to general ocular surface conditions or past surgery. In early phases of drug development, the inclusion and exclusion criteria may be very stringent, to maximize the chance of observing specific clinical effects of interest. These restrictive criteria may result in selection of a sample from a very narrow subgroup of the total patient population for which a treatment may eventually be indicated. However, in later confirmatory trials, subjects should more closely mirror the target population. The inclusion and exclusion criteria should be relaxed as much as possible to allow researchers the ability to suggest generalizations for routine patient care.

Selection of the Control Group

Control groups have one major purpose: to allow discrimination of patient outcomes (for example, changes in symptoms, signs, or other morbidity) caused by the test treatment from outcomes caused by other factors, such as the natural progression of the disease, observer or patient expectations, or other treatment. Therefore, the choice of control group is always a critical decision in designing a clinical trial.

In most cases, the primary choice is to use a concurrent control group. The test and control groups should be similar with regard to all baseline and on-treatment variables that could influence outcome, except for the study treatment. In MGD, such baseline factors could be related to age, ethnicity, systemic disease, concurrent medication, and environ-

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mental factors, to cite just a few examples. Randomization reduces potential bias between the experimental and the control group. To further minimize the risk of bias, the study should be double-masked, so that both the subject and the examiner are unaware of the medication versus placebo assignment. When double-masking is not possible, which may be the case in MGD if, for example, lid scrubbing is part of one treatment regimen (the examiner could remain masked), efforts to identify which outcome measures can be masked to an independent evaluator should be made as well as efforts to minimize subject discussion related to the therapy.

Currently there is no well-defined, accepted standard of care in the treatment of MGD. Therefore, careful discussion with regulatory agencies may be needed for study design issues such as a control paradigm. In the absence of an established standard of care, it is important to define the control or comparator treatment—for example, placebo control (vehicle) and/or lid hygiene.

Although choosing a comparator in a superiority trial in MGD may be straightforward, in a noninferiority trial for MGD, there is no established treatment with which to compare. Further, a clinically relevant noninferiority margin of error or range has to be determined. Other types of studies may include a crossover design. In such a case, it would be critical to address whether there is interference between treatments and what would define a suitable washout period. In any clinical trial in MGD, it is critical to address potential confounders, such as the effects of concurrent treatment (in the current literature, the most common concurrent treatments include lid hygiene and artificial tear substitutes), washout of current treatment, and treatment during the run-in phase of a study. Standard operating procedures to manage these situations should be clearly defined in the study protocol.

Duration of the Trial

In MGD, there has been a large variability in the duration of the studies reviewed. Pharmacologic trials tended to be of longer duration than those assessing other nonpharmacological factors and were more likely to include a follow-up period after treatment discontinuation. As in any clinical trial, the treatment duration must be sufficiently long to obtain the desired outcome. A follow-up period to address recurrence after treatment termination would be desirable. In pharmacologic treatment trials, the trial duration should correspond with the proposed clinical care treatment duration to adequately address any safety issues that the treatment regimen might create in a real-world setting.

Sample Size

The power of the study, calculated on the basis of the primary outcome measure in a study—for example 80% (generally accepted as the recommended minimum value)—is the ability of a test to detect an effect, if any.[33] For example, if a previous trial has demonstrated a clinically meaningful decrease in corneal staining, evaporation, or tear osmolarity with a certain treatment, such data would be used to calculate the number of patients needed to achieve (at least), with the desired probability, a similar magnitude of effect in the planned trial. Necessary components in calculating statistical power include effect size, variability, sample size, and significance level.[34] Given that there is limited published information available to assist with sample size or power estimates in MGD trials, the calculations are likely to be based on preliminary and/or uncertain data and information. Data from exploratory or early-phase studies continue to be needed. Presently, data comparing specific characteristics in normal and diseased subjects should be used to assist in obtaining data on a potential effect of a treatment and therefore in calculating sample size. An interim check (on masked data) to adjust the sample size may also be useful, but must be performed with extreme caution and is best suited in pilot work. A revised sample size may then be calculated by using suitably modified assumptions (ICH E9).[30] When estimating a sample size, additional subjects should be included to compensate for withdrawal or loss to follow-up. These additional subjects are especially important in longer term trials or trials with complicated or noxious therapies in which a higher withdrawal rate is expected. A sufficient sample size is also needed to appropriately address the safety of an intervention (ICH E1).[35]

Outcome Measures

Primary outcome measures or endpoints, as well as secondary outcome measures or endpoints, should be clearly defined in MGD trials. The selected outcome measures should provide the most clinically relevant and convincing evidence directly related to the objectives of the trial. Generally, the primary endpoint is one that demonstrates a clear quantitative measure of benefit. In MGD, the choice of outcome measures related to efficacy of an intervention would probably be dependent on the classification and severity of disease. The classification recommended by the Definition and Classification Subcommittee is based on pathophysiological changes in which the main categories are low- and high-delivery states. Consequently, in a low-delivery state such as an obstructive condition, a reasonable endpoint could include assessment of lid margin inflammation and/or gland obstruction. Likewise, disease severity or disease progression may be variables of interest. MGD severity staging, such as the scheme found in the Report on Management and Therapy, may include several clinical characteristics within a disease severity stage and could be used in clinical trials, but may lack the sensitivity of an individual grading scheme for a unique clinical test. Therefore, outcome measures have to be carefully selected to address the hypothesis of the proposed study.

In many of the past clinical trials, outcome measures have reflected ocular surface rather than lid signs (tear status and ocular surface staining). Such measures may reflect the concurrence of MGD and dry eye disease, especially in evaporative dry eye disease, in which lipid abnormalities are thought to lead to changes in tear film stability.[36] In such conditions, typical signs of dry eye disease (TBUT, vital staining of the cornea and conjunctiva, and Schirmer's test result) would be appropriate outcome measures for MGD. In addition, as discussed in the Report on Diagnosis, in the evaporative dry eye state, significant differences in tear turnover rate, evaporation, and osmolarity may be seen between evaporative dry eye and normal subjects. The use of such clinical endpoints is promising, but must have further evaluation. Accordingly, MGD trials should include adequate information about tear film parameters (typically included in the description of tear-deficient states), in addition to descriptions that delineate the extent of the lid margin disease. Endpoints associated with lid findings may be selected as primary or as important secondary outcome measures and graded using a uniform grading methodology. Of note, it is unclear whether existing grading scales reflect linear progression in severity, and efficacy may therefore be difficult to demonstrate for more severe disease.

As in dry eye disease, it would also be essential to evaluate treatment effects on symptoms specific to MGD but also including foreign body sensation or irritation; itching; burning, swollen eyelids; a feeling of dryness; excessive tearing; and a crust on the eye lashes, especially in the morning. These symptoms are very similar to those reported in dry eye disease.

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To better define and evaluate patient symptoms in MGD, a specific and validated questionnaire specific to MGD is highly desirable, not only to differentiate between dry eye and MGD, if possible, but also to address a response to treatment. The use of electronic symptom diaries may improve real-time data collection, data quality, and accuracy.

Depending on the etiology, manifestation, and severity of the disease, additional outcome measures such as tear and ocular surface characteristics may be highly relevant endpoints. The clinical value of commonly used endpoints such as (but not limited to) changes in lipid layer interference pattern, meibum expressibility, quality and composition, and tear evaporation rate should have further evaluation.

Surrogate Endpoints and Biomarkers

Besides moving science forward, the use of surrogate endpoints or biomarkers has potential benefits during drug development. For example, data may be obtained sooner or by more uncomplicated and less invasive methods and may be ethically preferable or less costly. However, in MGD, there is no information on the specificity or sensitivity of biomarkers, let alone knowledge about how they may change in response to therapy. From a regulatory perspective, the use of surrogate endpoints or biomarkers in clinical trials depends on which weight these are given and what claims would be associated with data relying on such endpoints. In exploratory trials during earlier development of a drug, a surrogate endpoint or biomarker may be used as a secondary, or even as a primary, endpoint. A surrogate endpoint could, for example, be used to obtain a proof of concept, to aid in dose selection, to give support on a mechanism of action, or for subgroup characterization. Also in confirmatory trials, surrogate endpoints or biomarkers may be included. Regulators are often liberal, or even encouraging, when such endpoints are used during early development or as exploratory endpoints in a confirmatory study. Again, it depends on which weight the results associated with these endpoints will be given. If, on the other hand, a surrogate is to be used as a primary endpoint, the link to and relevance of a clinical outcome, or an outcome that matters for the patient (short or long-term) must be established. Surrogate endpoints must be validated by using clinical trial data, with both the surrogate and true endpoint in a representative patient sample. In such validation, the following guidelines should be considered. The surrogate endpoint or biomarker should be:

- Mechanistically plausible
- Able to predict clinical outcome (earlier, or in parallel with the "true outcome")
- Able to measure efficacy, severity, and safety
- Able to change with intervention and to predict an effect of treatment on a clinical outcome
- Standardized and reproducible between investigators and clinical trial centers.

Methods of Minimizing Bias

In MGD, specific considerations should be given to masking, compliance to study treatment, washin/washout, concurrent treatment, and methods for handling missing data. The latter could be critical and should be handled differently; for example, based on whether the condition is expected to progress or improve during the study period without treatment or whether discontinuations are due to adverse effects of an active treatment.

Treatment

Treatment duration must be clearly defined. Most past clinical trials in MGD have lacked a washout period and did not monitor relapse after the study's end. Other studies allowed concurrent use of other treatment or treatment in the control group. Omitting washout or allowing concurrent medication may affect the ability to perform a robust efficacy or safety evaluation. If no confounding effects are suspected with a certain concurrent treatment, allowed (as well as not allowed) medications should nevertheless be predefined and monitored, and any potential effects on the study outcome should be identified.

Adherence to Study Protocol

Adherence to some management measures, including the use of lid scrubbing and hygiene, may be difficult to maintain. When such measures are included in a trial, it is critical that adherence be monitored with patient diaries. In addition, it may be wise to increase the sample size of the study, since a higher dropout may be expected.

Assay Sensitivity

Given that limited information is available on the magnitude of treatment effects in previous clinical trials in MGD, additional information would be of value before confirmatory therapeutic studies are performed that have a high probability of showing the desired outcome. Such information includes the magnitude of clinically relevant effect or noninferiority margins and which magnitude of a placebo response to expect.

Modifications of the Protocol

As previously discussed, interim analyses to assist in adjusting the sample size may be useful. In earlier phases of clinical development in MGD, an adaptive study design involving design modifications based on the results of an interim analysis may also be used to speed up the process of drug development or to allocate resources more efficiently without lowering scientific and regulatory standards. Assay sensitivity is especially essential during noninferiority trials, so that the trial data are not compromised. In such a trial, one way to ensure this would be to include a placebo group as a third arm.

Statistical Plan

As in any clinical trial, the principal features of the eventual statistical analysis of the data should be predefined and described in the statistical section of the protocol, for example, methodology for handling missing data, perhaps due to loss to follow up, noncompliance, or withdrawal due to adverse events. The ICH Topic E9, Statistical Principles for Clinical Trials,[30] should be considered.

Future studies would be well served by more clearly defining the study population, especially if a multicenter trial is planned. Including evaluation for dry eye disease will help in defining its association with MGD disease and determining the effect of treatment on signs and symptoms associated with dry eye disease.

Summary

We suggest the following main priorities in future clinical trials in MGD:

- Natural history of MGD
- The association between MGD and dry eye disease
- A specific and validated questionnaire for symptoms of MGD
- Standardized grading for lid and other signs in MGD
- Feasibility and clinical value of lipidomic and protein inflammatory mediators
- Validation of surrogate clinical outcomes related to MGD.

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