Journal of Cardiovascular Disease Research

ISSN:0975 -3583,0976-2833 VOL14, ISSUE 02, 2023

COMPARISON OF THE EFFICACY OF TOPICAL CYCLOSPORINE VS TOPICAL TACROLIMUS OVER 6 MONTHS IN PATIENTS OF MEIBOMIAN GLAND DYSFUNCTION (MGD)

Dr. Ishwar Singh[1], Dr. Harsimran Singh[2], Dr. Aseem Mehta[3], Dr. Chiman Lal[4*]

1. Associate Professor, Deptt of Ophthalmology, GMC Patiala, Punjab, India.
2. Professor, Deptt of Ophthalmology, GMC Patiala, Punjab, India.
3. Junior Resident, Deptt of Ophthalmology, GMC Patiala, Punjab, India.
4. Assistant Professor, Deptt of Ophthalmology, GMC Patiala, Punjab, India.

***Corresponding Author**

Dr. Chiman Lal, Assistant Professor, Deptt of Ophthalmology, GMC Patiala, Punjab, India.

Email Id: chimanparmjit@yahoo.co.in

ABSTRACT

Aim: To compare the efficacy of topical cyclosporine vs topical tacrolimus over 6 months in patients of meibomian gland disease (MGD).

Methods: A prospective, Randomized Trial on 100 patients was conducted and patients were divided into two groups. Group 1: eye drops cyclosporine (0.05%) BD and Group 2: eye ointment Tacrolimus (0.03%) HS per day, both for 4 months, along with conservative management to all the patients throughout the study. Follow-up was done at 7 days, 4 weeks, 3 months and 6 months. Severity of five main symptoms was measured on a 4-point categorical scale (0–3) according to patients' response to questions: itching, burning, foreign body sensation, dryness and eyelid swelling. Slit lamp examination was performed to assess and record the severity of seven signs on a 4-point categorical scale: MG secretion, number of plugged gland orifices, conjunctival injection, lid margin redness, lid margin debris, Tear break up time (TBUT), and ocular surface staining with fluorescein. MGD was diagnosed based on having at least two symptoms and two signs (one must be the presence of meibomian gland signs) with a minimum severity score of 2 for each.

Results: There was a predominant male distribution as 58% of patients were males. There was significant improvement at each follow-up in mean symptom score post-treatment with both cyclosporin and tacrolimus with no significant difference between two groups. There was

ISSN:0975 -3583,0976-2833 VOL14, ISSUE 02, 2023

significant improvement at each follow-up in mean sign score, Schirmer Test Score and total score post-treatment with both cyclosporin and tacrolimus with no significant difference between two groups. The common side effects of both the medications were transient stinging, transient redness and transient burning.

Conclusion: Both the drugs significantly improved the symptoms and signs in MGD patients. There was no significant difference between the efficacy of two drugs at 6 months. However, tacrolimus had minor side effects which last longer than cyclosporine but they were statistically not significant.

Keywords: Meibomian Gland Disease (MGD), Cyclosporin, Tacrolimus

INTRODUCTION

According to the International Workshop on MGD and the TFOS DEWS II, Meibomian Gland Dysfunction (MGD) is a chronic, diffuse abnormality of the Meibomian Glands, commonly characterized by obstruction of the terminal duct and/or quantitative/qualitative changes in the secretions of the meibomian glands. This may result in alteration of the tear film, clinically apparent inflammation, symptoms of eye irritation, and ocular surface disease. (1,2) MGD occurs as a result of terminal duct obstruction by thickened meibum that contains keratinized cell material formed by hyperkeratinization of the ductal epithelium. The obstruction of the Meibomian Glands may lead to intra-glandular cystic dilatation, gland dropout, meibocyte atrophy and low secretion, leading to increased evaporation of the tear film causing evaporative dry eye, increased bacterial growth and ocular surface inflammation and damage. 1 Alterations in the lipid phase of tear film points towards MGD, hence, it may, thus, be accepted that MGD is important, underestimated, and probably the most common cause of dry eye disease due to increase evaporation of tears (3) Topical Cyclosporine and topical Tacrolimus have both shown to have beneficial effects in the management of MGD. Although, the previous studies have shown the efficacy of both Topical Cyclosporine and topical Tacrolimus in the treatment of MGD, to the best of our knowledge there has been no study in India comparing their effects over extended period of 6 months. Therefore, this study was conducted to compare the efficacy of Topical Cyclosporine versus the efficacy of topical Tacrolimus over 6 months in patients of MGD.

ISSN:0975 -3583,0976-2833 VOL14, ISSUE 02, 2023

MATERIALS & METHODS

This study was conducted to compare the efficacy of Topical Cyclosporine versus the efficacy of topical Tacrolimus over 6 months in patients of MGD. Data was collected from the patients of MGD attending Ophthalmology outpatient department, Government Medical College, Patiala, who were willing to participate in the study. All participants signed an informed consent. Patient data was collected according to the proforma. All MGD patients of age 18 years and above were included. Exclusion criteria were therapy with systemic or topical antibiotics within 1 month before selection, contact lens wear, ocular diseases (such as keratitis, episcleritis, scleritis), punctal occlusion, liver disease, pregnancy and breast feeding, allergy to Cyclosporine and Tacrolimus, Allergic Keratoconjunctivitis, ocular and orbital surgery of any kind, altered lid anatomy and patients allergic to any component of procedural medication such as stains.

As it was a prospective, Randomized Trial on 100 patients so randomization was done by using closed envelopes for allocation to both the groups. The Meibomian gland assessment was done by a masked observer. The participants were divided into two groups: Group 1: eye drops cyclosporine (0.05%) BD and Group 2: eye ointment Tacrolimus (0.03%) HS per day, both for 4 months, along with conservative management to all patients throughout the study. Follow-up was done at 7 days, 4 weeks, 3 months and 6 months. Severity of five main symptoms was measured on a 4-point categorical scale (0–3) according to patients' response to questions: itching, burning, foreign body sensation, dryness and eyelid swelling. (Table 1). After recording visual acuity with Snellen's chart, Slit lamp examination was performed to assess and record the severity of seven signs on a 4-point categorical scale: MG secretion, number of plugged gland orifices, conjunctival injection, lid margin redness, lid margin debris, Tear break up time (TBUT), and ocular surface staining with fluorescein. (Table 2). MGD was diagnosed based on having at least two symptoms and two signs (one must be the presence of meibomian gland signs) with a minimum severity score of 2 for each.

Schirmer's Test was performed with a strip of commercially available pre-sterilized Whatman 41 filter paper measuring 5mm x 35mm without anaesthesia. A value less than 10 mm was taken as dry eye.

Tear Break Up Time (TBUT) was tested by instilling a 2%fluorescein dye into the inferior conjunctival fornix and measuring the time taken for the appearance of the first randomly distributed dark spot in the pre-corneal tear film under broad beam of cobalt blue light of slit lamp biomicroscope. A value less than 10 seconds was taken as abnormal.

ISSN:0975 -3583,0976-2833 VOL14, ISSUE 02, 2023

Ocular Surface Staining

The ocular surface staining score was adapted as a modification of panels in the Oxford scale and was performed before assessment of TBUT. The panel most similar to the pattern and

the number of dots on the cornea and conjunctiva was chosen, and the corresponding grade was applied. (Figure 1)

Statistical Analysis

The data was noted in excel format. Data was subjected to statistical analysis using SPSS version 22. Student t test and Chi Square test was used for assessment of level of significance. p- value less than 0.05 was taken as significant.

Table1: Grading of five symptoms in 100 patients with Meibomian gland disease

Symptom	Grade 0	Grade 1	Grade 2	Grade 3
1. Itching	None	Awareness	Desire to rub	Frequent rub
2. Foreign body sensation	None	Awareness	Desire to rub	Desire to close eyelids
3. Dryness	None	Awareness	Need drops	Frequent drops
4. Burning	None	Awareness	Desire to rub	Frequent rub
5. Eyelid Swelling	None	Noticeable	Obvious	Decrease in palpebral fissure

Symptom score for five symptoms of Meibomian gland disease (Max. score 15)

Table 2: Grading of seven signs in 100 patients with Meibomian gland disease

Signs	Grade 0	Grade 1	Grade 2	Grade 3
1. MG secretion (central lower eyelid)	Clear	Cloudy	Turbid with clumps	Solid with paste
2. Plugged MG orifice (middle lower eyelid)	None	Less than 1/3	1/3-2/3	More than 2/3
3. Bulbar conjunctival redness	None	Pink	Light red	Bright red

ISSN:0975 -3583,0976-2833 VOL14, ISSUE 02, 2023

4. Eyelid margin redness	None	Pink	Light red	Bright red
5. Eyelid margin debris	None	1-5	6-10	More than 10
6. Tear film breakup time (in seconds)	>10	8-10	5-7	<5
7. Ocular surface staining	4-point categorical panels (figure 4-3)			

Sign score for seven signs of Meibomian gland disease (Max. score 21)

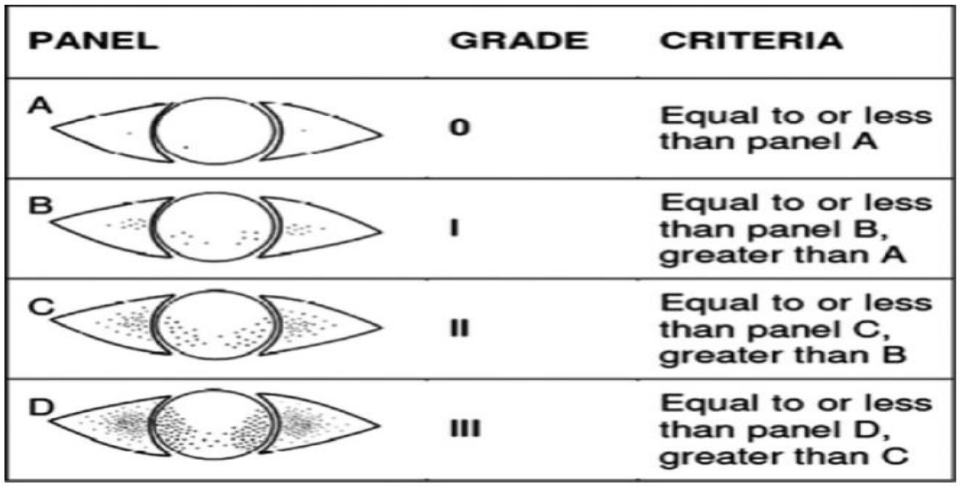

Figure 1: Ocular Surface Staining

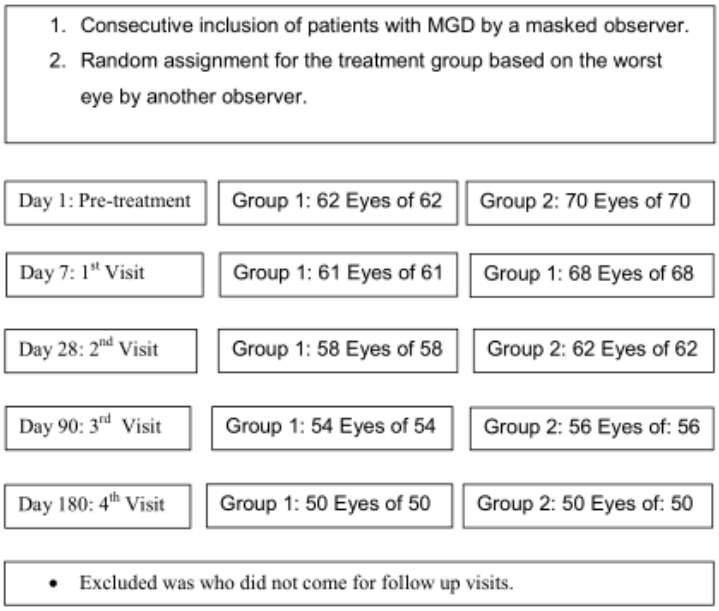

Figure 2: Flow diagram of participants

ISSN:0975 -3583,0976-2833 VOL14, ISSUE 02, 2023

RESULTS

There were 132 patients of whom 32 dropped out (Figure- 2) Therefore only 100 patients completed the study and they were divided into two groups.

The following inferences were drawn from the above study:

- The mean age of the patients for cyclosporine group was 60.38 years and for tacrolimus group was 59.76 years. So mean age in both the groups was comparable.
- There was a predominant male distribution as 58% of patients were males.
- The mean symptom score was 2.25 for cyclosporine group and 2.26 for tacrolimus group, which is comparable. The most common symptom was itching followed by dryness and foreign body sensation.
- There was significant improvement at each follow-up in mean symptom score post-treatment with both cyclosporin and tacrolimus with no significant difference between two groups.
- There was significant improvement at each follow-up in mean sign score, Schirmer Test Score and total score post-treatment with both cyclosporin and tacrolimus with no significant difference between two groups.
- The mean signs score in MGD at baseline was found to be 2.28 for cyclosporine group and 2.21 for tacrolimus group. The most prominent signs were Meibomian gland secretion and plugging.
- The common side effects of both the medications were transient stinging, transient redness and transient burning. 18 patients on tacrolimus had one or more side effects as compared to 8 patients on cyclosporin during first week of administration. At 4 weeks also the side effects were slightly higher in tacrolimus group but they were statistically not significant.

Table 3: Age and Gender Distribution

	All Patients	Cyclosporin	Tacrolimus	p value	Test
Age (Mean±SD)	60.07±11.96	60.38±12.11	59.76±11.93	0.797	t-test= 0.258
Gender (N)	F=44; M=56	F=23; M=27	F=21; M=29	0.340	X^2= 0.911

ISSN:0975 -3583,0976-2833 VOL14, ISSUE 02, 2023

Table 4: Mean Symptoms Score

Mean Symptoms Score	Baseline	7 Days	4 Weeks	3 Months	6 Months
Cyclosporin	2.25±0.42	2.10±0.43	1.30±0.44	0.80±0.47	0.60±0.39
Tacrolimus	2.26±0.60	2.04±0.55	1.22±0.48	0.73±0.38	0.47±0.35
p value	0.908	0.517	0.362	0.459	0.075

Table 5: Mean Signs Score

Mean Sign Score	Baseline	7 Days	4 Weeks	3 Months	6 Months
Cyclosporin	2.28±0.50	2.08±0.47	1.26±0.53	0.80±0.50	0.62±0.44
Tacrolimus	2.21±0.59	1.96±0.52	1.13±0.48	0.74±0.37	0.55±0.29
p value	0.546	0.254	0.226	0.516	0.301

Table 6: Total Score

Total Score	Baseline	7 Days	4 Weeks	3 Months	6 Months
Cyclosporin	2.27±0.43	2.09±0.42	1.28±0.46	0.80±0.45	0.62±0.39
Tacrolimus	2.24±0.56	2.00±0.50	1.18±0.44	0.74±0.34	0.51±0.29
p value	0.790	0.336	0.254	0.451	0.132

Table 7: Schirmer's Test Score

Schirmer's Test Score	Baseline	7 Days	4 Weeks	3 Months	6 Months
Cyclosporin	9.28±2.29	10.16±2.25	11.68±1.81	13.30±2.06	14.44±2.03
Tacrolimus	9.68±2.05	10.30±2.31	12.02±2.11	13.34±2.60	14.60±2.14
p value	0.360	0.760	0.390	0.932	0.702

ISSN:0975 -3583,0976-2833 VOL14, ISSUE 02, 2023

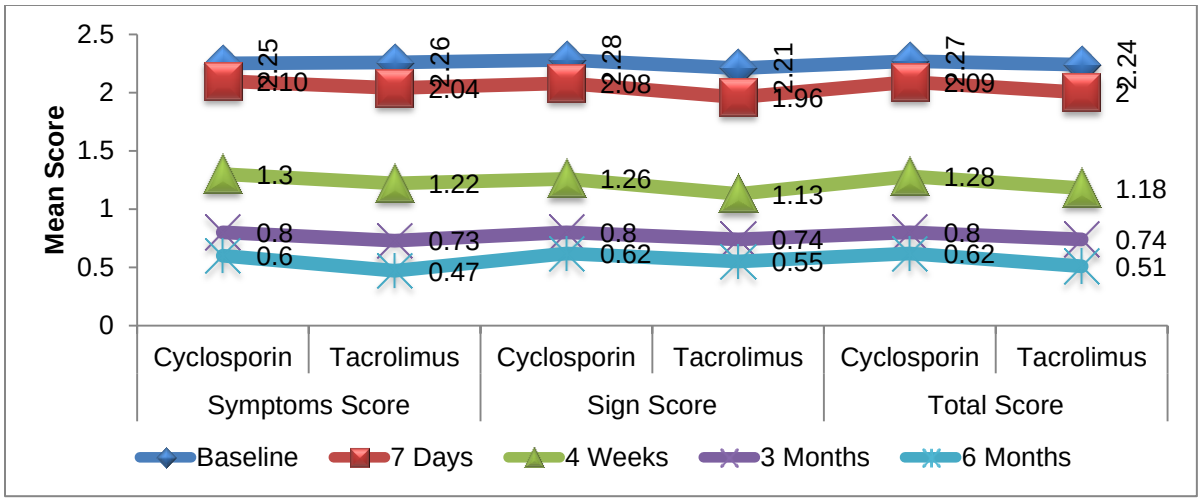

Figure 3: Comparison of sign, Symptoms and total score

TABLE 8: SIDE EFFECT PROFILE

Follow up Visit	Group	Transient Stinging	Transient Redness	Transient Burning	p Value
7 Days	Tacrolimus	7 (14%)	5 (10%)	6 (12%)	3.19
	Cyclosporin	3 (6%)	2 (4%)	3(6%)	(0.074)
4 Weeks	Tacrolimus	4 (8%)	3 (6%)	2 (4%)	1.40
	Cyclosporin	1 (2%)	1 (2%)	0 (0%)	(0.237)
3 Months	Tacrolimus	0(0%)	0(0%)	0(0%)	--
	Cyclosporin	0(0%)	0(0%)	0(0%)	
6 Months	Tacrolimus	0(0%)	0(0%)	0(0%)	--
	Cyclosporin	0(0%)	0(0%)	0(0%)	

ISSN:0975 -3583,0976-2833 VOL14, ISSUE 02, 2023

DISCUSSION

Cyclosporin and tacrolimus both are calcineurin inhibitor. Cyclosporine is more commonly used in Meibomian Gland Dysfunction than tacrolimus. While cyclosporine is available as topical eye drops (0.05%) whereas tacrolimus is available as eye ointment (0.03%) for human use. Cyclosporin is a cyclic polypeptide with 11 amino acids and is obtained from fungus. It is a highly selective immunosuppressant and act by inhibiting

calcineurin. It acts by inhibiting T-lymphocyte proliferation (selectively suppresses cell mediated immunity). Lymphocytes are arrested in G0-G1 phase. And there is no effect on suppressor T cells and humoral immunity remains intact. Whereas tacrolimus is relatively newer immunosuppressant and more powerful than cyclosporine. It has the same mechanism of action as of cyclosporine but binds to different cytoplasmic protein and subsequent action is same as that of cyclosporine.

This was a hospital-based study done to evaluate the effect of treatment on MGD with the use of topical cyclosporine as compared to topical tacrolimus. Therefore, we conducted a prospective randomized trial on a minimum 100 patients with MGD.

The mean age of the patients in our study was comparable in Cyclosporine and Tacrolimus groups- 60.38±12.11 years and 59.76±11.93 years respectively. A similar hospital-based study, done in central India, screened 3410 subjects who were 20 years or older, attending the outpatient department and found Meibomian Gland Dysfunction in 272 (71 symptomatic) subjects with a mean age of 53.3±15.2 (20–84) years. [4] The patients who were symptomatic for MGD were 47.8±15 years, 60% below 60 years of age. A large proportion of patients (54%), in our study were above or equal to 60 years age. A study by Gao et al. (2020) showed that the prevalence of MGD increases with age, significantly and is most prevalent in 50–59-year age group. [5] The prevalence of obvious obstructive Meibomian Gland Dysfunction was 0.9% in younger individuals of 17-40 years in a study from Ghana. [6] There was a predominant male distribution in our study as 56% of patients in our study were males, although there was no significant difference in gender distribution according to age groups. A few studies have previously

found higher MGD prevalence in males. [7] Hassanzadeh et al. (2021) studied the global prevalence of MGD and found a wide variation all over the world with a pooled prevalence of

ISSN:0975 -3583,0976-2833 VOL14, ISSUE 02, 2023

35% in clinical studies. They also found that men were more prone to having MGD than women. [8]

The presentation of MGD is multivariate depending upon the cause. It can be hypersecretory, hyposecretory, non-obvious due to gland loss or obstructive type. [9] The hyposecretory or obstructive type of MGD usually present with dry eye state, worse ocular symptoms and obstructive MGD. (9) In order to include symptomatic MGD patients in our study, we used symptom and sign score grading of MGD for establishing the diagnosis as used in a previous clinical trial by Kashkouli at al. (2015) and Benedetti et al. (2019) [10,11] Similar grading has been used in other studies which assessed the role ofantibiotics in MGD. Furthermore, the signs and symptoms score were used to assess the severity of MGD. The only drawback with this grading may be its inability to include non-obvious and non-symptomatic early MGD.

The mean symptom score in our study at baseline was comparable in Cyclosporine (2.25±0.42) and Tacrolimus (2.26±0.60) group. Benedetti et al. (2019) observed that the most common symptom was itching followed by dryness and foreign body sensation, which is similar to our study. [11] Kashkouli et al. (2015) reported the most common symptom as dryness, foreign body sensation followed by itching. [10] Foulks et al. (2003) reported foreign body sensation as the most common symptom in MGD. [12] Therefore, most common symptom in MGD may vary slightly, but itching and foreign body sensation are two most common symptoms of MGD. There was significant improvement at each follow-up, in our study, in mean symptom score post-treatment with both Cyclosporine and Tacrolimus with no significant difference between two groups. Baudouin et al. (2017) in their study reported that Cyclosporine A was well tolerated and effectively improved the signs and symptoms in patients with moderate to severe DED over 6 months. Sakassegawa et al. (2017) in their study reported that 0.03% tacrolimus ointment can improve some symptoms and some ocular surface status in patients with refractory posterior blepharitis. [13]

The signs score in MGD in our study at baseline was found to be 2.28±0.50 in cyclosporine group and 2.21±0.59 in tacrolimus group with no significant difference in both the groups at baseline. Kashkouli et al. (2015) reported similar sign scores at baseline as compared to our study. [10] The most prominent signs were Meibomian gland secretion and plugging in our

ISSN:0975 -3583,0976-2833 VOL14, ISSUE 02, 2023

study, because it was mandatory to include one of these two in diagnosis of MGD. The overall signs improved significantly in both Cyclosporine and Tacrolimus groups. Perry et al. (2006) in their study investigated the efficacy of topical cyclosporine A 0.05% in the treatment of MGD (posterior blepharitis). At the 3-month visit, several objective examination findings were statistically significantly (P < 0.05%) improved in the CsA group compared with the placebo group. The study concluded that topical CsA may be helpful in the treatment of meibomian gland dysfunction (posterior blepharitis). [14]

Sakassegawa et al. (2017) in their study observed statistical difference in the outcome measurements of meibomian gland secretion, conjunctival hyperemia, Rose Bengal and fluorescein scoring for the Tacrolimus group. [13] The Schirmer‟s test was done to evaluate dry eye disease associated with MGD, it showed reduced values of 9.28±2.29 in Cyclosporine group and 9.68±2.05 in Tacrolimus group at baseline; both improved at 6 months. Rubin et al. (2006) in their study reported that posterior blepharitis improved significantly from the initial study visit with cyclosporine treatment and Cyclosporine provided greater improvements in Schirmer‟s scores (P< 0.001) and tear break up time (P = 0.018) than tobramycin/ dexamethasone after 12 weeks of treatment. Eyelid health also improved in both groups. The mean improvement in meibomian gland secretion quality was significantly greater with cyclosporine. [15]

The common side effects of both the medications are transient stinging, redness and burning. None of the patients in our study had any serious side effects following the drug administration. Pucci et al. (2015) in their study reported that in about 2/3 of patients, ocular stinging, pain and burning was seen following the administration of the tacrolimus and cyclosporine, which tended to improve within 1-2 weeks. [16] The strengths of this study are that it is a randomized prospective trial with an adequate sample size. The follow-up of this study is 6 months, which is more than most of the previously performed studies. Also, we observed that at 6 months there is no difference between topical cyclosporin and topical tacrolimus, in terms of MGD improvement. The limitation of this study is that we did not include the patients with any systemic illness in our study this may be a limitation for practical application of these results to general population.

CONCLUSION

In conclusion, this randomized prospective clinical trial compared the effect of topical cyclosporine versus topical tacolimus in patients with MGD and found that both drugs

ISSN:0975 -3583,0976-2833 VOL14, ISSUE 02, 2023

significantly improved the symptoms and signs in MGD patients. There was no significant difference between the efficacy of two drugs at 6 months. However, tacrolimus had minor side effects which last longer than cyclosporine but they were statistically not significant.

REFERENCES

1. Nichols KK, Foulks GN, Bron AJ, Glasgow BJ, Dogru M, Tsubota K, et al. The international workshop on meibomian gland dysfunction: executive summary. Invest Ophthalmol Vis Sci. 2011 Mar 1;52(4):1922-9.
2. TFOS DEWS II REPORT [https://www.tfosdewsreport.org/report-diagnostic_methodology/131_36/en/].
3. Bron AJ, Tiffany JM. The contribution of meibomian disease to dry eye. Ocul Surf. 2004 Apr;2(2):149-65.
4. Chatterjee S, Agrawal D, Sharma A. Meibomian Gland Dysfunction in a Hospital-Based Population in Central India. Cornea. 2020 May;39(5):634-639.
5. Gao J-G, Chen J, Tang Y, Chen D-N. Prevalence of Meibomian Gland Dysfunction in staffs and faculty members of a Chinese university.Int J Ophthalmol. 2020;13(10):1667–70.
6. Asiedu K, Kyei S, Dzasimatu SK, Morny EKA. Meibomian Gland Dysfunction in a Youthful Clinical Sample in Ghana. Optom Vis Sci. 2018 Apr;95(4):349-353.
7. Hashemi H, Asharlous A, Aghamirsalim M, Yekta A, Pourmatin R, Sajjadi M, et al. Meibomian gland dysfunction in geriatric population: tehran geriatric eye study. Int Ophthalmol. 2021 Jul;41(7):2539-2546.
8. Hassanzadeh S, Varmaghani M, Zarei-Ghanavati S, Heravian Shandiz J, Azimi Khorasani A. Global Prevalence of Meibomian Gland Dysfunction: A Systematic Review and Meta-Analysis. Ocul Immunol Inflamm. 2021 Jan 2;29(1):66-75.
9. Xiao J, Adil MY, Chen X, Utheim ØA, Ræder S, Tønseth KA, et al. Functional and Morphological Evaluation of Meibomian Glands in the Assessment of Meibomian Gland Dysfunction Subtype and Severity. Am J Ophthalmol. 2020 Jan;209:160-167.
10. Kashkouli MB, Fazel AJ, Kiavash V, Nojomi M, Ghiasian L. Oral azithromycin versus doxycycline in meibomian gland dysfunction: a randomised double-masked open-label clinical trial. Br J Ophthalmol. 2015 Feb;99(2):199-204.

ISSN:0975 -3583,0976-2833 VOL14, ISSUE 02, 2023

11. De Benedetti G, Vaiano AS. Oral Azithromycin and oral Doxycycline for the treatment of Meibomian Gland Dysfunction: A 9-month comparative case series. Indian J Ophthalmol. 2019 Apr;67(4):464–71.
12. Foulks GN, Bron AJ. Meibomian gland dysfunction: a clinical scheme for description, diagnosis, classification, and grading. Ocul Surf. 2003 Jul;1(3):107-26.
13. Sakassegawa-Naves FE, Ricci HMM, Moscovici BK, Miyamoto DA, Chiacchio BB, Holzchuh R, et al. Tacrolimus Ointment for Refractory Posterior Blepharitis. Curr Eye Res. 2017 Nov;42(11):1440-1444.
14. Perry HD, Doshi-Carnevale S, Donnenfeld ED, Solomon R, Biser SA, Bloom AH. Efficacy of commercially available topical cyclosporine A 0.05% in the treatment of meibomian gland dysfunction. Cornea. 2006 Feb;25(2):171-5.
15. Rubin M, Rao SN. Efficacy of topical cyclosporin 0.05% in the treatment of posterior blepharitis. J Ocul Pharmacol Ther. 2006 Feb;22(1):47-53.
16. Pucci N, Caputo R, di Grande L, de Libero C, Mori F, Barni S, et al. Tacrolimus vs. cyclosporine eyedrops in severe cyclosporine-resistant vernal keratoconjunctivitis: A randomized, comparative, double-blind, crossover study. Pediatr Allergy Immunol. 2015 May;26(3):256-261.