 DOI: 10.18231/2395-1451.2017.0026

Observational comparative study to evaluate the efficacy of oral azithromycin and oral doxycycline in management of meibomian gland dysfunction

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Abstract

Introduction: "Meibomian gland dysfunction (MGD) is thought to be the leading cause of dry eye disease".[(1)] The pathophysiology of MGD is complex and bacterial infection is a cause of MGD remains controversial. "Doxycycline is a long acting analogue of tetracycline which has been used to treat MGD through its antimicrobial, anti-inflammatory and anti metalloproteinase properties, with fewer side effects than tetracycline".[(2,3)] This comparative and clinical study is being done to evaluate efficacy and compliance of oral doxycycline and oral azithromycin in meibomian gland dysfunction who were not responding to conservative management.

Methods: The study was carried out from April 2016 to September 2016 in our institute. 100 patients were enrolled in the study. Thorough ophthalmic examination was done. Schirmer tests 1 and 2 and TBUT (tear film break up time) were performed to check for dry eye. Patients were called for 3 follow-up and whole ophthalmic examinations were repeated each time.

Results: Total 100 patients were included in the study. Of these 59 males and 41 were females. In both group signs and symptoms improvement from pretreatment to last follow up was statistically significant (p=0.000). Improvement of symptoms and signs in both group was almost equal, so p-value is insignificant, when comparing between both groups (p=0.714). The side effects in doxycycline group was more as compared to azithromycin group at all follow up (p=0.012).

Conclusion: This study demonstrated that both oral doxycycline and azithromycin are effective in patients with MGD. The side effects observed in doxycycline group were significantly higher in all follow up visits as compared to azithromycin group.

Therefore, a five day course of oral azithromycin is suggested based on better clinical improvement, shorter treatment duration, less side effects and low cost.

Keywords: Azithromycin, Comparative study, Doxycyclin, Management, Meibomian

Introduction

Meibomian gland dysfunction (MGD) is a chronic problem of the meibomian glands, commonly characterized by terminal duct obstruction and or qualitative/quantitative changes in the glandular secretion. This may result in alteration of the tear film, clinically apparent inflammation, and ocular surface disease.

"Clinical symptoms are usually chronic and include burning, grittiness, dryness or a foreign body sensation, redness, crusty eyelids, or fluctuating vision. Clinical signs include lid margin hyperemia, crusting of the lashes, plugging or inspissation of the meibomian gland orifices, abnormal, thickened meibomian gland secretions, foamy tears, and tear film debris or an unstable tear film".[(4)]

Cleansing, warm compresses and the massage are the three contemporary mode of treatment for MGD. Amongst the treatment modalities topical application of azithromycin eye ointment, artificial tear drops and systemic tetracyclines, (doxycycline being most frequently used) as well as systemic azithromycin are the treatment modalities available.

This comparative and clinical study is being done to evaluate efficacy (symptom and sign scores) and compliance of oral doxycycline and oral azithromycin in meibomian gland dysfunction who were not responding to conservative management (eyelid warming/ massage/ cleaning and artificial tears).

Materials and Methods

This was a prospective, observational and comparative study with serial sample collection of a sample size of 100 cases (50 in each group) completed in a duration of 1 year. Approval from ethical committee of Institute taken before starting study.

Inclusion criteria consisted of all patients diagnosed with MGD above the age of 18 years.

Exclusion criteria consisted of altered lid anatomy for any reason, contact lens wearing, veneral or atopic kerato-conjunctivitis, ocular and ocular adnexal surgery, pregnancy and breastfeeding, history of liver diseases, allergy to azithromycin or cyclones, systemic/ topical antibiotic taken within 1 month prior to inclusion and history of antipsychotic, antihistaminic and antidepressant medication.

Assessment of patient: A detailed ocular and medical history followed by complete eye examination has been done in 100 patients coming to OPD in our hospital. Patients were divided 50 each in doxycycline and azithromycin group. Patient's consent was taken for the procedure and for involving his/her data in the study. Various visual parameters in accordance with the Study Performa had been recorded. These include uncorrected

visual acuity (UCVA), best corrected visual acuity (BCVA) done using Snellen's Chart.

Severity of five main symptoms was measured on a four point categorical scale (0–3) according to patient's response to questions: itching, burning, foreign body sensation, dryness and eyelid swelling.

Slit lamp examination was performed to assess and record the severity of six signs on a four point categorical scale: meibomian gland secretion, number of plugged gland orifices, conjunctival injection, lid margin redness, lid margin debris, tear break up time (TBUT).

Schirmer test 1 and schirmer test 2 performed.

Treatment:

Group 1:- Oral five day azithromycin (500mg on day 1 and then 250 mg/day)

Group 2:- 1st week oral doxycycline (200 mg/day) then rest 3 weeks oral doxycycline (100mg/day)

On every visit the patient had undergone a detailed eye examination and various visual parameters had been re-checked and recorded specially, TBUT. All data collected according to above methods had been analyzed with the help of biostatical methods.

Patients were serially assigned to either a 5-day oral azithromycin course (500 mg on the first day and then 250 mg per day for the following four days) or a 1-month oral doxycycline course (100 mg twice a day for 1 week then 100mg once a day for 3 weeks). Doxycycline was instructed to be taken with a full glass of water while sitting for a few hours before going to bed and keeping a couple of hours between any supplement and doxycycline.

Each patient's symptoms or signs were given a score of 0 to 3. The symptom score of each subject was calculated by adding the score (0–3) of five symptoms which resulted in a range of 0–15. The sign score of each patient was also calculated by adding the score (0–3) of seven signs which resulted in a range of 0–21. The total score (0–36) of each patent was calculated and recorded by adding the scores of symptoms (0–15) and signs (0–21) at each visit.

Observation and Results

The study included total 100 patients out of which 59 (59%) were male and 41 (41%) were female. In azithromycin group there were 28 (56%) males and 22 (44%) females. In doxycycline group there were 31 (62%) male and 19 (38%) female. In both groups male patients were more than female patients. The mean age in azithromycin group of male was 49.39 (±9.19) and that of female was 47.23 (±10.14) and the mean age in doxycycline group of male was 50.94 (±14.19) and that of female was 51.26 (±10.55). In doxycycline group mean age of both male and female was more than in azithromycin group. In azithromycin group there were Diabetic (12%) and hypertensive (18%). In doxycycline group there were Diabetic (24%) and hypertensive (18%). The chief complaints in azithromycin group were Itching (100%), foreign body sensation (100%), burning (84%) and dryness (16%). The chief complaints in doxycycline group were foreign body sensation (100%), Itching (98%), burning (86%) and dryness (12%). No patient in both group had complained about eye lid swelling.

Table 1: Comparison of symptoms and signs among Azithromycin and Doxycycline group at pretreatment and in all follow up

	Azithromycin		Doxycycline		p value
	Mean	SD	Mean	SD	
Pre-treatment					
Symptoms	7.50	1.26	7.60	1.35	0.704
Sign	8.70	1.28	8.38	1.87	0.321
Total	16.20	2.01	16.18	2.39	0.964
1st Follow up					
Symptoms	2.36	1.27	2.50	1.29	0.587
Sign	3.22	1.20	2.84	1.27	0.127
Total	5.58	2.19	5.34	2.13	0.581
2nd Follow up					
Symptoms	0.82	0.69	0.76	0.77	0.683
Sign	2.08	0.63	2.04	0.80	0.783
Total	2.92	0.96	2.80	1.30	0.603
Last Follow up					
Symptoms	0.62	0.23	0.62	0.40	0.701
Sign	1.22	0.76	1.30	0.78	0.608
Total	1.84	1.09	1.92	1.08	0.714

In both Azithromycin group and doxycycline group mean of pretreatment and last follow up symptoms and signs were all most same. The p value of pretreatment symptoms (0.704) and signs (0.321) of both group indicate that there was no statistical significant difference among patients in both group. The p value of last follow up visit symptoms (0.701) and signs (0.608) of both group indicate that there was no statistical significant difference among patients in both group. In azithromycin group mean of symptoms (7.50) and signs (8.70) at pretreatment clinically improved to mean of symptoms (0.62) and signs (1.22) at last visit. In doxycycline group mean of symptoms (7.60) and signs (8.38) at pretreatment clinically improved to symptoms (0.62) and signs (1.33) at last visit.

Table 2: Comparison of pretreatment and last follow up signs in Azithromycin and Doxycycline group

Group	MG SECRETION (Central lower eyelid)	Plugged MG orifice (central lower eyelid)	Bulbar conjunctival redness	Eyelid margin redness	Eyelid margin debris	Tear breakup time (seconds)
Azithromycin (Pretreatment)	1.34 (0.48)	2.18 (0.39)	1.78 (0.42)	1.36 (0.53)	1.64 (0.49)	0.40 (0.54)
Doxycycline (Pretreatment)	1.28 (0.54)	2.14 (0.35)	1.86 (0.35)	1.34 (0.48)	1.68 (0.47)	0.28 (0.50)
p value	0.556	0.590	0.303	0.843	0.677	0.248

Group	Plugged MG orifice (central lower eyelid)	Bulbar conjunctival redness	Eyelid margin debris	Tear breakup time (seconds)
Azithromycin (Last Followup)	0.70 (0.46)	0.02 (0.14)	0.46 (0.50)	0.04 (0.20)
Doxycycline (Last Followup)	0.80 (0.40)	0.00 (0.00)	0.42 (0.50)	0.10 (0.30)
p value	0.253	0.322	0.691	0.244

The difference in signs in azithromycin and doxycycline group at pretreatment was not statistically significant. Even at last followup there was no statistical difference observed among signs in Azithromycin and Doxycycline Group.

Table 3: Comparison of pretreatment and followup symptoms and signs in azithromycin and doxycycline group

	Symptoms		p value	Sign		p value
	Pre Treatment	Last Follow up		Pre Treatment	Last Follow up	
Azithromycin	7.50 ± 1.26	0.62 ± 0.63	0.000	8.70 ± 1.28	1.22 ± 0.76	0.000
Doxycycline	7.60 ± 1.35	0.62 ± 0.60	0.000	8.38 ± 1.87	1.30 ± 0.78	0.000

In both azithromycin and doxycycline group, when pretreatment and last follow up symptoms and signs were compared, they showed highly significant p- value(p=0.000), indicating that both the treatment were equally effective in MGD patients.

Table 4: Comparison of Side effects in azithromycin and Doxycycline group patients in all follow up visits

	Nausea	Abdominal Cramp	Diarrhoea	Decreased Appetite	P value
1st Visit					
Azithromycin	5 (10%)	3 (09%)	0 (00%)	8 (16%)	0.002
Doxycycline	9 (18%)	8 (16%)	0 (00%)	15 (30%)	
2nd Visit					
Azithromycin	2 (04%)	1 (02%)	0 (00%)	2 (04%)	0.001
Doxycycline	7 (14%)	8 (16%)	0 (00%)	8 (16%)	
3rd Visit					
Azithromycin	1(02%)	1(02%)	0 (00%)	2 (04%)	0.012
Doxycycline	3 (06%)	3 (06%)	0 (00%)	7 (14%)	

The p value of Side effects in both azithromycin and doxycycline groups at first visit (0.002) and at last followup (0.012) indicate that there was significant difference among group, indicating that azithromycin group had fewer side effects than doxycycline group.

The percentage of all the side effects in azithromycin group like nausea (10%), abdominal cramp(09%), loss of appetite (16%)at first follow up were significantly less than in doxycycline group like nausea(18%), abdominal cramp(16%), loss of appetite (30%).

The percentage value of all side effects in azithromycin group like nausea (2%), abdominal cramps (2%) and loss of appetite (4%) at last follow up were significantly less than in doxycycline group like nausea (6%), abdominal cramps (6%), and loss of appetite (14%).

Discussion

While the pathogenesis of MGD is still unclear and complex, both inflammation and bacterial colonisation are, to a different extent, playing a role.[5,6] Although conservative management may be effective in the management of MGD, oral antibiotic/ anti-inflammatory treatment is suggested when the improvement is slow or incomplete.[16] Some antibiotics with anti-inflammatory effects helps in controlling the bacterial colonisation and eyelid inflammation.[5,7,8]

Kashkouli M et al[7] shows that both group pretreatment symptoms (p=0.3) and signs (p=0.1) does not show significant difference. But at last follow up both group symptoms (p=0.1) does not shows significant difference but sign (p<0.001) does shows significant improvement indicating that azithromycin group shows better improvement that doxycycline group.

In our study, in both groups we found that there was no statistically significant difference between pretreatment signs (p=0.704) and symptoms (p=0.321) and at last follow up sign (p=0.701) and symptoms (p=0.608), but when we compared pretreatment and last follow up signs and symptoms in within group, it shows significant improvement (p=0.000) in both the groups.

Although the role of doxycycline in the treatment of MGD has been shown previously in Dougherty J et al,[9] its side effects and subsequently low compliance of the patients sometimes result in stopping treatment by himself.

Kashkouli M et al[7] gastrointestinal side effects in doxycycline group were 30% (15/50) at 1st follow up, 26% (13/50) at 2nd follow up and 14% (7/50) at 3rd follow up.

In our study, gastrointestinal effects were reported by 15 patients (30%) in the first week after starting the doxycycline, decreased to 22% (11/50) at the end of the 1-month treatment course, and then to 14% (7/50) at the last follow.

Bakar et al[10] reported that the side effects of systemic azithromycin were minimal and well tolerated in most patients treated for papulo-pustular rosacea. This study showed mild and temporary side effects which did not require treatment to be discontinued. The most common side effect was decreased appetite, which has also been reported by Greene et al.[11] However, we found 2 patients still having decreased appetite 8 weeks after stopping the medication which cannot be explained.

As per Kashkouli M et al[7] side effects observed in azithromycin and doxycycline group at first follow up were almost equal (p=0.24), at 2nd follow up doxycycline group had significantly higher side effect (p=0.002) and at last follow up again both groups should similar side effects. (p=0.11).

In this study, occurrence of side effects is more in doxycycline group compared to azithromycin group in all three follow ups(p=0.002, p=0.001 and p= 0.012). Among the side effects, decreased appetite was noted to be clinically more significant in both the groups.

The cost of 1-month treatment with doxycycline is almost 4 times more than 5-day treatment with oral azithromycin. Since MGD is a chronic disease, multiple 5-day course of azithromycin would be cheaper than long term daily oral doxycycline. We have observed that compliance of patients in azithromycin group was better than patients in doxycycline group.

Conclusion

This study demonstrated that both oral doxycycline and azithromycin in patients with MGD are effective. Both group showed equal improvement in symptoms (statistically insignificant).The azithromycin group, however, had a relatively better effect in sign (statistically insignificant). The side effects observed in doxycycline group were significantly higher (statistically significant) in all follow up visits as compared to azithromycin group.

Therefore, a five day course of oral azithromycin is recommended based on better clinical improvement, shorter treatment duration, less side effects and low cost. As MGD is chronic diseases, longer treatment duration might be required, so short course of azithromycin (5-days) can be repeated without any significant side effects.

Further studies are recommended to assess different dosage and duration of oral azithromycin, oral verses topical azithromycin and oral as well as topical azithromycin in treatment of MGD patient.

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