Vol: 07, Issue 01

OPHTHALMOLOGY PAKISTAN

www.ophthalmologypakistan.com

Original Article

Comparison Of Efficacy Of Fenofibrate Versus Bevacizumab In The Reduction Of Diabetic Macular Edema

Author's Affiliation

Irum Raza
Nishtar Hospital Multan

Tehseen Mahmood Mahju
Mayo Hospital Lahore

Chaudhary Nasir Ahmad
Mayo Hospital Lahore

Correspondence Author:

Correspondence to:

Irum Raza,
Nishtar Hospital Multan

ABSTRACT:

PURPOSE: To compare the efficacy of fenofibrate versus bevacizumab in the reduction of diabetic macular edema (DME).

METHOD: Ninety patients were divided into two groups. Group A was given capsule fenofibrate 200mg orally once daily . Group B was injected with three intravitreal bevacizumab injections at one monthly interval. Patients were then called for follow up visits at the end of 3rd, 6th and 12th month. On every visit, ocular and systemic investigations were repeated. Data was analyzed by SPSS version 20 and presented in the form of tables and graphs.

RESULTS: The mean and standard deviation of age was 58.37 ± 5.48 while age range was 51-70 years. Patients were divided into three different age groups. Most of the patients belonged to age group of 51-57 years (50%). 59% patients were females. Grouping of patients according to HbA1c level showed that it had definite effect in the reduction of central macular thickness (CMT). 29.17% reduction was seen in patients with 6.5 to 7.5% HbA1c. However, cholesterol level was not found to have significant effect on final outcome (p value = 0.763). Statistically significant improvement in visual acuity (VA) was found in group B (p value = 0.05). Efficacy of fenofibrate versus that of bevacizumab in the reduction of CMT was found out to be 28.9% and 11.11% respectively with p value 0.03.

CONCLUSION: Fenofibrate is more efficacious than intravitreal bevacizumab in the reduction of DME in the long run. It is especially useful in patients who are phobic to intravitreal injections.

KEYWORDS: Fenofibrate, bevacizumab, diabetic macular edema.

INTRODUCTION:

Diabetic retinopathy (DR) is one of the common microvascular hazards of diabetes Mellitus (DM).[1,2] Diabetic macular edema (DME) or the swelling of macula, can occur at any stage of DR. It is now the major cause of vision loss especially in working age population[3]

There are multiple risk factors for the development of DME including type and duration of diabetes, age, sex, hypertension, nephropathy, glycemic control (glycosylated hemoglobin i.e HbA1c) and serum lipids.[4] The intensive glycemic and blood pressure control are the well understood and stressed upon factors. But the contribution of lipids in the pathogenesis of DR and DME is less clear.[5] However few studies have shown a strong relationship of serum lipids with DME.[6] A high ratio of total to high-density lipoproteins (HDL) and elevated low-density lipoproteins (LDL) are reported to be responsible for the development of clinically significant macular edema. Increased total lipoproteins, low-density lipoproteins (LDL) and triglycerides are implicated in the progression of retinopathy and the development of DME.

Lipid lowering approach may, therefore, be helpful in reducing diabetic retinopathy events, particularly DME. Statins and fibrates are the two classes of anti hyperlipidemic drugs used for this purpose. Fenofibrate is a readily available fibrate. Two randomized controlled trials, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) and the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) have used fenofibrate and have confirmed its benefit in management of DR. FIELD study says that fenofibrate also reduces the need for laser treatment in DME.[7]

Besides systemic treatment, DME responds well to ocular therapies including laser and intra vitreal anti vascular endothelial growth factors (VEGF). Among anti-VEGF's, bevacizumab is most commonly prescribed because of its low cost and easy availibilty.[8] But because of its temporary effect, has to be repeated multiple times, does not give long lasting effects and also has ocular side effects.

This study was conducted for two main reasons. Firstly, no previous such study was ever conducted in Pakistan and secondly, the objective relationship of fenofibrate and DME is not documented clearly till yet. On the other hand, relationship of anti-VEGF and DME is clearly understood. Thus the rationale of my study was to see the effects of fenofibrate on the progression of DME in comparison to intravitreal bevacizumab injection which is damaging and interventional.

MATERIALS AND METHODS:

This quasi experimental study was carried out in Ophthalmology department, King Edward Medical University/ Mayo hospital, Lahore from 1st July, 2015 to 30th September, 2016. There were total 90 patients of DME who were enrolled in this study. Patients were selected during first three months on the basis of non-probability purposive sampling technique. Inclusion criteria were type II diabetics with DME with non-proliferative diabetic retinopathy (NPDR) in at least one eye of the patient, with central macular thickness (CMT) more then and equal to 300 µm on optical coherence tomography (OCT), HbA1c less then or equal to 10% and with blood pressure value ≤150/90 mmHg. While exclusion criteria were history of renal or liver disease, mixed maculopathy, previous laser photocoagulation, retinal thickening resulting from epiretinal membranes or vitreomacular traction and poor visual acuity (VA) of 6/60.

Proper permission was taken from institutional ethical committee to conduct this study. Patients were selected from out-door patient department (OPD) of Ophthalmology department of Mayo hospital, Lahore. A formal informed consent was taken from the patients after brief description of method, duration and possible outcome failure of treatment. They were ensured about the safety of treatment and also that the confidentiality of data will be maintained. After fulfilling the inclusion and exclusion criteria, patients were enrolled in study.

After enrollment, the detailed history was taken about the symptoms. A special systemic inquiry was made about the dyslipidaemia. Previous treatment taken was also asked. A detailed examination including visual acquity and macular function tests was done. OCT was done to record the numerical value of CMT. In addition to ocular examination, systemic examination was also made. Systemic investigations including the fasting glucose level, HbA1c and complete fasting cholesterol profile were done. Blood pressure was also checked.

Then all the patients were divided into two groups depending upon envelop picked up by them via drawing method technique. Group A was given capsule fenofibrate 200mg orally once daily in collaboration with a physician. Group B was injected with three intravitreal bevacizumab injections with one monthly interval. Statins were not used to control the confounders. Good glycemic control was also advised. Patients were then called for follow up visits at the end of 3rd, 6th and 12th month. 12th month visit was final visit in this study. At each visit, detailed examination and OCT was done. All the systemic investigations were also repeated.

All the data was entered in the proforma designed (copy attached).

DATA ANALYSIS AND STATISTICAL PROCEDURE:

All the data was entered and analyzed with the help of computer software SPSS version 20 to find out frequencies and percentages of study variables i.e., gender, deranged fasting cholesterol level, HbA1c. Descriptive statistics were applied to calculate mean and standard deviation for the age of the patients, duration for reduction of CMT.

Confounding variables like age, gender, duration of diabetes were controlled by stratification of data. Chi-square test was

applied to compare the results of two groups and p value less then or equal to 0.05 was considered as significant.

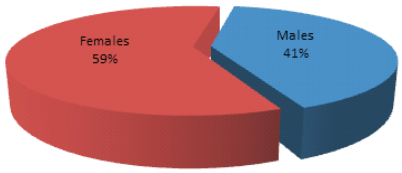
RESULTS:

Total 90 patients were included in the study. The mean and standard deviation of age was 58.37 ± 5.48 with the range of 51-70 years. Patients were divided into three different age groups. This division and its effect on the final outcome are shown in table 1.

Table 1: Age of patients

Age group	No. of patients
51-57 years	45 (50%)
58-64 years	28 (31.1%)
65-70 years	17 (18.9%)

Gender distribution of patients is shown in graph 1.



All the patients were divided into two groups on the basis of levels of HbA1c. Then its effect on the final outcome i.e improvement of CMT was assessed as depicted in table 2.

Table 2: Effect of HbA1c on outcome

HbA1c	CMT Improved	CMT Not Improved	Improvement Percentage
6.5- 7.5% (48)	14	34	29.17
7.6- 8.5% (28)	3	25	10.71
8.6- 10.0% (14)	1	13	7.14

Fenofibrate treated patients were divided into two groups to see the effect of level of cholesterol on final outcome (table 3). Surprisingly, it shows that cholesterol level has nothing to do with the improvement of CMT (p value = 0.763).

Table 3: Effect of cholesterol level on final outcome in fenofibrate treated patients

Cholesterol level	CMT improved	CMT not improved	P value
Deranged	8	18	0.763
Not deranged	5	14	

During this study, we also noted the duration of improvement of macular edema. The mean and standard deviation for this duration was found to be 10.38 ± 1.04 months.

VA assessed on all follow-ups was compared. This comparison showed that in group A, the difference between baseline and 3rd month and between 3rd and 6th month were non-significant (0.82 and 0.36) but between 6th and final visit was significant (p value=0.05). However in group B, difference between baseline and 3rd month visit and between 3rd and 6th month visits were statistically significant with p values 0.0003 and 0.001 respectively. However comparison of 6th month and final visit was not significant (p value = 0.10).

Table 4: Improvement of VA

Drug	Improvement of VA at different visits	p values
Fenofibrate	Baseline to 3rd month	0.82
	3rd to 6th month	0.36
	6th to 12th month	0.05
Bevacizumab	Baseline to 3rd month	0.0003
	3rd to 6th month	0.001
	6th to 12th month	0.1

The calculated CMT on all the visits were compared for both drugs. The main interest of all this exercise was to find out the expected numerical reduction in CMT with either drug. The results are shown in table 5.

Table 5: Improvement of CMT

Follow ups	Average CMT in µm		p value
	Fenofibrate	Bevacizumab	
Baseline	434	459	Baseline to 3rd month=0.22
3rd month	395	370	3rd to 6th month=0.44
6th month	358	330	6th to 12th month=0.03
12th month	275	313	

The main interest of study i.e efficacy of fenofibrate and bevacizumab in terms of reduction of CMT was found out to be 28.9% and 11.11% respectively with p value 0.03 as shown in table 6.

Table 6: Efficacy of drug

Drug	Effective	Not effective	p value
Fenofibrate	13	32	0.03
Bevacizumab	5	40	

DISCUSSION:

Diabetic retinopathy (DR) is one of the leading causes of

blindness all over the world. The two most vision threatening forms of DR are DME and proliferative diabetic retinopathy (PDR). Photocoagulation is the standard treatment for both DME and PDR.[9] However, this procedure imposes permanent retinal damage and threatens the vision. That's why other modalities were sought which can halt the progression of retinopathy as well as save the vision.

Vision saving modalities include systemic as well as ocular therapies. Among the systemic therapies, an oral lipid-lowering drug, fenofibrate is gaining maximum attention of researchers after its use in two major trials, FIELD and ACCORD studies. This drug slowly enhances its effect which is long lasting and also free of ocular complications. It reduces the progression of DR and DME[10] and also need for laser treatment. Among ocular therapies, injection of intravitreal bevacizumab is most frequently performed modality now-a-days. Although it gives immediate improvement of DME and vision but is associated with number of ocular side effects which can be even more dangerous than DME itself. Furthermore, this agent has not been proved to reduce DR progression and may increase cardiovascular events with its long-term use. The long-term efficacy and safety of bevacizumab has not been established till yet. Also worth noting is that it is more expensive than fenofibrate.[11] keeping in view all these facts, we compared the efficacies of these two therapies to find out the better drug with ocular as well as systemic safety.

We took 90 patients of DME with mean age of 58.37 ± 5.48 years. Out of these 90 patients, 59% were females and 41% were males. Mean age of patients is close to that seen in FIELD study[12]. This is because only type II diabetics were included in both studies.

Luckily the glycemic control of most of our patients was between 6.5 - 7.5%. It was just by chance. The percentage of improvement in patients with different glycemic control turned out as expected i.e most of the improved cases of CMT were seen in patients with 6.5 - 7.5% HbA1c. This is well in accordance with most of the studies.[13,14] Macky and Mahgoub[15] stated in their article that tight and rapid control of hyperglycemia doesn't improve the CMT but longer duration control of HbA1c plays the magic. Difference in durations of two studies and constantly controlled HbA1c in our patients before entry into and throughout the study make the two outcomes well understood. This signifies the long-term good control of DM as stated in same study[15]. Difference in the treatments given in two studies may also be accountable for the outcome.

Effects of serum cholesterol level on improvement of DME are studied by multiple research workers. Few authors like Christopher, et al[16] favor it. Whereas it is in confliction with few other studies.[17,18] Our finding too contradicts this concept. We found that it has nothing to do with the improvement of macular edema as clarified in table 3. Christopher's study[16] is a review study whereas Keech's study[17] was the sub-study of FIELD study. Similar ages of patients and dose of fenofibrate given in two studies may be responsible for the similar outcome.

The mean duration of improvement of DME with fenofibrate turned out to be about 10 months which is very close to that reported in study of Jared and co-authors.[19]

The assessment of improvement of visual acuity showed that fenofibrate did not produce significant effect on visual acuity initially but a satisfactory result on final visit. This is contrary to the findings of both ACCORD and FIELD studies[11]. Reduction in visual acuity in these studies was related to development of cataract and PDR. On the other hand, no candidate in our study had developed clinically significant cataract and we only included the patients of DME with NPDR. Visual acuity improvement in bevacizumab group was initially statistically significant. Later this effect weaned off and it remained no longer statistically significant on last visit. This is due to the well understood fact that bevacizumab's action is short lived just for 4-6 weeks and visual acuity deteriorates to previous level after 8-12 weeks post injection.[20] This is somewhat in contradiction to study of Atul Kumar and Subijay Sinha.[21] Huge difference in the final visits of two studies i.e. 12 months versus 6 months illustrates the point. Additionally, previously photocoagulated eyes were also included in Atul's study but we excluded such eyes.

The final outcome of this study was very dramatic and opposite to that expected. Very well marked initial improvement noted in group B gradually weaned off so that on last visit it didn't remained statistically significant. This is very well in contrast to results of previous studies[21,22]. Reason being the final follow up period in these studies was short i.e 6 months and while in our study it was at 12 months. A recent study by Arevale, et al gives highly statistically significant p value of 0.0001 in patients of DME even after 5 years.[23] This is very well explained with more number of injections in their study (8.4 ± 7.1) as compared to our (3 injections). Response in group A was exactly opposite to this i.e. initially it was very discouraging but with the follow ups, improvement increased and it became statistically significant over group B on final visit. However, the improvement percentage in our study is lesser than those of ACCORD and FIELD sub studies which gave figure of 40% and 36% improvement in DR respectively.[6,17,19,24] Few notable points elaborate this difference. Firstly, these studies were done over 4 and 5 years respectively. Secondly, ACCORD study also used statins in combination with fibrates. MacuFen study, a recent study didn't find any significant improvement in macular thickness with fenofibrate.[25] The markedly reduced dose of fenofibrate used in macufen study seems to be responsible for the results.

CONCLUSIONS:

Fenofibrate is more efficacious than bevacizumab in terms of reduction of DME. Its action is slow in onset but long lasting. It is free of ocular side effects as compared to bevacizumab. It is good for patients who are phobic to intra vitreal injections. It was a short study both in term of time frame and number of patients to exactly map out the merits and demerits of the two drugs. Further longer duration studies should be done to cover the limitations of this study.

REFERENCES:

1. Cheung N, Mitchell P, Wong YT. Diabetic retinopathy. The Lancet. 2010 Jul 10;376(9735):124-36.
2. Klein R, Klein BE. Are individuals with diabetes seeing better?: a long-term epidemiological perspective. Diabetes. 2010 Aug;59(8):1853-60.
3. Sharma N, Ooi JL, Ong J, Newman D. The use of fenofibrate in the management of patients with diabetic retinopathy: an evidence-based review. Aust Fam Physician. 2015;44(6):367-70.
4. Arbab TM, Hanif S, Iqbal S, Mirza MA. Hypertension as risk factor in diabetic retinopathy in type-2 diabetes. Pak J Ophthalmol. 2008;24(4):201-3.
5. Sasongko MB, Wong TY, Nguyen TT, Kawasaki R, Jenkins A, Shaw J, et al. Serum apolipoprotein AI and B are stronger biomarkers of diabetic retinopathy than traditional lipids. Diabetes Care. 2011Feb;34(2):474-9.
6. Wright AD, Dodson PM. Medical management of diabetic retinopathy: fenofibrate and ACCORD eye studies. Eye (Lond). 2011 Jul;25(7):843-9.
7. Javey G, Schwartz SG, Flynn HW. Emerging pharmacotherapies for diabetic macular edema. Exp Diabetes Res. 2012.
8. Stefanini FR, Arevalo JF, Maia M. Bevacizumab for the management of diabetic macular edema. World J Diabetes. 2013 Apr15;4(2):19-26.
9. Ansquer JC, Crimet D, Foucher C. Fibrates and statins in the treatment of diabetic retinopathy. Curr Pharm Biotechnol. 2011Mar1;12(3):396-405.
10. Garcia-Ramírez M, Hernández C1, Palomer X, Vázquez-Carrera M, Simó R. Fenofibrate prevents the disruption of the outer blood retinal barrier through downregulation of NF-κB activity. Acta Diabetol. 2016 Feb;53(1):109-18.
Choi JS, Kim EY, Kim MJ, Giegengack M. Factors affecting successful isolation of human corneal endothelial cell. Cell Transplant. 2014;23(7):645-54.
11. Noonan JE, Jenkins AJ, Ma JX, Keech AC, Wang JJ, Lamoureux EL. An update on the molecular actions of fenofibrate and its clinical effects on diabetic retinopathy and other microvascular end points in patients with diabetes. Diabetes. 2013 Dec;62(12):3968-75.
12. Nainggolan L. Fenofibrate works as well in women with diabetes as in men. Medscape. Aug 18;2014.
13. Chew EY, Davis MD, Danis RP, Lovato JF, Perdue LH, Greven C, et al. The effects of medical management on the progression of diabetic retinopathy in persons with type 2 diabetes: the Action to Control Cardiovascular Risk in Diabetes (ACCORD) eye study. Ophthalmol. 2014 Dec;121(12):2443-51.
14. Rajalakshmi R, Prathiba V, Mohan V. Does tight control of systemic factors help in the management of diabetic retinopathy? Indian J Ophthalmol. 2016 Jan;64(1):62-8.
15. Macky TA, Mahgoub MM. The effect of glycemic control on visual and anatomic outcomes in response to therapy for diabetic macular edema. Eur J Ophthalmol. 2013;23:94-100.
16. Mathew C, Yunirakasiwi A, Sanjay S. Updates in the management of diabetic macular edema. J Diabetes Res. 2015;2015:794036.
17. Keech AC, Mitchell P, Summanen PA, O'Day J, Davis TM, Moffitt MS, et al. Effect of fenofibrate on the need for laser treatment for diabetic retinopathy (FIELD study): a randomised controlled trial. Lancet. Nov 2007.
18. Ozer PA, Unlu N, Demir MN, Hazirolan DO, Acar MA, Duman S. Serum lipid profile in diabetic macular edema. J Diabetes Complications. 2009 Jul-Aug;23(4):244-8.
19. Knickelbein JE, Abbott AB, Chew EY. Fenofibrate and diabetic retinopathy. Curr Diab Rep. 2016 Oct;16(10):90.
20. Abu El-Asrar AM, Al-Mezaine HS. Advances in the treatment of diabetic retinopathy. Saudi J Ophthalmol. 2011 Apr;25(2):113-22.
21. Kumar A, Sinha S. Intravitreal bevacizumab (Avastin) treatment of diffuse diabetic macular edema in an indian population. Indian J Ophthalmol. 2007 Nov-Dec;55(6):451-5.
22. Tareen IU, Rahman A, Mahar PS, Memon MS. Primary effects of intravitreal bevacizumab in patients with diabetic macular edema. Pak J Med Sci. 2013 Jul;29(4):1018-22.
23. Arevalo JF, Lasave AF, Wu L, Acon D, Farah ME, Gallego-Pinazo R, et al. Intravitreal bevacizumab for diabetic macular oedema: 5-year results of the Pan-American Collaborative Retina Study group. Br J Ophthalmol. 2016 Dec;100(12):1605-10.
24. Simó R, Hernández C. Advances in the medical treatment of diabetic retinopathy. Diabetes Care. 2009 Aug;32(8):1556-62.
25. Massin P, Peto T, Ansquer JC, Aubonnet P, MacuFEN Study Investigators FT. Effects of fenofibric acid on diabetic macular edema: the MacuFen study. Ophthalmic Epidemiol. 2014 Oct;21(5):30-17.