Original articles

Atorvastatin in clinically-significant macular edema in diabetics with a normal lipid profile

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Abstract

Introduction: Lipid-lowering drugs preserve vision and reduce the risk of hard exudates in clinically-significant macular edema(CSME) in diabetics with an abnormal lipid profile. But their role in reducing CSME in diabetics with a normal lipid profile is not yet known.

Objective: To evaluate the role of atorvastatin in CSME in diabetics with a normal lipid profile.

Materials and methods: A prospective, randomized clinical trial was carried out. Thirty CSME patients with a normal lipid profile were randomly divided into Group A and B. Atorvastatin had been started in Group A four weeks prior to laser treatement. The main outcome measures were any improvement or deterioration in visual acuity and macular edema and hard exudates at six months follow-up. ***Statistics:*** Both the groups were compared using unpaired t test for quantitative parameters and chi-square test for qualitative parameters. A p value of < 0.05 was taken as significant.

Results: Visual acuity, macular edema and hard exudates resolution was not significantly different in the two groups ($P = 0.14, 0.62, 0.39$ respectively).

Conclusion: Atorvastatin does not affect treatment outcome in CSME with a normal lipid profile over a short term follow-up.

Key–words: lipid lowering drugs, clinically-significant macular edema, diabetic retinopathy

Introduction

Clinically significant macular edema (CSME) is the commonest cause of moderate visual loss in diabetic retinopathy (DR). Control of elevated blood pressure, serum glucose, serum lipids and proteinuria along with laser photocoagulation has emerged as standard treatment of patients with CSME. The Early Treatment Diabetic Retinopathy Study (ETDRS) established that elevated cholesterol levels at baseline increases the risk of visual loss by 50 % compared to lower serum cholesterol levels (Klein et al, 1991). ETDRS data suggested that lipid lowering drugs helped in preserving vision and reducing the risk of hard exudates in CSME (Chew et al, 1996). Statins are fairly safe lipid lowering drugs. They are anti HMG Co- A reductase inhibitors and also have anti thrombotic, anti inflammatory and anti proliferative properties (Sever et al, 2003). Their efficacy has already been established in CSME with dyslipidemia (Gupta et al, 2004). Recently the role of atorvastatin in improvement of endothelial function and also ocular

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blood flow has been emphasized (Dobrucki et al, 2001; Ozkiris et al, 2007). Histopathology of diabetic retinopathy has been likened to atherosclerotic changes in coronary artery disease (CAD) [Michael et al 2003]. Multicentric trials have now well established the role of lipid lowering drugs in prevention of coronary artery disease in diabetics with dyslipidemia as well as with normal lipid profile (Wood et al, 1998). The target levels of lipids have been found to be much lower in diabetic patients and a continuous linear relationship has been found between blood low density lipoproteins (LDL) and CAD, without any definite threshold level below which a lower concentration is not associated with any lower risk (Chen et al, 1991; Heart 2002). If we generalize the above findings in view of histopathological similarity between CAD and CSME, atorvastatin may also be found to be helpful in reducing edema and exudation in CSME in diabetics with normal lipid profile. To the best of our knowledge there is no study that has evaluated the role of lipid lowering drugs in CSME patients with normal lipid profile. The present study was carried out to evaluate the role of atorvastatin in CSME in diabetics with normal lipid profile.

Materials and methods

This was a prospective randomized study including 30 eyes of 30 non- insulin dependent diabetic patients with CSME. We included eyes with non-proliferative diabetic retinopathy (NPDR) with CSME that presented to Retina services of our institute which is a tertiary eye care center. The study was conducted in accordance with Declaration of Helsinki and the guidelines for good ethical clinical practice. The study was approved by our institute ethics committee. The study included diabetic patients with normal lipid profile i.e. total cholesterol < 190mg %, LDL < 115mg %, HDL > 40mg % and serum triglycerides < 180mg % was taken as standard. The data from one eye was included in the analysis. In case of bilateral CSME, worse eye was included in the study. After enrollment all the patients were evaluated by endocrinologist for control of diabetes mellitus and other associated metabolic derangements if present. All the patients were subjected to strict metabolic control for four to six weeks, including any change in dosage of oral hypoglycaemic agents or insulin, before subjecting them to laser treatment.

We excluded eyes with significant media opacities that precluded fundus photography / fundus fluorescein angiography, any other ocular ailment or ocular or systemic surgery within three months before randomization, diabetic retinopathy with macular ischemia, cystoid macular edema, proliferative diabetic retinopathy, neovascularization of iris, very severe non proliferative diabetic retinopathy, cases of myopathy, hepatic disease, myocardial infarction or other heart ailments, uncontrolled hypertension, nephropathy (serum creatinine > 2 mg %), anemia with hemoglobin less than 10gm %, debilitating systemic illness and uncontrolled blood sugar level. We also excluded pregnant females, premenopausal females, patients with acute liver or renal disease, idiopathic lung fibrosis or patients who were already on statins or immuno- suppressants.

The patients were randomized into two groups of 15 patients each using random dot tables. Group A patients were administered Atorvastatin (daily dose of 20 mg) through out the study period starting four weeks prior to laser treatment. Group B patients were given placebo during study period.

Detailed history was obtained from all. All eyes underwent a detailed ocular examination including assessment of the best-corrected Snellen's visual acuity, pupillary reactions, intraocular pressure using Goldman applanation tonometer, slit lamp biomicroscopy especially to look for iris neo-vascularization and cataract. Stereoscopic fundus evaluation was done with +90D and +20 D lens documenting the extent and location of retinal thickening and hard exudates. Fundus photographs and fundus fluorescein angiography was performed for all patients using Zeiss digital imaging system. Grading of hard exudates was done by studying the 30° colored fundus photographs of field 2 by two observers (SN, AM) as per ETDRS grading at baseline and at six months follow up.

All patients were evaluated for haemoglobin, packed cell volume, fasting blood sugar, post prandial blood sugar, glycosylated haemoglobin, blood

pressure, 24 hour urinary proteins, renal function tests, ECG, lipid profile and liver function tests (LFT). Routine hematology and blood biochemistry was preferred after an overnight fast (12 hours). Systemic investigations were done at time of enrolment, at three months and at end of six months to ensure metabolic control through out the study period. All the patients were subjected to focal/grid laser treatment using 532 nm Nd YAG green laser.

All patients had minimum of six months follow up. The follow up was scheduled at three monthly intervals. During follow up visits patients were interviewed regarding possible adverse effects like myopathy and other side effects of drugs. A detailed ocular and systemic examination was done. The patients were subjected to LFTs/CPK-MM, electromyography (EMG) if required.

Treatment outcome

The outcome was evaluated at final visit in terms of visual acuity (VA), hard exudates (HE) and macular edema (ME) status. Successful visual acuity outcome was regarded as improvement (two lines gain in VA) or stabilization (within two lines of initial VA). Unsuccessful outcome was taken as deterioration of VA (loss of two lines). Successful macular edema outcome was taken as resolution or partial resolution of ME. Persistence or progression of ME was regarded as unsuccessful outcome. Hard exudates status was regarded as improved, stable or worsened depending on any change in grade of hard exudates.

Statistical analysis

Both the groups were compared using unpaired t test for quantitative parameters and chi square test for qualitative parameters. P value of < 0.05 was taken as significant.

Results

The study included 30 patients with age ranging from 40 -75 years with the mean of 58.2 ±6.85 in group A and 53.6 ± 7.65 in group B. Male to female ratio was similar in both the groups. All were metabolically stable NIDDM patients at the time of randomization. Of these, 27 were on oral hypoglycemic drugs for control of diabetes (15 in group A and 12 in group B) and three (group B) were using insulin injections along with oral hypoglycemic agents. The duration of diabetes ranged from five to 25 years (mean of 11.93 $\pm$ 3.83 in group A and 10.53 $\pm$ 5.62 in group B). The demographic profile, the type and treatment of diabetes mellitus were comparable in the two groups. Systemic investigations, including mean Hb, glycosylated Hb, blood urea, serum creatinine and 24 hour urinary proteins and lipid profile were normal and the values were comparable in group A and B at baseline. There were 7 hypertensives in group A and 8 in group B. The type of retinopathy, the extent of CSME, involvement of centre of fovea by CSME and severity of hard exudates were also comparable in the two groups at baseline (P>0.05) (Table 1).

Table 1
Extent of CSME and hard exudates at baseline

	Grade	Group A	Group B	P value
Type of NPDR	Mild Moderate Severe	8(53.3 %) 5(33.3 %) 2(13.3 %)	3(20 %) 11(73.3 %) 1(6.6 %)	>0.05
CSME size		2.55DA$\pm$1.28	2.70DA$\pm$1.16	>0.05
Grade of hard exudates	1 2 3 4	3 9 2 1	2 5 7 1	>0.05

All eyes in Group A had successful visual outcome. In Group B 13(86.66 %) eyes had successful visual outcome and two eyes (13.33 %) had unsuccessful visual outcome. No significant difference in the visual outcome between the two groups was seen (p>0.05) (Table 2).

Table2
Final visual and macular edema outcome

Outcome		Successful N (%)	Unsuccessful N (%)	X^2	P value
Visual outcome	Group A	15 (100 %)	0 (0.00 %)	2.14	0.14
	Group B	13 (86.67 %)	2 (13.33 %)		
Macular edema outcome	Group A	13 (86.67 %)	2 (13.33 %)	0.24	0.62
	Group B	12 (80 %)	3 (20 %)		

Successful macular edema outcome was seen in 13 eyes in group A (Figure 1) and 12 eyes in group B (Figure 2). There was no significant difference in the two groups. Complete resolution of CSME was seen in six eyes (40 %) in group A (Foveal thickness (FT) on Stratus OCT was 180 ± 8um) and eight eyes (53.33 %) in group B (FT=173± 10um). Partial resolution of CSME was seen in seven eyes (46.67 %, FT= 279 ± 15um) in group A and four eyes (26.66 %, FT= 263 ± 9um) in group B. Persistence of CSME was seen in two eyes (13.33 %, FT= 386 ± 11um) in group A and three eyes (20 %, FT= 354 ± 17um) in group B. CSME outcome in both the groups was comparable (p>0.1) (Table 2).

In all but one eye there was some decrease in exudation after laser procedure however only the eyes showing change in grade of hard exudates (ETDRS grading) was recorded as change. Decrease in severity of grade of hard exudates was seen in seven (46.66 %) eyes of group A and five (33.33 %) eyes of group B. Hard exudates were stable in seven (46.66 %) eyes in group A and in 10 (66.66 %) eyes of group B. One eye in group A (Table 3) showed increased severity of grade of hard exudate (6.66 %). The increase in severity of hard exudates could not be attributed to any obvious cause. The compliance to treatment was ensured. The patient had been metabolically stable during follow up. There was no significant difference in the decrease of severity of hard exudates (X^2 = 1.86, p>0.1) between the two groups at final follow up.

The final visual outcome did not show any significant association to baseline variables including demographic profile, systemic investigations, type of diabetic retinopathy, size and extent of CSME, (p>0.05). The final visual outcome was significantly associated with severity of hard exudates (p<0.05).

Table 3
Hard exudates outcome

Hard exudates	Group A	Group B	$\chi 2$	P value
Improved	7(46.66 %)	5(33.33 %)	1.86	0.39
Stable	7(46.66 %)	10(66.66 %)		
Worsen	1(6.66 %).	0		

Discussion

Diabetes is known to be associated with a high incidence of dyslipidemia. The use of lipid lowering drugs in the management of diabetic retinopathy is not new. The association of dietary intake of fat with exudative diabetic maculopathy has been studied as early as 1965 (Ernst, 1965). Ernst reported decrease in retinal hard exudates in eight diabetic patients after two to three years of carbohydrate rich and fat poor diet. The studies using earlier generation of lipid lowering drugs in diabetic retinopathy were disappointing. HMG Co A reductase inhibitors have been established as safe and efficacious drugs in management of diabetic retinopathy with dyslipidemia (Freyberg et al, 1994; Comer et al, 2004; Le et al, 2000). The adverse effects have been reported in 0.7-2.4 % cases. Atorvastatin may be safely used in dose of 10-80 mg per day. However lower dose is found to be as effective as higher dose in primary prevention of CAD (Newman et al, 2006; Grundy et al, 2004). We used 10mg per day in the present study without any side effects.

Statins are the treatment of choice for typical diabetic dyslipidemia which is associated with high triglycerides and low high density lipoproteins. Apart from decreasing risk of coronary artery disease, atorvastatin has beneficial effect in decreasing hard exudates severity and clinically significant macular edema in diabetics with dyslipidemia. Dramatic regression of hard exudates has been reported after correction of dyslipidemia in diabetics with severe hard exudates over a mean follow up of 18 weeks (Gupta et al, 2004).

Michael Cusick et al showed histopathological evidence of regression of hard exudates and macular edema after reduction of elevated serum lipid levels in dyslipidemic patients (Michael et al, 2003). He demonstrated lipid laden macrophages and the changes which could be compared to atherosclerotic changes in CAD that occur in larger vessels as macropathy. Now-a-days trends are shifting towards use of lipid lowering drugs as primary preventive measure for CAD in type II diabetics with

normal lipid profile. There is a continuous linear relationship between blood LDL and CAD without any definite threshold below which a lower concentration is not associated with lower risk (Heart, 2002; Szatrowski et al, 1984; Jacobs et al, 1992). Atorvastatin in patients with LDL<4.14 mmol (160mg/dl) is effective to decrease CAD events by 36 % and stroke by 48 %. The adult treatment panel III on national cholesterol control program issued evidence based guidelines on cholesterol management (Expert, 2001). In high risk persons for CAD like diabetes the recommended LDL-C goal is < 100mg/dl but when the risk is very high LDL-C goal is <70mg/dl (The DALI study, 2001; Raikou 2007). Due to the histopathological similarity between diabetic retinopathy and CAD, atorvastatin could also have a role to play in diabetic retinopathy with normal lipid profile. However the present study did not show any significant decrease in hard exudates after atorvastatin in patients with normal lipid profile. In fact one of the eyes showed increased severity of hard exudates despite being on atorvastatin. Thus there could be other unknown factors leading to hard exudation. This patient had normal lipid profile, stable cardiac and renal status and well controlled sugar levels. The compliance to drug was also assured in this patient. This apparent increase in grading could have been due to foveal migration of hard exudates after laser treatment.

Recent studies have also shown beneficial effect of atorvastatin on ocular blood flow by decreasing the vascular resistance and increasing peak systolic velocity of central retinal artery and ophthalmic artery (Ozkiris, 2007). Atorvastatin improves endothelial function by increasing activity of nitric oxide due to decreased LDL oxidation. However the study did not comment about progression or regression of diabetic retinopathy and CSME after atorvastatin. In the present study no significant association of atorvastatin was seen with visual outcome as well as macular edema resolution after laser.

The limitations of the present study are the small sample size and only qualitative assessment of macular edema.

Conclusion

The results of CAD may not be generalized for diabetic retinopathy and atorvastatin may not have any role in CSME with normal lipid profile.

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