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REBOUND AFTER INTRAVITREAL INJECTION OF BEVACIZUMAB IN PERSISTENT DIABETIC MACULAR EDEMA

Ophthalmology

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ABSTRACT

Retrospective non-randomized study of 36 eyes of type-2 diabetes patients with persistent diabetic macular edema, who received single intravitreal bevacizumab with follow up for six months without any further intervention. Primary outcome measure was the change in central macular thickness(CMT). Secondary outcome measure was the change in best corrected visual acuity(BCVA). Baseline mean CMT was 534.93±110.48 µ. Mean CMT at month six was 359.1 ± 109.3 µ, the change being significant (p=0.03). Decrease in mean CMT at all the follow ups was significant as compared to baseline. Rebound was observed at month four, five and six. At month four, 20(55.6%) eyes had rebound edema compared to month three. Significant improvement in BCVA was noted at each follow up compared to baseline (1.58 ± 0.27). Single intravitreal bevacizumab was effective in improvement in BCVA and reduction of macular edema for six month period with rebound of edema from month three.

KEYWORDS

Diabetic Retinopathy, Macular Edema, Inrtavitreal, Macular Thickness, Bevacizumab

INTRODUCTION

Diabetes mellitus is a major cause of avoidable blindness all over the world. Patients with diabetic retinopathy (DR) are 25 times more likely to become blind than non diabetics.1 Diabetic macular edema (DME) is the major cause of vision impairment in diabetes and has been defined as edema within 1 disk diameter of the fovea and is present in 9%of the diabetic population.2The Early Treatment Diabetic Retinopathy Study (ETDRS) demonstrated that macular grid and/or focal photocoagulation reduced the incidence of moderate visual loss due to clinically significant macular edema (CSME) by 50% over 3 years. However despite laser photocoagulation, 12% of eyes with CSME experienced loss of 15 or more ETDRS letters and only 3% eyes experienced a gain of 3 or more lines of vision.3 This suggests of a distinct subgroup in DME patients resistant to conventional laser photocoagulation. Poor outcome despite laser photocoagulation in eyes with diffuse DME has been reported.4 Higher HbA1C value has been reported in type 2 diabetes patients with persistent DME.5 Vascular endothelial growth factor (VEGF) has been shown to play a major role in macular edema.6 Hypoxia is a major inducer of VEGF gene transcription and VEGF thus liberated increases retinal vascular permeability.7 Anti VEGF has been proposed as a therapy of DME. Recently published report of RESOLVE study has demonstrated efficacy & safety of intravitreal ranibizumab (IVR) in DME.8 In RESTORE study both ranibizumab monotherapy and ranibizumab combined with laser produced more significant gain in visual acuity over standard laser in patients with DME.9 Intravitreal bevacizumab (IVB) used as primary treatment of diffuse DME demonstrated stability or improvement in BCVA, OCT, and FA at 24 months, with no evident difference between doses of 1.25 or 2.5 mg.10 IVR with deferred laser (>24 weeks) demonstrated maximum gain in BCVA compared to other groups (IVR+ prompt laser and triamcinolone +prompt laser) at the end of 2 years.11 Study on rebound of macular edema after IVB in persistent DME may give us an idea about the possible deferment period for repeat injection of IVB or for laser when treatment is planned with combined IVB and laser. The aim of our study was to determine the incidence and pattern of rebound macular edema over a six month period following single IVB of (1.25 mg) in the treatment of persistent diabetic macular edema.

METHOD

We reviewed the clinical records of type 2 diabetes patients who received single IVB for persistent DME between April 2009and February 2011 at a tertiary care medical college in eastern India and were followed up at least for six months without any further intervention. Diabetes was defined on the basis of treatment history of the patient. Clinically significant macular edema was defined according to ETDRS. The diffuse DME was defined on slit-lamp biomicroscopic examination as retinal thickening (clinically significant DME as defined by the ETDRS), and diffuse fluorescein leakage involving the centre of the macula on fluorescein angiography (FA) with less than 33% of leakage associated with microaneurysms. Persistent DME was defined as clinically detectable CSME despite two sessions of focal laser photocoagulations (FLP) that were performed at least 3 months before the current diagnosis. In our institute the patients with glaucoma, ocular hypertension, history of stroke, pregnancy, allergy to bevacizumab were not injected with IVB. Pre injection best corrected distance visual acuity (BCVA) of < 6/18 and central macular thickness of at least 250µ thickness was needed for inclusion in our study. Eyes with any session of photocoagulation within last three months or history of more than two sessions of laser, any intraocular surgery, any other intravitreal injection, any epiretinal membrane (ERM) or vitreomacular traction in OCT image, macular ischemia in FA image, loss of vision attributable to other causes were excluded. Patients with baseline proteinuria and HbA1C ≥ 8.5% were excluded. When both eyes were eligible, the eye with higher CMT was included. The following parameters were recorded at the baseline: BCVA by Snellen's chart and converted to logMAR units, intraocular pressure measurement, fluorescein angiography by a single certified photographer (TRC.50DX, Topcon corp., Tokyo, Japan) and OCT scan (Stratus OCT-3, Carl Zeiss Meditec, Inc, Dublin, CA). The OCT scan was done by using the Macular Thickness scan protocol. The best quality macular thickness maps (signal strength 7 or more) at each visit were analyzed to produce the Macular Thickness Map, consisting of thickness values in 9 subfields distributed in 3 concentric circles with diameters of 1, 3, and 6 mm. Each patient received intravitreal injections of 0.05 ml (1.25 mg) of bevacizumab using a 30 gauge needle under topical anaesthesia with proparacaine. Records of monthly follow up for six months were collected. Primary outcome measure was the change in central macular thickness after intravitreal bevacizumab. Secondary outcome measure was the change in BCVA. Effective treatment was defined as decrease in macular thickness of >30% compared to baseline thickness. A rebound was defined as the recurrence foveal thickness ratio ≥ 110% compared to immediate previous visit after initial decrease. Statistical analysis was done with statistical software SPSS Version 16.0.0. The patients were included in the study with informed consent and institutional ethics committee permitted the study.

RESULT

36 eyes of 30 consecutive patients were included in the study. Age range was 49-67 years, mean age being 59.8±6.2 years. Eighteen (60%) were male and 12(40%) were female. Sixteen were right eyes and 20 were left eyes. All had associated non proliferative DR (NPDR). Mean HbA1C was 7.6±0.8. Mean duration of diabetes was 15.5± 5.8 years.Baseline mean CMT was 534.93±110.48 µ (Table 1).

Table 1: Serial measurements of central macular thickness (CMT) and best corrected visual acuity (BCVA) over six month.

	Baseline	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6

Mean CMT(μ)	534.93± 110.48	240.63± 49.87	202.4± 61.3	214.36 ±. 36.6	273.6± 48.9	313.7± 63	359.1 ± 109.31
Change in mean CMT(μ) from baseline	-	-294.3± 101.6	-331.3 ± 86.7	-320.6 ± 109.1	-261.7 ± 93.4	-220.9 ± 100.1	-175.7 ± 94.9
BCVA (logMAR)	1.58 ± 0.27	0.75 ± 0.26	0.78 ± 0.31	0.83 ± 0.39	0.82 ± 0.17	0.88 ± 0.31	1.02 ± 0.34

First month post injection change in mean CMT after one month was significant (p=0.03). At second month further decrease in mean CMT was observed and change in mean CMT from month one CMT was -92.3 ± 56.7μ. At month three mean CMT increased which was 106.3% compared to month 2 CMT. However change in mean CMT at month three compared to baseline was significant (p=0.03). At month four, mean CMT increased which was 127.7% compared to month three CMT. At month five, mean CMT further increased, the increase being 110.9% compared to month four CMT. At six month post injection, the mean CMT increased further which was 114.6% compared to month five CMT. However the mean change in CMT at month 6 from baseline was significant (p=0.03). Only one subject showed an increase in CMT at sixth month, compared to baseline CMT.

22 eyes demonstrated treatment efficacy (> 30% decrease in CMT compared to baseline) at all follow ups. At month one no eye demonstrated rebound edema (compared to baseline value). At month two, only two (5.6%) eyes demonstrated rebound edema compared to month one. At month three, only five (13.9%) eyes demonstrated rebound edema compared to month two. At month four, rebound edema was observed in 20(55.6%) eyes compared to month three. At month five, five (13.9%) eyes had rebound edema compared to month four. At month six, six (16.7%) eyes demonstrated rebound edema compared to month five. At six month, rebound edema was observed in 23(63.9%) eyes h compared to month three. The maximum decrease in mean CMT compared to previous visit occurred at month one and maximum increase in mean CMT compared to previous visit occurred at month four (Figure1). At month three no significant correlation of rebound macular edema with duration of diabetes (p=0.073) and HbA1C was (p=0.698) was observed.

Significant improvement of BCVA was noted at each follow up compared to baseline. At month one, compared to baseline, twenty five (69.4%) eyes demonstrated improvement, two (5.6%) eyes had further deterioration and nine (25%) eyes had stabilization of BCVA. At three months, compared to baseline, 24(66.6%) eyes demonstrated improvement, two (5.6%) eyes had deterioration and 10 (27.8%) eyes had stabilization of BCVA. At six months, compared to baseline, 22(61.1%) eyes demonstrated improvement, two (5.6%) eyes further deterioration and 12 (33.3%) eyes had stabilization of BCVA. At six month, compared to month three, four (11.2%) patients demonstrated worsening of BCVA. Two (5.6%) patients demonstrated deterioration of visual acuity at all visits. One of these two patients developed severe inflammatory reaction in anterior chamber two days following injection which was treated with topical corticosteroid with complete subsidence of inflammation. No other ocular or systemic side effects of injection were seen throughout the study period.

DISCUSSION

In this study our aim was to assess the persistence of efficacy of a single dose of IVB in persistent DME. Our study has shown that a single dose of bevacizumab (1.25 mg in 0.05 ml) was effective in improving visual acuity as well as reducing macular edema in persistent DME. However improvement of both visual acuity and central macular thickness was short lived.

Statistically significant improvement in mean BCVA compared to baseline occurred at each follow up. Three out of the 4 patients who failed to improve in BCVA, demonstrated significant reduction in CMT. The reason for their non improvement was hard exudates involving fovea and retinal pigment epithelium atrophy. Spectral OCT could have been more informative in such cases.

There was significant improvement in CMT following IVB. Maximum improvement was seen in the third month post injection. A rebound increase in CMT was seen in the sixth month showing that the beneficial effects of bevacizumab injection was short lived. The reduction in CMT however was statistically significant in all the three follow ups in all the patients. Studies done in the past on the effect of IVB on recalcitrant diabetic macular edema have shown similar results. Short term efficacy of IVB in recalcitrant diabetic macular edema was observed in previous studies.12,13,14 Long term decrease of CMT was observed with repeated IVB in chronic diffuse macular edema.15 Kumar A et al observed that IVB resulted in significant decrease in macular thickness and improvement in VA in 3 months but the effect was somewhat blunted though still statistically significant at the end of 6 months.16 Our study also corroborates with the above findings. Mean time interval for recurrence of macular edema after two consecutive ranibizumab injections was 2.4 months and 1.2 months for branch retinal vein occlusion (BRVO) and central retinal vein occlusion groups, respectively.17 In macular edema due to BRVO treated with IVB, a rebound of macular edema was more likely to occur when IVB is initiated early before the macular edema reaches the maximum level.18 However we included only those cases with persistent edema. Hence early treatment was not the cause of rebound in our study.

Our study population comprised of patients who were not cured by laser. We excluded patients with HbA1c ≥ 8.5, thereby eliminating one major cause of treatment failure.5 Change in mean CMT showed rebound edema at each follow up starting from month four, when we compared with mean CMT of immediate previous visit. At month four, 55.6%% eyes demonstrated rebound edema compared to month three This probably signifies the need for intervention in the form of repeat injection/laser at month three to maintain the beneficial effect. At six month, although 63.9% patients had rebound edema compared to month three, only four (11.2%) patients demonstrated decrease in visual acuity. This suggests absence of any linear relationship between rebound macular edema and decrease in BCVA. This was a retrospective analysis. Prospective trial may be planned to overcome this limitation. The present study shows that a single dose of 1.25 mg of IVB brings about a significant short lived improvement in the functional and anatomical parameters in patients of persistent diabetic macular oedema with rebound from month three, suggesting further intervention at an earlier period than this.

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