Original Article

Effect of intravitreal bevacizumab in diabetic macular edema

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ABSTRACT

Objective: To report the effect of intravitreal bevacizumab (Avastin) on visual acuity and central macular thickness in patients with diabetic macular edema (DME), who have already received macular laser photocoagulation.

Methodology: This Prospective, interventional case series study was conducted at the Department of Ophthalmology, Isra University and Hospital, Hyderabad, and Al-Ibrahim Eye Hospital, Karachi, from July 2009 to March 2010. Twenty four eyes with diffuse DME were treated with intravitreal injection of bevacizumab 1.25mg in 0.05ml. Evaluation at baseline and follow-up visits included visual acuity by ETDRS chart, slit lamp examination, applanation tonometry, fundus fluorescein angiography, and macular thickness measurement by optical coherence tomography. Central macular thickness on optical coherence tomography (OCT) and best corrected visual acuity were measured at baseline and at one month and three months after the intravitreal injection.

Results: At baseline, the mean BCVA was 1.033±0.16 logMAR. This improved to 0.90±0.22 (p=<0.0001) and 0.94±0.20 logMAR (p=0.001) at one month and three months, respectively. Mean central macular thickness was 520.40±139.1 µm at baseline, which decreased to 385.90±98.30 µm (p<0.0001) at one month and to 427.40±112.6 µm (p=<0.0001) at three months.

Conclusion: Intravitreal bevacizumab injection results in significant improvement in visual acuity and reduction in central macular thickness to produce a clinically meaningful and statistically significant benefit in patients with DME; this beneficial effect was shown to persist for up to three months.

KEY WORDS: Diffuse DME, Intravitreal bevacizumab, VEGF.

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INTRODUCTION

Macular edema is a manifestation of diabetic retinopathy that can lead to central vision loss. Data from the population-based Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) study estimates the prevalence of diabetic macular edema (DME) in persons with 15 or more years of diabetes to be approximately 20% in those with type 1 diabetes; 25% in those with type 2 diabetes taking insulin and 14% in those with type 2 diabetes not taking insulin.[1] To date, the only treatment conclusively demonstrated to be of long term benefit for diabetic macular edema is laser photocoagulation. The Early Treatment Diabetic Retinopathy Study (ETDRS) showed

that laser treatment reduced the 3-year rate of moderate vision loss (3 or more lines of acuity loss) by 50%. However, only 17% of eyes showed any improvement in visual acuity (VA), and less than 3% had visual improvements of three or more ETDRS lines.[2] Moreover, a significant number of patients with DME remain refractory to laser treatments and this has driven many investigators to seek alternative treatments. Other possible therapies include triamcinolone injections[3], oral protein kinase C inhibitors[4], intravitreal aptamers[5], antibodies directed against vascular endothelial growth factor (VEGF) [6], and vitrectomy.[7]

VEGF has been implicated as an important factor in the breakdown of the blood-retinal barrier, with increased vascular permeability resulting in retinal edema in diabetic patients through affecting endothelial tight junction proteins.[8] While the normal human retina contains VEGF, its levels are significantly elevated in eyes with DME.[9] Therefore anti-VEGF treatments have been proposed as an alternative adjunctive treatment for DME.[6] Bevacizumab (Avastin, Genentech Inc., San Francisco, CA) is a complete full-length humanized antibody that binds to & competitively inhibits all isoforms of the VEGF-A family. While bevacizumab is currently approved for the treatment of metastatic colorectal cancer, metastatic breast cancer, and non-small cell lung cancer [10], it is widely used as an off-label treatment for retinal vein occlusion[11], neovascular age-related macular degeneration[12], DME[13], proliferative diabetic retinopathy[14], rubeosis irides[15], and retinopathy of prematurity.[16] Although intravitreal use of bevacizumab is an off-label option its use has risen exponentially in the last few years mainly due to its efficacy and economic considerations.

Based on these observations, we evaluated the beneficial effect of intravitreal bevacizumab, after macular laser photocoagulation, on visual acuity and central macular thickness in DME, in which VEGF is known to play a key role in increasing the vascular permeability.

METHODOLOGY

This prospective, interventional case series study was conducted at the Ophthalmology department, at the Isra University and Hospital, Hyderabad, and Al-Ibrahim Eye Hospital, Karachi, between July 2009 and March 2010. Twenty four eyes of eighteen patients were given off-label intravitreal bevacizumab. The administration of intravitreal bevacizumab was approved by the institutional review board of the Isra University. Intravitreal bevacizumab injection was prepared and dispensed by the pharmacy at the Aga Khan University Hospital, Karachi. The inclusion criteria were eyes having diffuse DME visible clinically and on Fundus Fluorescein Angiography (FFA) after having received some form of macular laser photocoagulation before but not less than six months ago, having best corrected visual acuity (BCVA) < 6/36, and having central macular thickness > 250μm on OCT. The exclusion criteria were eyes with proliferative diabetic retinopathy; only focal macular edema due to leaking microaneurysms; prior history of vitrectomy or any other intraocular surgery within the last 6 months; laser treatments including pan-retinal photocoagulation, posterior capsulotomy, or macular photocoagulation within the last 6 months; angiographic evidence of ischemic maculopathy; evidence of vitreo-macular traction on OCT; and presence of comorbid ocular conditions that might have affected the visual acuity.

Visual acuity was measured by Early Treatment Diabetic Retinopathy Study (ETDRS) chart. Anterior segment was examined with slit lamp and biomicroscopic evaluation of fundus was carried out with non-contact +90D lens. Intraocular pressure (IOP) was checked with Goldmann applanation tonometer. FFA was performed in all the patients. Central macular thickness was measured with OCT (Stratus OCT, Carl Zeiss, Germany). The disease process and the treatment options were discussed with the patient. All patients provided written informed consent, and they were informed of the off-label use of the drug and its potential risks and benefits, as well as the likelihood that additional treatments might be required. Using a sterile eyelid speculum and topical anesthesia, followed by a prep with povidone iodine, bevacizumab in dose of 1.25 mg in 0.05 ml was injected using a 30-gauge needle on a 1 ml syringe into the vitreous cavity through the pars plana 3.0-4.0 mm posterior to the limbus; topical antibiotic eye drops were prescribed to be used six hourly for three days. Patients were followed up after one week and regularly afterwards, for at least three months, after the injection. At each visit, patients were asked regarding any adverse events and detailed evaluation was carried out, with special emphasis on BCVA, fundoscopy findings, central macular thickness (CMT) with OCT and possible side-effects i.e. rise in IOP, inflammation and endophthalmitis. Systemically all the patients were monitored for blood pressure rise, chest pain and thromboembolic events. Main outcome measures were BCVA and central macular thickness as measured with OCT. These parameters were evaluated

at one month and at three months after the injection. Each patient's visual acuity was converted to logMAR scale for analysis. The paired *t*-test was used for comparison of preoperative and postoperative BCVA and central macular thickness. For all statistical tests, a *p* value <0.05 was considered statistically significant. The data were analyzed using SPSS statistical software.

RESULTS

Twenty four eyes (18 patients) with a minimum of three months follow-up were included for analysis. The mean patient age was 57.2±9.2 years, and 55% were male patients. Macular laser photocoagulation had already been applied once in 8 eyes and twice in 16 eyes. Baseline characteristics are depicted in Table-I.

At baseline, the mean BCVA was 1.033±0.16 logMAR. This improved significantly to 0.90±0.22 (*p*=<0.0001) and 0.94±0.20 logMAR (*p*=0.001) at one month and three months, respectively. At 3-month follow-up, the BCVA was slightly decreased, but was still statistically significant compared to the baseline. The visual acuity results are summarized in Table-II. Final BCVA analysis at three months demonstrated that 14 (58%) of 24 eyes improved, 7 (29%) eyes remained stable, and three (12%) eyes deteriorated, as compared to the baseline (Table-III).

Mean central macular thickness was 520.40±139.1 µm (range: 281-750 µm) at baseline by OCT. This decreased significantly to 385.90±98.30 µm (*p*=<0.0001) and 427.40±112.6 µm (*p*=<0.0001) at one month and three months, respectively. However, at 3-month follow-up, mean central macular thickness increased as compared to the one month follow-up, but was still statistically significant compared to the baseline (*p*=<0.0001). Table-IV summarizes the OCT-measured macular thickness results. Figure.1 shows the changes in BCVA and OCT- measured central macular thickness after intravitreal bevacizumab injection. There were no cases of endophthalmitis, uveitis, IOP increase, or severe decrease in vision immediately after injection. At three months, no ocular or systemic adverse events were reported, including thromboembolic events (cerebrovascular accidents, transient ischemic attacks, myocardial infarctions, or peripheral vascular disease).

Table-I: Baseline characteristics of the study eyes.

Variables	
Gender (no.)	
Male	10 (55%)
Female	08 (45%)
Age (years), Mean ±SD	57.2 ±9.2
Range = 38 – 70 years	
Macular laser treatment (no.)	24
Once	08 (%)
Twice	16 (%)
Mean follow-up period (months)	7.31+ 2.16
Baseline visual acuity (logMAR), Mean + SD	1.033 ±0.16
Baseline central macular thickness (µm), Mean ±SD	520.4 ±139.1

DISCUSSION

At present, the management of diffuse DME remains a challenge. Many treatment modalities are being investigated in order to improve the patients' vision. VEGF has been shown to be an endothelial cell-specific mitogen, angiogenic inducer and vascular permeability factor; it increases the permeability of retinal vessels by increasing the phosphorylation of tight junction proteins.[17] It was found that the concentration of VEGF in the vitreous increased and correlated with the severity of macular edema in patients with DME[18], therefore anti-VEGF therapy is expected to show reduction of DME. The off-label use of intravitreal injection of bevacizumab is based on the results of clinical reports clearly indicating an increase in visual acuity and a decrease in macular thickness. Bevacizumab has attracted interest because of its much lower cost compared to other anti-VEGF agents e.g. ranibizumab and pagabtanib.

Intravitreal injections involve risks inherent to the surgical technique and those derived from local and systemic adverse effects of the drugs. The intravitreal injection of triamcinolone acetonide brings about the well-known side-effects[19], i.e. raised IOP, progression

Table-II: Comparison of mean logMAR BCVA between baseline and post intravitreal bevacizumab at 1 and 3 months.

Visual Acuity (logMAR)	*Mean ±SD*	*Comparison*	*P-values*
Baseline (A)	1.033 ±0.16	— —-	— —
At 1st month (B)	0.9 ±0.22	A Vs B	< 0.0001
At 3rd month (C)	0.94 ±0.2	A Vs C	0.001

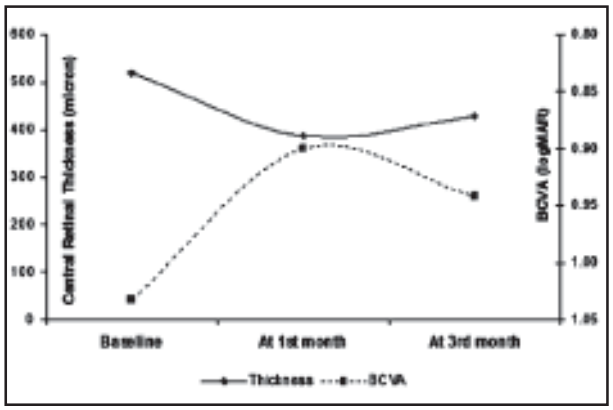

Fig-1: Changes in BCVA and central macular thickness after intravitreal bevacizumab.

of cataract and risk of endophthalmitis derived not only from the surgical technique but also from the immunosuppressant effect of the drug. Injection related complications have been reported following intravitreal use of anti-VEGF drugs, but no drug – related ocular toxic effect has been reported. However, the possibility of a systemic adverse effect (cerebrovascular and cardiovascular thromboembolic events) after intravitreal injection of bevacizumab does exist.[13,20]

We report the results of 24 consecutive eyes with diffuse DME treated with intravitreal bevacizumab which resulted in both anatomical and functional improvement. All the patients had received macular laser photocoagulation before, without much improvement in visual acuity. We conformed to the widely used concentration of the drug (1.25mg). Intravitreal bevacizumab was well tolerated by our patients, and no ocular or systemic adverse effects were noticed during the study. Our results show improvement in mean logMAR BCVA from a baseline of 1.033±0.16 to 0.90±0.22 and decrease in mean central macular thickness from 520.40±139.1 µm to 385.90±98.30 µm at one month after the injection. However, recurrence of macular edema occurred after initial improvement and the results at three month follow up show an increase in mean central macular thickness to 427.40±112.6 µm and deterioration in mean BCVA to 0.94±0.20. A retinal penetration study revealed the absence of

Table-III: Best-Corrected visual acuity (BCVA) analysis.

BCVA	*At 1 month (No. of eyes)*	*At 3 month (No. of eyes)*
Improvement	18 (75%)	14 (58.3%)
Deterioration	00	03 (12.5%)
No Change	06 (25%)	07 (29.2%)

bevacizumab four weeks after the injection, which may suggest the limited effect of the drug on suppression of VEGF activity.

Other studies[21-24] has also shown short-term improvement in visual acuity and reduction in OCT-measured macular thickening, following intravitreal bevacizumab injection. Nagasawa T et al[21] injected intravitreal bevacizumab in twenty eyes with persistent DME; their results show a significant decrease in macular thickness and an insignificant improvement in BCVA, but there was recurrence of macular edema four weeks after the injection. Seo JW et al[22] conducted a study on thirty eyes with DME treated with intravitreal bevacizumab; they reported significant improvement in mean BCVA and mean central macular thickness on OCT lasting for up to three months. Kumar A and Sinha S[23] treated twenty eyes with DME with two intravitreal bevacizumab injections, six weeks apart; they concluded that intravitreal bevacizumab resulted in a significant decrease in macular thickness and improvement in visual acuity at three months but the effect was somewhat blunted, though still statistically significant at the end of six months. A phase 2 randomized clinical trial of intravitreal bevacizumab for DME conducted by the Diabetic Retinopathy Clinical Research Network[13] reported a greater reduction in macular thickness and improvement in BCVA in eyes treated with intravitreal bevacizumab, as compared to those treated with laser photocoagulation, but endophthalmitis developed in one eye treated with intravitreal injection. Kook D et al[24] evaluated the long-term efficacy of bevacizumab for the treatment of chronic diffuse DME after previous treatment with laser, IVTA or vitrectomy; they treated 126 patients with multiple intravitreal bevacizumab injections

Table-IV: Comparison of central macular thickness between baseline and post intravitreal bevacizumab at 1 and 3 months.

Central Macular thickness (µm)	*Mean ±SD*	*Comparison*	*P-values*
Baseline (A)	520.4 ±139.1	– –-	– –
At 1st month (B)	385.9 ±98.3	A Vs B	< 0.0001
At 3rd month (C)	427.4 ±112.6	A Vs C	< 0.0001

and followed them for 6-12 months; they concluded that even in cases with chronic diffuse diabetic macular edema, a long-term decrease of central retinal thickness and a gain in mean BCVA can be observed following repeated intravitreal injections of bevacizumab. The results of our study and those of the above mentioned studies suggest that a single intravitreal bevacizumab injection leads to short–term improvement in BCVA and reduction in central macular thickness in patients with DME; repeated intravitreal bevacizumab injections may be necessary to maintain a beneficial effect over a longer period of time.

In conclusion, our study suggests that inhibition of VEGF by intravitreal bevacizumab injection results in significant improvement in BCVA and reduction in central macular thickness to produce a clinically meaningful and statistically significant benefit in patients with diabetic macular edema, who had already received macular laser photocoagulation; this beneficial effect was shown to persist for up to three months. The limitations of this study are its non-randomized status, use of an off-label drug, small sample size and short follow-up period. Though the positive results of this prospective, nonrandomized study preclude any estimation of the long-term efficacy or safety of intravitreal bevacizumab, they are quite promising and suggest the need for further longer prospective randomized studies.

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