Primary effects of intravitreal bevacizumab in patients with diabetic macular edema

Iftikhar-ul-Haq Tareen1, Azizur Rahman2, P.S Mahar3, Muhammad Saleh Memon4

ABSTRACT

Objective: To evaluate the efficacy of primary intra vitreal bevacizumab (IVB) injection on macular edema in diabetic patients with improvement in best corrected visual acuity (BCVA) and central macular thickness (CMT) on optical coherence tomography (OCT).

Methods: This prospective interventional case series study was conducted at Retina Clinic, Al-Ibrahim Eye Hospital, and Isra Postgraduate Institute of Ophthalmology Karachi. Between December 2010 to June 2012. BCVA measurement with Early Treatment in Diabetic Retinopathy Study (ETDRS) charts and ophthalmic examination, including Slit-lamp bio microscopy, indirect ophthalmoscopy, Fundus fluorescein angiography (FFA) and OCT were done at the base line examination. At monthly interval all patients were treated with 3 injections of 0.05 ml intra vitreal injection containing 1.25 mg bevacizumab. Patients were followed up for 6 months and BCVA and OCT were taken at the final visit at 6 month.

Results: The mean BCVA at base line was 0.42±0.14 Log Mar units. This improved to 0.34±0.13, 0.25±0.12, 0.17±0.12 and 0.16±0.14 Log Mar units at 1 month after 1st, 2nd 3rd injection and at final visit at 6 months respectively, a difference that was statistically significant (P > 0.0001) from base line. The mean 1mm CMT measurement was 452.9 ± 143.1 µm at base line, improving to 279.8 ± 65.2 µm (P < 0.0001) on final visit. No serious complications were observed.

Conclusions: Primary IVB at a dose of 1.25 mg on monthly interval seems to provide stability and improvement in BCVA and CMT in patient with DME.

KEY WORDS: Best Corrected Visual Acuity (BCVA), Central Macular Thickness (CMT), Diabetic Macular Edema (DME), Intra Vitreal Bevacizumab (IVB).

INTRODUCTION

With the increasing prevalence of diabetes in the world wide, Diabetic retinopathy (DR) remains the major threat to sight in the working-age population. It remains as a major cause of blindness in developing countries.1 According to the Diabetic Association of Pakistan – World Health Organization (DAP-WHO) survey (1994-1998), overall prevalence of Diabetes is 11.47% in Pakistani population.2 Another study has revealed that 25% of those patients, that present to the health care facilities in Pakistan with diabetes suffered from retinal complications.3 The Wisconsin study4 reported that 9% of diabetic population had macular edema with in 1 disc diameter of the fovea.
A study carried out at Al Ibrahim Eye Hospital (2011) showed that 39.8% of patients registered at retinal clinic were suffering from DR, out of which 45% were having Clinically Significant Macular Edema (CSME).5

Retinal hypoxia is the primary cause of DR which increases the expression of vascular endothelial growth factor (VEGF). It is an endothelial cell-specific mitogen which induces angiogenesis and increase vascular permeability by affecting endothelial tight-junction protein.6 In ocular vascular disease such as DME, VEGF levels has been found considerably higher in macular region.7 The Early Treatment Diabetic Retinopathy (ETDRS) shows 3-year risk of moderate visual loss due to macular edema was 32%, and focal macular laser photocoagulation was effective in the treatment of DME. ETDRS demonstrated that immediate focal laser photocoagulation reduced the risk of moderate visual loss by 50% (from 24% to 12%, 3 year after initiation of treatment). However, 12% of treated eyes still lost ≥ 15 ETDRS letters at 3-year follow-up interval. Furthermore, only 3% of laser-treated eyes experienced a gain of ≥ 3 lines of vision.8 The failure of laser photocoagulation in these eyes has prompted interest in other treatment modalities such as Anti-VEGF agents, intravitreal triamcinolone acetonide (IVTA),10 pars plana vitrectomy (PPV)11 or treatment with protein Kinase C inhibitors.12

Food and Drug Administration (FDA) has approved bevacizumab (Avastin, Genentech Inc. South San Francisco, CA, USA) a fusion protein with human antibody backbone against VEGF, it binds and inhibits all the active forms of VEGF and is used in the treatment of metastatic colorectal cancer. Some studies had found it useful in the reduction of macular edema secondary to central retinal vein Oclusion (CRVO), vascular permeability and neovascularization secondary to age-related macular degeneration (AMD).14

The purpose of this study was to evaluate the best corrected visual acuity (BCVA) measured on ETDRS chart and central macular thickness (CMT) carried out on optical coherence tomography (OCT) after a series of 3 injection of IVB at interval of one month and at mean follow up of 6 months after 1st injection.

METHODS

All patients were followed up for 6 months. Approval of the study was obtained from the institutional ethical committee, and informed consent was obtained from all patients. The study followed the principles of Declaration of Helsinki.

Patients with evidence of DME were included in this study. DME is defined as the evidence of diffuse retinal thickening, hard exudates (with out a circinate ring pattern) involving the center of the macula (clinically significant diabetic macular edema as defined by ETDRS), or both and Diffuse fluorescin leakage involving the center of the macula on FFA, and Central Macular Thickening (CMT) on Optical Coherence Tomography (OCT).

The exclusion criteria included patients with DME who had been treated previously with laser photocoagulation, intra vitreal triamcinolone or any Anti-VEGF therapy elsewhere. The patients with Macular ischemia, uncontrolled intraocular pressure, intra ocular surgery within past 6 months, history of vitreo retinal surgery of the study eye, or any evidence of epiretinal membrane or vitreomacular traction were excluded.

After detailed history each patient underwent baseline examination which included BCVA measurment with ETDRS charts and ophthalmic examination, including slit lamp bio microscopy and dilated fundus examination with +90 diopter lens and indirect ophthalmoscopy. All patients had fundus fluorescien angiography (FFA).Baseline CMT was analyzed by OCT using 6 diagonal slow 6mm radial line scan on Topcon analyzer (Tokyo, Japan).

Procedure: All eyes had several drops of local anesthetic (Alcaine – Alcon, Belgium) with dilatation of pupil (Mydriacyl 1% - Alcon, Belgium) before the procedure. After the eye had been prepped in standard fashion using 5% povidoniodine, an eye lid speculum was used to stabilize the eyelids and the injection of 1.25 mg (0.05 ml), bevacizumab was performed at 3.5 to 4mm posterior to the limbus through the inferiortemporal pars plana with a tuberculosis syringe and 30 gauge needle. After injection, retinal artery perfusion was checked with the indirect ophthalmoscopy. A single drop of antibiotic (Vigamox – Alcon, Belgium) is instilled and patients were instructed to administer topical antibiotics for one week.

All patients were examined at one week and one month after the first injection. At 1st month visit BCVA was recorded and 2nd injection was administered and the same was repeated after one month and the 3rd injection was administered .The patients were followed-up for 6 months and final
BCVA and CMT were taken at the final visit at 6 month after the first injection.

RESULTS

A total of 49 diabetic patients were enrolled in this study. Seven of our patients were lost the follow-up or were excluded due to exclusion criteria from the study. The final data of 78 eyes of 42 patients with a minimum follow up of 6 months after 1st injection of bevacizumab were included for analysis. The patients had a mean age of 53.5 ± 11.4 years, and 25(59.52%) were male, 17(40.47%) were female.

Within one month after the initial bevacizumab injection improvements in BCVA were observed, and these significant changes continued throughout the 6 months follow up period. The mean BCVA at baseline was 0.42 ±0.14 Log Mar units. At one month after the 1st injection BCVA improved to 0.34±0.13 Log Mar unit, a difference that was statistically significant (P<0.0001). This improvement in BCVA was maintained after 2nd and 3rd injections which were 0.25±0.12 Log Mar units and 0.17±0.12 Log Mar units respectively. In addition the mean BCVA at 6 month follow up examination was 20/25 (0.16±0.14 Log Mar units), a statistically significant difference from baseline BCVA (P<0.0001).(Table-I)

Further subgroups analysis demonstrated that after 1st injection, 49(62.8%) eyes improved one or more ETDRS line of BCVA,27(34.6%) eyes remained stable and 2(2.5%) decreased one or more ETDRS lines of BCVA. This trend continued after 2nd and 3rd injection, and at 6 month follow up examination, 16(20.5%) eyes remained stable, 57(73.0%) eyes improved one or more ETDRS lines and 5(6.4%) eyes had decreased one or more ETDRS lines of BCVA. (Table-II)

Fig.1: Optical Coherence tomography (OCT) imaging of a 52 years old diabetic male with a history of loss of vision in both eyes to 20/160, Right eye (a) Left eye (b), in which diabetic macular edema had developed. The OCT shows a marked resolution in macular edema and improvement of Central Macular Thickness (CMT) after treatment.

DISCUSSION

This study reports on 78 consecutive eyes with DME treated with Intravitreal Bevacizumab, which resulted in both anatomic and functional improvement. In most of patients improvement of

| Table-I: Mean Log Mar value for the BCVA 1 month after each injection & at 6 month follow up examination. |
|---------------------------------|----------------|----------------|----------------|
| BCVA                           | Mean Log Mar Unit | Std Deviation  | Snellen equivalent |
| At baseline                    | 0.42 ±0.14        | 20/50          |                |
| After 1st injection            | 0.34 ±0.13        | 20/40          |                |
| After 2nd injection            | 0.25 ±0.12        | 20/30          |                |
| After 3rd injection            | 0.17 ±0.12        | 20/25          |                |
| At 6 month Follow up           | 0.16 ±0.14        | 20/25          |                |

| Table-II: Best Corrected Visual Acuity (BCVA) analysis by subgroups (78 eyes). |
|-----------------------------------------------|----------------|----------------|----------------|----------------|----------------|----------------|
|                                              | After 1st Injection | After 2nd Injection | After 3rd injection | At 6 month follow up |                  |
|                                              | No of eyes | Percentage   | No of eyes | Percentage   | No of eyes | Percentage   | No of eyes | Percentage   |
| Improved ≥ 1 ETDRS lines                    | 49         | 62.8%        | 53        | 67.9%        | 54         | 69.2%        | 57         | 73.0%        |
| Remained stable                             | 27         | 34.6%        | 22        | 28.2%        | 21         | 26.9%        | 16         | 20.5%        |
| Decreased ≥ 1 ETDRS lines                   | 2          | 2.5%         | 3         | 3.8%         | 3          | 3.8%         | 5          | 6.4%         |
BCVA were detected with in the first month after the 1st injection and continued throughout the study period. (Fig.2) The exact pathophysiologic mechanism responsible for DME remains uncertain, retinal hypoxia and various rheological disturbances play a role in the disruption of the inner blood-retinal barrier associated with metabolic alterations. The long term circulatory disturbance may lead to functional vascular obstruction, relative retinal ischemia, and release of cytokines such as VEGF. Funatsu et al reported that level of VEGF was elevated in vitreous fluid of subjects with DME. VEGF causes conformational changes in the tight junctions of retinal endothelium and plays a major role in increasing vascular permeability in the progression of DME.

Several treatment methods for DME are under investigation. ETDRS has demonstrated that, the risk of visual loss from DME can be reduced by laser photoocoagulation. However, in some eyes macular edema may persist despite laser photoocoagulation. Therefore clinicians had developed interests in other treatment methods such as pharmacologic therapies. Intravitreal triamcinoline acetonide (IVTA) injection has some promising results but this treatment modality is not without its risks and complication. These complications were related to the injection procedure or to the corticosteroid suspension. Oral protein Kinase C inhibitors had demonstrated efficacy in prevention of visual loss from DME. Currently Fluocinolone Acetonide vitreous inserts are under investigations showing some promising results.

![Primary effects of IVB in DME](image)

The important role of VEGF in the breakdown of the blood-retinal barrier and vascular permeability resulting in retinal edema is clear. Therefore, the rationale for use of anti-VEGF agents for treatment of DME is significant. Bevacizumab (Avastin; Genentech, Inc) is a fusion protein with human antibody backbone that binds to all sub types of VEGF and used successfully in tumor therapy as a systemic drug. Recently off label use of IVB injection has been presented in small cohorts of patients with macular edema from various causes like CRVO, AMD and Proliferative Diabetic Retinopathy (PDR). As VEGF disrupts the inner blood-retinal barrier and causes extravasation of fluids by affecting endothelial tight junctions. Therefore, VEGF inhibition by IVB has been emerged as a target molecule for the treatment of DME.

There are several studies in the literature on the intravitreal administration of anti-VEGF for DME. Recently Khan et al published a report of 26 eyes, followed up for 3 months after IVB injection. The mean BCVA at baseline 0.726 Log Mar was improved to 0.452 Log Mar at 3rd month. Flourescien leakage stopped in 25 (96.15%) eyes. Kumar and Sinah reported results of 20 eyes with DDME treated with IVB at a dose of 1.25 mg that had not responded to previous photoocoagulation. They concluded that IVB resulted in a significant decrease in macular thickness and improvement in BCVA at 3 month. Ozkiris A presented results of 30 eyes, out of which 24 (80%) eyes showed increased visual acuity after mean, follow up time of 5.6 months after IVB injection. BCVA improved from 1.09±0.23 Log Mar (at baseline) to 0.90±0.17 Log Mar at 1st month and 0.77±0.26 Log Mar at the last visit. The mean edema map values significantly decreased by 33.3%. Arevalo et al published a report of 24-month anatomic and visual acuity response after primary intravitreal bevacizumab in patients with Diffuse Diabetic Macular Edema (DDME). They compared 2 different doses of intravitreal bevacizumab, 1.25 mg and 2.5 mg respectively. They found that primary IVB at doses of 1.25 or 2.5 mg seem to provide stability and improvement in BCVA, OCT, and FA results in DME at 24 months.

The results of our study compare favorably with these reports and confirm their findings. In our study, we found that improvement in BCVA was achieved within a month after 1st IVB injection. A further improvement was achieved after each injection of bevacizumab and was maintained at 6 months follow up. BCVA in our study improved from 0.42±0.14 Log Mar unit at base line to mean
so results cannot be generalized. Third, this study was carried out in a single center to avoid bias in follow-up time. Second, there is no control group to compare the treated eyes with DME treated with IVB and to evaluate the safety and efficacy of this treatment method. Our study has some limitations. First, the follow-up time was relatively short, but visual and anatomical responses were apparent during the follow-up time. Second, there is no control group in this study as randomization was not possible. Third, this study was carried out in a single center so results cannot be generalized.

CONCLUSION

This study demonstrated that IVB injection is an effective approach with promising results for the primary treatment of DME. IVB at a dose of 1.25mg on at least monthly interval seems to provide stability and improvement in BCVA and CMT in DME at 6 months. However evaluation in a multicenter, randomized, controlled clinical trial comparing IVB with other treatment modalities is needed to evaluate the safety and efficacy of this treatment method.

Conflict of Interest: The authors have no conflict of interest and is not supported or funded by any Drug company or any other source.

REFERENCES
1. Zimmet P, Alberti KG, Shaw J. Global and social implication of the diabetes epidemic. Nature. 2001;414:782-787. doi:10.1038/414782a.
2. Iqbal F, Naz R. Patterns of diabetes mellitus in Pakistan: An overview of the problem. Pak J Med Res. 2005;44:86-89.
3. Khan AJ. Prevalence of diabetic retinopathy in Pakistani Subjects: A pilot study. J Pak Med Assoc. 2004;54:60-66.
4. Klein R, Klein BE, Moss SE, Mathew DD, DeMet DL, et al. the Wisconsin Epidemiologic Study of Diabetic retinopathy. iv. Diabetic macular edema. Ophthalmology. 1984;91:1464-1474. PMID: 6521896
5. Khan A, Qidwai U. Frequency and patterns of eye diseases in retina clinic of a tertiary care hospital in Karachi. Pak J Ophthalmol. 2011;27:155-159.
6. Ferrara N. Vascular endothelial growth factor: basic science and clinical progress. Endocrine Review. 2004;25:581-611. doi: 10.1210/er.2003-0027
7. Funatsu H, Yamashita H, Sakata k, Noma H, Mimura T, Suzuki M, et al. Vitreous levels of vascular endothelial growth factor and intracellular adhesion molecule 1 are related to diabetic macular edema. Ophthalmology. 2005;112:806-816. doi:10.1016/j.opth.2004.11.045.
8. Early Treatment Diabetic Retinopathy Study Research Group. Treatment technique and clinical guidelines for photocoagulation of diabetic macular edema. Early Treatment Diabetic Retinopathy Study report No 2. Ophthalmology. 1987;94:761-774.
9. Heritoglou C, Kook D, Neubauer A, Wolf A, Priglinger S, Strauss R, et al. Intravitreal bevacizumab (Avastin) therapy for persistent diffuse diabetic macular edema. Retina. 2006;26:999-1005.
10. Gillies MC, Sutter FK, Simpsson JM, Simpson JM, Larsson J, Ali H, et al. Intravitreal triamcinolone for refractory diabetic macular edema: two-year results of a double-masked, placebo-controlled, randomized clinical trial. Ophthalmology. 2006;113:1533-1538. doi:101016/j.opth.2006.02.065.
11. Pendergast SD, Hussan TS, William GA, Cox MS, Margherio RR, Ferrone P, et al. Vitrectomy for diffuse diabetic macular edema associated with a taut premacular posterior hyaloid. Am J Ophthalmol. 2000;130:178-186.
12. Campochiaro PA, C99-PKC412-003 Study Group. Reduction of diabetic macular edema by oral administration of the Protein Kinase C inhibitor PKC 412. Invest Ophthalmol Vis Sci. 2004;45:922-931. doi:10.1167/iovs.03-0953
13. Thapa R, Poudyal G. Short term results of intravitreal bevacizumab for the treatment of macular edema secondary to retinal vein occlusion. Nepal J Ophthalmol. 2013;5:63-68. doi.org/10.3126/njop.v5i1.7823.
14. Robert L, Avery MD, Dante J, Reramici MD, Melvin D, Rabena BS, et al. Intravitreal bevacizumab (Avastin) for neovascular Age-Related Macular Degeneration. Ophthalmology. 2006;113:363-372. doi:101016/j.opth.2005.11.019.
15. Ozkiris A, Ekerlíc K. Complication of intravitreal injection of triamcinolone acetonide. Can J Ophthalmol. 2005;40:63-68. doi:10.1058/eye.2008.40.
16. Campochiaro PA, Brown DM, Pearson A, Chen S, Boyer D, Morono JR, et al. Sustained delivery fluocinolone Acetonide vitreous inserts provide benefit for at least 3 years in patients with Diabetic macular edema. Ophthalmology. 2012;119:2129-2132. doi:10.1016/j.opth.2012.04.030.
17. Avery RL, Pearlman J, Pieramici DJ. Intravitreal bevacizumab (Avastin) in the treatment of proliferative diabetic retinopathy. Ophthalmology. 2006;113:1695-1705.
18. Khan A, Amir AC, Zahid C. Intravitreal bevacizumab for treatment of diabetic macular edema. Pak J Ophthalmol. 2012;28:3-9.
19. Kumar A, SinhaS. Intravitreal bevacizumab (Avastin) treatment of diffuse diabetic macular edema in an Indian population. Indian J Ophthalmol. 2007;55:451-455.
20. Ozkiris A. Intravitreal bevacizumab (Avastin) for primary treatment of diabetic macular edema. Eye. 2009;23:616-620. doi:10.1038/eye.2008.40.
21. Arevalo JF, Fromow G, Quiroz MH, Sanchez JG, wu L, Maia M, et al. Pan-American Collaborative Retina Study Group. Primary intravitreal bevacizumab (Avastin) for diabetic macular edema: results from Pan-American Collaborative Retina Study group at 24 months. Ophthalmology. 2009;116:1488-1497. doi:10.1016/j.opth.2009.03.016.

Authors Contribution:
IT: Conceived and designed the protocol, did data collection and statistical analysis, manuscript writing and editing.
AR: was involved in clinical management of patients.
P.SM and SM: Critically reviewed the manuscript for final publication.