ORIGINAL ARTICLE

Visual Outcome After Intravitreal Bevacizumab (Avastin) in the Treatment of Diabetic Macular Oedema

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ABSTRACT:

Objective: To evaluate the visual outcome after intravitreal injection of bevacizumab (Avastin) in patients with diabetic macular edema.

Materials and Methods: A prospective study was conducted in PNS Shifa Hospital from 15 March 2010 to 15 Dec 2011 in patients with diabetic macular edema who were treated with at least one intravitreal injection of bevacizumab 1.25 mg in 0.05 ml. Patients underwent Snellen's visual acuity testing and detailed ophthalmic examination before the procedure and monthly follow-up visits for three months.

Results: There were 104 eyes of 71 consecutive patients with a mean age of 61.8 years (SD 16.1). The patients received a mean of 1.39 (SD1.35) injections of bevacizumab per eye. No adverse events were observed. The mean central macular thickness at baseline was 835 micron which improved to a mean of 360 micron at 3rd month ($P < 0.001$). The mean baseline acuity was log MAR = 0.52(SD 0.19) and at one month log MAR =0.22 (SD 0.20); the difference was significant ($P = 0.001$). At last follow-up of 3 months, the mean visual acuity was log MAR = 0.20 (SD 0.19), which was significantly better than baseline ($P < 0.001$). Visual acuity improved in 89 eyes.

Conclusion: Intravitreal bevacizumab resulted in a significant decrease in macular edema and improvement in visual acuity. The number of patients in this study was limited and the follow-up was too short to make any specific treatment recommendations, but the favorable short-term results suggest the need for further study.

Keywords: Avastin; Bevacizumab; Diabetic macular edema; Intravitreal injections; Vascular endothelial growth factor.

INTRODUCTION:

The commonest cause of visual impairment in diabetic patients is macular oedema. The pathogenesis of diabetic macular oedema (DME) is not yet clear. The important pathophysiology of DME is the loss of retinal capillary pericytes, resulting in increased vascular permeability.[1,2,3,4] The Early Treatment Diabetic Retinopathy Study (ETDRS) showed that the risk of moderate visual loss due to macular oedema was 32% at 3-years. Focal macular laser photocoagulation was effective in a large prospective multicenter randomized clinical trial of ETDR. [5] Efficient laser treatment could not be performed in many while some treated eyes were found to be resistant to photocoagulation due to diffuse macular oedema. Thus the failure of laser photocoagulation had warranted the need for other treatment modalities, such as intravitreal triamcinolone acetonide (IVTA) injection[6,7] or pars plana vitrectomy[8,9] .The primary cause of diabetic retinopathy is retinal hypoxia , which increases production of vascular endothelial growth factor (VEGF). VEGF is a potent inducer of vascular permeability that causes leakage from retinal vessels and contributes to DME [10]. Bevacizumab (Avastin), is a full length, humanized monoclonal antibody against VEGF, that inhibits all the active forms of VEGF, and approved by the Food and Drug Administration for the treatment of metastatic colorectal cancer.[11,12] It has shown beneficial effects in many ocular diseases.[13,14,15] There are only two studies showing the beneficial effect of intravitreal bevacizumab as a primary treatment for persistent DME.[16,17]

Present study was conducted to evaluate the visual outcome after intravitreal injection of bevacizumab (Avastin) in patients with diabetic macular edema (DME).

PATIENTS AND METHODS:

This is a prospective clinical trial in which diabetic patients coming for ophthalmic check up were seen in Eye OPD of PNS Shifa from 15 March 2010 to 15 December 2012. Consecutive patients with DME were included and treated based on a standardized protocol over a period of 21 months with monthly follow-up visits. Detailed routine eye examination was carried out. Best corrected visual acuity was noted. Optical coherence tomography imaging (SD-OCT, Spectralis, Heidelberg Engineering) and Digital fundus fluorescein angiography (FFA, Canon) were done before the procedure and at monthly intervals during the follow-up period for three months. All findings were documented on a specially designed performa. Patient with DME, having clear media, not having prior laser photocoagulation and willing for intravitreal bevacizumab therapy were included for the study. Patients having glaucoma, uveitis, vitreous hemorrhage, proliferative vitreo-retinopathy, retinal detachment uncontrolled systemic hypertension, severe renal dysfunction, nephrotic syndrome, and dysproteinemias or receiving vasoactive drugs were excluded.

A total of 104 eyes of 71 patients were included in this study that underwent intravitreal bevacizumab injection as the primary treatment for DME. All patients had macular oedema with hyperfluorescent leakage on fundus fluorescein angiography. Before intravitreal bevacizumab injection, no eye had received any laser treatment for

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Received: 28-8-2014
Revised: 29-12-2014
Accepted: 12-1-2015

DME. All patients were fully informed about the treatment and informed consent was obtained from each patient. The study followed the tenets of Declaration of Helsinki. Baseline parameters were documented including best-corrected visual acuity (BCVA), intraocular pressure, FFA findings and OCT. BCVA for each eye was checked using Snellen chart at 6 meters. The average VA was computed by converting the value to the LogMAR equivalent, and taking the average of the LogMAR values as described by Holladay. [18] Statistical calculations were performed using LogMAR values for VA. All patients received minimum of one intravitreal bevacizumab (Avastin® Genentech) injection at a dose of 1.25 mg (0.05 ml) and later if required at monthly intervals. All intravitreal injections were performed under local/ topical anaesthesia with all aseptic precautions in the operating room. The lid was prepared with povidone-iodine 5% and also applied directly to the eye. Bevacizumab was filled and packed under sterile conditions by the Aga Khan University Hospital institutional pharmacy, Karachi, using insulin syringes. It was injected into the anterior vitreous, 3.5 mm posterior to the limbus in pseudophakic eyes and 4.0 mm posterior to the limbus in phakic eyes. A cotton-tipped applicator was applied at the injection site immediately after the removal of the needle to prevent reflux. Topical moxifloxacin drops(Megamox,Sante) were applied four times daily for 1 week.

The eyes were examined after 1 week and every 4 weeks. Response to the treatment was monitored by VA assessment, FFA, and OCT. Potential drug or injection-related complications were recorded, if present. Patients received re-injections when there was a recurrence. Recurrence was defined when there was a decrease in BCVA associated with an increase of intraretinal fluid due to macular oedema as observed on FFA and/or OCT. The t test was used for statistical analysis of changes in visual acuity and central retinal thickness (CRT). A P-value of less than 0.05 was considered to be statistically significant.

RESULTS:

There were 48 males and 23 females.The mean age of the patients was 61.87±16.15 years (range, 24-90 years). Patients having clinically significant macular oedema were enrolled and completed 12 weeks of follow-up. 5 (7.04%) cases received a second intravitreal injection of bevacizumab, and 6 (8.4%) needed more than three injections. The mean VAs, and IOPs of the patients before and after intravitreal bevacizumab injection are presented in Table 1. Baseline mean visual acuity was 0.52 LogMAR (20/63), ranging from 1.0 LogMAR (20/200) to 0.10LogMAR (20/26) and baseline mean 1-mm CRT was 545 (range 835-360) µm, as measured by OCT. There was statistically significant difference in VA after bevacizumab injection when compared with pretreatment values (P<0.001). After a mean follow-up period of 3 months, VA improved in 89 of 104 eyes (85.6%) with a mean of 2.4±1.6, and 2.8±2.0 Snellen lines at 1 and 3-months, respectively. VA remained unchanged in 15(14.4%) eyes, and decreased in 4 (3.8%) eyes and showed increased fluorescein leakage on FFA (Table 1).

Table: 1

Mean Log MAR Value for the Visual Acuities and IOPs of Patients Before and After Intravitreal Bevacizumab Injection

	Log MAR value	IOPs (mmHg)
Pre Inj	0.52±0.19	15.0±2.1
1 month	0.22±0.20	15.8±2.2
3 months	0.20±0.21	15.1±2.4

IOP=intraocular pressure; Pre Inj=pre-injection.

93(89.4%) eyes showed a reduction in macular oedema on OCT after intravitreal bevacizumab injection. Oedema decreased from a baseline highest mean value of 835 micron to a lowest mean value of 360 at the last examination. Mean reduction of macular oedema at 1 and 3-month were statistically significant when compared with preinjection values (P<0.001). Average IOP values at 1, 2 and 3-month, were not statistically significant when compared with pre injection values.

Safety

After 06 months of follow-up, no severe ocular or systemic adverse events like endophthalmitis, retinal detachment, traumatic cataract, uveitis, thromboembolic event, systemic hypertension or kidney failure were reported. No progression of avascular areas was observed in fluorescein angiography. No patient developed neovascularisation of the optic disc, of the iris or elsewhere in the retina. Mild anterior chamber cellular reaction was observed in 12 eyes (11.53%), but the inflammation resolved within a week with topical corticosteroid. No other injection- or drug-related complications were observed.

DISCUSSION:

DME may persist in some eyes despite laser treatment or intravitreal injection of triamcinolone acetonide (IVTA injection), but is not without risks.[19,20] and complications can be due to the injection procedure or due to the steroid suspension. The efficacy of IVTA appears to be transient and repeated injections may be required. In diabetic patients, blood-retina barrier is broken with the production

of VEGF causing increased vascular permeability resulting in retinal oedema. Thus Anti-VEGF therapy may be a promising treatment option for DME.

Intravitreal injection of pegaptanib was reported by Cunningham[21, 22, 23] to have better VA outcomes with reduction in central retinal thickness and less additional therapy with laser photocoagulation.

Intravitreal bevacizumab safety has been confirmed by previous studies, has been shown to be effective in the treatment of oedema due to various etiologies.[24,25,26,27,28]

Results of our study have shown that intravitreal bevacizumab appears to be effective in the primary treatment of DME. In our study, 85.5% eyes showed an improvement in VA with a decrease in fluorescein leakage on FFA. The results of our study confirm previous reports showing the beneficial effect of intravitreal bevacizumab in the treatment of DME. An increase in VA of at least three lines was observed in 81 of 104 eyes at a 6-week follow-up, and in 89 of 104 eyes completing 12 weeks of follow-up. Mean reduction in central macular thickness was 17.2% at 6 weeks, 25.65% at 12 weeks after the injection. In this study, VA increased with a mean of 2.4, 2.7, and 2.8 Snellen lines at 1 and 3-month, respectively. Similar results were seen by study conducted by Haritoglou [16]

This high success in our study may be explained by performing intravitreal bevacizumab injection as the primary treatment of DME or a short duration of DME in our patients. Consistent with a decrease in CRT as seen by OCT, fluorescein angiography revealed a reduction in the area of leakage. No patient showed evidence of severe drug-related systemic or ocular adverse events during multiple treatments for as long as 6 months. Even if the study was too small to provide solid data on safety, several comparable studies showed similar results. [13,14,15,16,17]Although nearly all patients showed an immediate response to intravitreal bevacizumab treatment with a reduction in retinal thickness and an increase in visual acuity, macular oedema had not resolved completely in 10 patients even after four injections.

CONCLUSION:

The use of intravitreal bevacizumab has shown to reduce the extravasation from blood vessels, and inhibition of neovascularization. It have beneficial effect in the treatment of macular oedema. Large randomised controlled clinical trials are needed to evaluate the long-term efficacy of intravitreal bevacizumab as a primary treatment in patients with diabetic macular oedema.

REFERENCES:

1. Antcliff RJ, Marshall J. The pathogenesis of edema in diabetic maculopathy. Semin Ophthalmol 1999; 14: 223-32.
2. Ciulla TA, Amador AG, Zinman B. Diabetic retinopathy and diabetic macular edema: pathophysiology, screening, and novel therapies. Diabetes Care 2003; 26: 2653-64.
3. Pelzek C, Lim JI. Diabetic macular edema: review and update. Ophthalmol Clin North Am 2002; 15: 555-63.
4. Ozkiris A, Evereklioglu C, Oner A, Erkilic K. Pattern electro retinogram for monitoring the efficacy of intravitreal triamcinolone injection in diabetic macular edema. Doc Ophthalmol 2004; 109: 139-45.
5. Early Treatment Diabetic Retinopathy Study Research Group. Treatment techniques and clinical guidelines for photocoagulation of diabetic macular edema. Early Treatment Diabetic Retinopathy Study Report Number 2. Ophthalmology 1987; 94: 761-74.
6. Jonas JB, Kamppeter BA, Harder B, Vossmerbaeumer U, Sauder G, Spandau UH. Intravitreal triamcinolone acetonide for diabetic macular edema: a prospective, randomized study. J Ocul Pharmacol Ther 2006; 22: 200-7.
7. Martidis A, Duker JS, Greenberg PB, Rogers AH, Puliafito CA, Reichel E et al. Intravitreal triamcinolone for refractory diabetic macular edema. Ophthalmology 2002; 109: 920-7.
8. Otani T, Kishi S. A controlled study of vitrectomy for diabetic macular edema. Am J Ophthalmol 2002; 134: 214-29.
9. Yamamoto T, Akabane N, Takeuchi S. Vitrectomy for diabetic macular edema: the role of posterior vitreous detachment and epimacular membrane. Am J Ophthalmol 2001; 132: 369-77.
10. Nguyen QD, Tatlipinar S, Shah SM, Haller JA, Quinlan E, Sung J et al. Vascular endothelial growth factor is a critical stimulus for diabetic macular edema. Am J Ophthalmol 2006; 142: 961-9.
11. Presta LG, Chen H, O'Connor SJ, Chisholm V, Meng YG, Krummen L et al. Humanization of an anti-vascular endothelial growth factor monoclonal antibody for the therapy of solid tumors and other disorders. Cancer Res 1997; 57: 4593-9.
12. Chen Y, Wiesmann C, Fuh G, Li B, Christinger HW, McKay P et al. Selection and analysis of an optimized anti-VEGF antibody: crystal structure of an affinity-matured Fab in complex with antigen. J Mol Biol 1999; 293: 865-81.
13. Iliev ME, Domig D, Wolf-Schnurrbursch U, Wolf S, Sarra GM. Intravitreal bevacizumab (Avastin) in the treatment of neovascular glaucoma. Am J Ophthalmol 2006;142: 1054-6.
14. Oshima Y, Sakaguchi H, Gomi F, Tano Y. Regression of iris neovascularization after intravitreal injection of bevacizumab in patients with proliferative diabetic retinopathy. Am J Ophthalmol 2006; 142: 155-8.

15. Yoganathan P, Deramo VA, Lai JC, Tibrewala RK, Fastenberg DM. Visual improvement following intravitreal bevacizumab (Avastin) in exudative age-related macular degeneration. Retina 2006; 26: 994-8.
16. Haritoglou 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.
17. A.Ozkirs. Intravitreal Bevacizumab for Primary Treatment of Diabetic Macular Oedema. Eye 2009; 23(3):616-20.
18. Holladay JT. Proper method for calculating average visual acuity. J Refr Surg 1997; 13: 388-91.
19. Ozkiris A, Erkilic K. Complications of intravitreal injection of triamcinolone acetonide. Can J Ophthalmol 2005; 40: 63-8.
20. Jonas JB, Kreissig I, Degenring RF. Retinal complications of intravitreal injections of triamcinolone acetonide. Graefes Arch Clin Exp Ophthalmol 2004; 242: 184-5.
21. Cunningham Jr ET, Adamis AP, Altaweel M, Aiello LP, Bressler NM, D'Amico DJ et al. Macugen Diabetic Retinopathy Study Group. A phase II randomized double-masked trial of pegaptanib, an anti-vascular endothelial growth factor aptamer, for diabetic macular edema. Ophthalmology 2005; 112: 1747-57.
22. Costa RA, Jorge R, Calucci D, Melo Jr LA, Cardillo JA, Scott IU. Intravitreal bevacizumab (avastin) for central and hemicentral retinal vein occlusions: IBeVO study. Retina 2007; 27: 141-9.
23. Friedlander SM, Welch RM. Vanishing disc neovascularization following intravitreal bevacizumab (avastin) injection. Arch Ophthalmol 2006; 124: 365.
24. Feiner L, Barr EE, Shui YB, Holekamp NM, Brantley Jr MA. Safety of intravitreal injection of bevacizumab in rabbit eyes. Retina 2006; 26: 882-8.
25. Ziemssen F, Grisanti S, Bartz-Schmidt KU. The international intravitreal bevacizumab safety survey. Br J Ophthalmol 2006; 90: 1440-1.
26. Augustin AJ, Puls S, Offermann I. Triple therapy for choroidal neovascularization due to age-related macular degeneration: verteporfin PDT, bevacizumab, and dexamethasone. Retina 2007; 27: 133-40.
27. Ziemssen F, Deuter CM, Stuebiger N, Zierhut M. Weak transient response of chronic uveitic macular edema to intravitreal bevacizumab (Avastin). Graefes Arch Clin Exp Ophthalmol 2007; 245(6): 917-8.
28. Mason III JO, Albert Jr MA, Vail R. Intravitreal bevacizumab (Avastin) for refractory pseudophakic cystoid macular edema. Retina 2006; 26: 356-7.