Original article

Anatomical and visual outcome of intravitreal bevacizumab (Avastin) in patients with diabetic macular edema

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Abstract

Background: Intravitreal bevacizumab has been shown to be an effective treatment of diabetic macular edema. **Objective:** To assess the anatomical and visual outcome of intravitrealbevacizumab (Avastin) in patients of diabetic macular edema. **Materials and methods:** 52 eyes of 33 patients with diabetic retinopathy with CSME were included in this study. Detailed ophthalmic examination, including best-corrected visual acuity(BCVA), stereoscopic biomicroscopy, and retinal thickness measurement by Optical coherence tomography (OCT), was done at baseline and at each follow-up visit. All patients were treated with 0.05 mL intravitreal injection containing 1.25 mg of bevacizumab and repeat injection was given in cases of recurrent/persistent subretinal or intraretinal fluid shown by OCT and deterioration of BCVA. **Results:** All patients completed 6 months of follow-up with mean number of 2.78 intravitreal injections per eye.The mean BCVA at baseline was 0.80 log MAR, with significant changes 0.68 (p=0.012), 0.63 (p=<0.001) and 0.60 log MAR (p=<0.001) at 6 weeks, 3 months, and 6 months respectively.Final BCVA analysis demonstrated that 25 eyes (48.07%) remained stable and 22 (42.30%) improved ≥2 lines on BCVA. The mean central retinal thickness was 449.03 μm at baseline and it decreased significantly to 410.09 (p<0.001),345.76(p<0.001), 344.55(p<0.001) and 326.51(p<0.001) at 1st day , 6 weeks, 3 months and 6 months post injection, respectively. Mean macular volume changed significantly from baseline of 10.77 μm to 10.33μm (p<0.001) 8.97 (p<0.001), 8.82 (p<0.001), 8.95 (p<0.001) at 1st day , 6 weeks, 3 months and 6 months post injection respectively. **Conclusion:** Intravitreal bevacizumab injection resulted in significant improvement in BCVA, central retinal thickness and total macular volume in patients with diabetic retinopathy with CSME, and this beneficial effect is maximum at 6 weeks. Also, slight reduction in these parameters at 3 month follow up suggests that visual improvement and stable macular thickness can be maintained longer with injection frequency of probably 6-12 weeks.

Keywords: Diabetic macular edema, Intravitreal bevacizumab, anatomical outcome, visual outcome

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Introduction

Diabetic macular oedema (DME) is a common sight threatening complication affecting working age population both in the developed and in the developing world. Overall prevalence

of diabetic retinopathy (DR) is about 35% and of that 7% has PDR, 7% has DME, and 10% are affected by this vision-threatening diabetic retinopathy (Joanne et al. 2012). In Nepal, hospital based study showed about one fifth of population with diabetic retinopathy had CSME (Paudyal et al, 2008). If diabetic retinopathy is untreated there is 25-30% risk of developing CSME with moderate visual loss and with treatment risk drops by 50% (ETDRS, 1987).

Exact etiopathaogenesis of DME is not known, although breakdown of inner blood retinal barrier is the most reasonable explanation. Retinal hypoxia is the primary cause of DR, which increases expression of vascular endothelial growth factor (VEGF). VEGF is a potent inducer of vascular permeability that has been known to cause leakage from retinal vessels and contribute to DME (Antcliff et al, 1999; Pelzek, 2002; Nguyen et al, 2006).

VEGF occurs naturally in the body. VEGF promotes blood vessel growth and makes retinal vessels leaky. Bevacizumab (Avastin, Genentech Inc., South San Francisco, CA, USA), a full length, humanized monoclonal antibody against VEGF, also binds and inhibits all the biologically active forms of VEGF, and was initially used systemically tostop new blood vesselsin patients with cancer (Presta et al, 1977). Blocking VEGF with Avastin can reduce vascular leakage and lessen macular edema. Reducing macular edema can stabilize and improve vision. Ranibizumab (2012) and Aflibercept (2014) are FDA approved intravitreal drugs for the treatment of DME. But Bevacizumab is being in use worldwide as off level and has also been proved to be useful in the treatment of DME (Stefanini et al, 2014, Seo JW et al, 2009). It was first used for treatment of Neovascular AMD (Philip J Rosenfeld, 2011)

So far, there has not been any documented case series on the outcome of the use of bevacizumab (Avastin) in patients with DME in Nepal. The present study was conducted to evaluate the outcome of the use of Avastin in the Nepalese patients with DME at our hospital setting.

Materials and methods

In this interventional case series, consecutive patients attending retina clinic of Tilganga Institute of ophthalmology between January 2010 to October 2011, with a clinical diagnosis of DME, were included. A written informed consent was obtained from all the participants, and they were informed about the off- label use of the drug and its potential risks and benefits, as well as the likelihood that additional treatments might be required. Patients with (i) macular edema secondary to causes other than DR (ii) DME previously treated with intravitreal triamcinolone and/or other anti VEGF (iii) laser treatment done within previous 3 months (iv) corneal diseases, inflammatory eye diseases, optic neuropathy and age related macular degeneration (v) any ocular surgery within previous 6 months (vi) uncontrolled hypertension with thromboembolic events; were excluded.

Each patient underwent a detailed eye examination, including BCVA with ETDRS chart,slit lamp examination,intraocular pressure (IOP) by Goldmann applanation tonometry and fundus evaluation under mydriatic (FEUM) by indirect ophthalmoscopy using 90 Dioptre and 20 Diopter lenses. Macular OCT (stratus Zeiss Humphrey 2004) was used to assess central macular thickness (CMT) and Total macular volume (TMV) of the study eye and was recorded on the first visit and on subsequent follow up visits. CMT was defined as the mean retinal thickness in the circular zone of diameter 1 mm centered on the fovea.The sum of the volume of the neural retina in the central 6 mm was defined as *TMV.*Fundus fluorescein angiography (FFA) was done when indicated.

Patients were seen on day one, 6 weeks, 3 months and 6 months post injection and

earlier as needed. During each visit, patients were re-evaluated. Repeat injection was given to recurrent/ persistent cases (Compared with preinjection status) or until macular edema subsided. Intravitreal Bevacizumab was supplemented with grid/focallaser once macular edema improved and some patients were also given pan retinal photocoagulation (PRP) for developing proliferative DR during the study period.

To compare the visual outcomes of eyes, we defined, at least increments of BCVA by two lines in the ETDRS chart as "improved," or decrement of 2 lines as "decreased" and other cases as "unchanged."(Seo JW et al, 2009)

The procedure was performed in the operation theatre. Topical anesthesia (4% lignocaine) was applied after cleaning the ocular surface with povidone iodine (5%) and using a sterile drape. Patients then received a unilateral intravitreal injection of 0.05 ml volume containing 1.25 mg of Avastin using a sharp 27 gauge or 30 gauge needles at a distance of 3.5 mm posterior to limbus in psedoaphakic eyes and 4.0 mm posterior to limbus in phakic eyes. The needle was carefully removed using sterile cotton applicator to prevent reflux. After injection, antibiotics eye drop (ciprofloxacin) was applied four times a day for 1 week.

The collected data was entered in to the Microsoft excel 2007 spreadsheet. The changes in the average value of the continuous outcome variables from baseline to different follow ups has been evaluated through the Wilcoxon signed rank test. The continuous outcome variables were compared across two independent groups by using Mann Whitney test and across three independent groups by Kruskal - Wallis test. The correlation between number of injections and final outcome variables such as BCVA, TMV and CMT was assessed by using Spearman's correlation coefficient. All the statistical analysis was carried out by using the statistical software STATA 9.0 (Stata Corp, College Station, Tex). $P<0.05$ was defined as statistically significant.

Ethical clearance was obtained from the institutional review board (IRB) of Tilganga Institute of Ophthalmology.

Results

A total of 52 eyes of 33 individuals (34 males and 18 females) were studied. The mean age of patients was 58.59 (40 -76)years. All the patients completed follow up and were of type II diabetes mellitus and mean duration of diabetes was 11.88 (4 – 25) years. Inonly 19% of the participants, diabetes was under control at the time of presentation. Majority of patients were in severe non proliferative diabetic retinopathy(NPDR) group (76.92. %) followed by moderate proliferative diabetic retinopathy(PDR) group (15.38%) and early PDR(7.69%). Out of total, 19% of patients received laser at least 3 months priorto the first injection of Bevacizumab, 81% did not receive any kind of laser therapy for CSME. Cataract was found in majority of eyes 44(77%), 7(13%) were psedoaphakic and 5(10%) were having phakic clear lens.

The mean BCVA improved from 0.80 to 0.60 at 6 months. The mean BCVA 0.80±0.46, which did not change significantly on the first day 0.77±0.40 (p=0.39), but significant changes were seen on 6 weeks 0.68± 0.46(p=0.012), 3 months 0.63± 0.45(p=<0.001) and at 6 months 0.60± 0.42 logMAR (p=<0.001). Marked improvement was observed after 6 weeks (Figure 1).

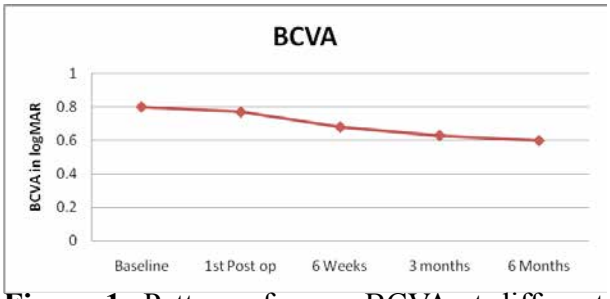

Figure 1: Pattern of mean BCVA at different follow up period

Final BCVA analysis by subgroup demonstrated that vision remained stable in majority on first day post injection. Vision improved in 22 eyes(42.30%), remained stable in 25 (48.07%) and deteriorated in 5(9.61%) at final follow up of 6 months (Table 1).

Table 1: Best corrected visual acuity (BCVA) analysis from baseline values.

	First POD No. of eyes %	6th week No. of eyes %	Third month No. of eyes %	Sixth month No .of eyes %
Decreased ≥2lines of BCVA	3 (5.7%)	8 (15.3%)	6 (11.53%)	5 (9.61%)
Remained Stable	44 (84.6%)	26 (50%)	24 (46.15%)	25 (48.07%)
Improved ≥2lines of BCVA	5 (9.6%)	18 (34.6%)	22 (42.30%)	22 (42.30%)

The mean CMT was 449.03±177.92 µm at baseline and it decreased significantly to 410.09±160.37 ($p<0.001$), 345.76±117.77 ($p<0.001$), 344.55±160.45 ($p<0.001$) and 326.51± 175.06 µm ($p<0.001$) at 1st day, 1 month, 3 months and 6 months respectively. CMT significantly improved from day 1 and this improvement continued throughout the 6 months. Marked improvement was seen from day 1 to 6 weeks (Figure 2)

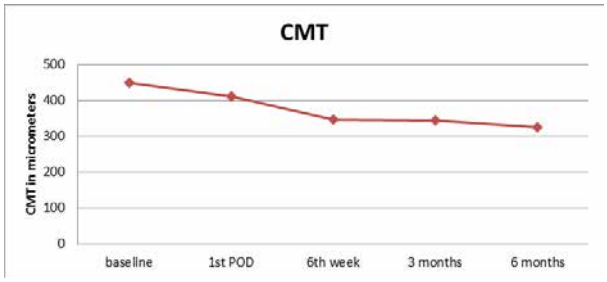

Figure 2: Pattern of CMT in follow up

Mean macular volume changed significantly from baseline value of 10.77± 3.55 µm ± to 10.33± 3.48µm ($p<0.001$) 8.97±2.04µm. ($p<0.001$), 8.82±1.88µm ($p<0.001$), 8.95±3.26µm ($p<0.001$) at 1st day, 1 month, 3 months and 6 months respectively. There was significant change/improvement in macular volume from baseline to first post operative day and this improvement continued throughout the 6 months (Figure 3).

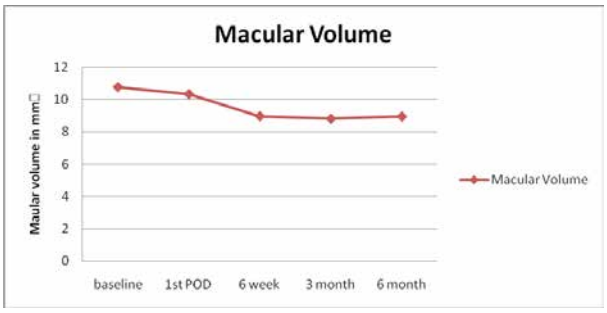

Figure 3: Pattern of Macular volume in different follow up time

Best corrected visual acuity, CMT and macular volume were found to be improved significantly when baseline values were compared with six months follow up, in patients who received LASER therapy at least 3 months prior to the injection than in the group which had not received laser (Table 2, 3). Mean baseline values of BCVA, CMT and macular volume were higher in comparison to those who received laser therapy in past.Only seven eyes did not receive any kind of laser therapy during entire period of the study. CMT was significantly different in laser and non laser group when observed at final follow up. Mean CMT was higher in laser group than non laser group.

Table 2: Changes in BCVA, CMT and TMV among subjects who received LASER therapy 3 months prior to 1st Bevacizumab injection

Characteristics		Baseline	6months	p* value
logMAR BCVA	n Mean±SD Median Range	10 0.71 ± 0.27 .69 0.3− 1.00	10 0.37 ± 0.26 .3 0 − 0.78	0.005
CMT (µm)	 Mean±SD Median Range	10 416.70 ± 110.13 389.5 304 − 624	10 345.60 ± 95.74 370.5 202 − 452	0.028
TMV (in mm^3)	n Mean±SD Median Range	10 9.12 ± .952 9.07 7.61–10.59	10 8.40 ± .887 8.44 7.17–9.72	0.021
*Wilcoxon signed-rank test n, number; SD, Standard deviation log MAR BCVA, logarithm of minimal angle of resolution best corrected visual acuity. CMT, central macular thickness; TMV, total macular volume				

Table 3: Changes in BCVA, CMT and TMV among subjects without prior intervention (therapy in past)

Characteristics		Baseline	6months	p* value
logMAR BCVA	n Mean±SD Median Range	42 0.83 ±0 .49 0.6 0.18− 1.78	42 0.66 ± 0.43 0.6 0 − 1.78	0.005
CMT (µm)	 Mean±SD Median Range	42 456.881 ± 190.76 425 154 − 941	39 321.61 ± 190.84 235 119 − 964	<0.001
TMV (in mm^3)	n Mean±SD Median Range	42 11.17 ± 3.82 10.14 6.94–24.41	39 9.09 ± 3.62 8.1 5.26 - 26.41	<0.001
*Wilcoxon signed-rank test n, number; SD, Standard deviation log MAR BCVA, logarithm of minimal angle of resolution best corrected visual acuity. CMT, central macular thickness; TMV, total macular volume; IOP, Intra ocular pressure				

Out of 52 eyes, one eye progressed to advanced proliferative retinopathy and one developed vitreous hemorrhage during follow up.

Mean number of intravitreal injection was 2.78 ±0.99 (range 1 – 5).Number of injection given was found to bepositively correlated with BCVA (p=0.041*)*. There was no significant association of macular volume (p=0.61) and CMT (p=0.11) with number of injections.

No severe injection related complications, such as phakic lens injury, endophthalmitis or uveitis, glaucoma, retinal detachment and RPE tear were encountered during follow up. Only Subconjunctival hemorrhages were noted in 3 eyes. There were no cases of elevated blood pressure or cardiovascular related accidents during the entire follow-up.

Discussion

Diabetic macular edema is a manifestation of diabetic retinopathy that produces loss of central vision. Although several treatment methods are under investigation,the use of

Visual improvement at 6 months in this study (0.20 logMAR) was similar to the studies of Arevalo et al, 2009 and Soheilian et al, 2011 (0.27 & 0.24logMAR, respectively) Lam et al, 2009 had observed an improvement of 0.11 logMAR at 6 months. The differences might be related to better mean baseline BCVA in Lam et al study, 2009, with 0.61 compared with 0.80, 0.87 and 0.78 in the present study and studies by Arevalo et al, 2009 and Soheilian et al, 2011, respectively. Therefore, patients in Lam et al, 2009 had more potential for visual gain after treatment. Also, in this study mean baseline CMT was 449.03 ± 177.92, and it was observed that better response to intravitreal bevacizumab persisted in eyes with initial CMT > 350. Subgroup analysis showed that intravitreal bevacizumab seemed to be more effective in eyes which were treatment naïve as significant anatomical and visual improvements were only observed in eyes which had no previous DME treatment. In present study also, only 19% of eyes received grid /focal laser photocoagulation at least 3 month prior to first injection and almost 81% of study eyes were treatment naïve so there was significant visual and anatomic outcome. Best corrected visual acuity; CMT and macular volume were found to be change significantly when baseline values were compared with 6 months, irrespective of whether patient had received grid/focal laser photocoagulation or not. Mean baseline values of BCVA, CMT and macular volume were higher in group who did not receive any kind of treatment for DME in comparison to those who had received grid/focal laser therapy.

All eyes received an IVB at the initial visit; however, recurrences were retreated at the discretion of the treating physician. Further injections were given in cases of recurrent subretinal or intraretinal fluid shown by OCT and visual deterioration. Although we cannot establish the optimal administration time or dosage from this study, we could estimate that VA increases with decreased macular edema at 6 weeks post injection with blunted effect at 8-12 weeks post injection necessitating another injection at this time or later. The Indications and intervals for retreatment remains controversial. It remains unclear whether it is necessary to follow a strict treatment regimen as performed in the VISION and the MARINA trial that evaluated the effect of pegaptanib or ranibizumab, where injections were performed every 6 weeks for at least 2 years orevery 4 weeks for 6 months, respectively. Roh et al,2008, considered CMT > 250 mmor deterioration of VA of at least 5 ETDRS letters score as compared with the previous value as the criteria for reinjection, with an interval of at least 12 weeks. Kook et al, 2008,performed a reinjection when the CMT changed by > 100 mm with an associated VA deterioration of > 5 ETDRS letters (Haritoglou et al, 2006).The criteria and interval for retreatment remains a matter of ongoing debate.

Most patient (48%) visual acuity remained stable inspite of significant reduction of CMT and macular volume, this is because 40 eyes (77%) in our study were having some type of cataract and around 13% were psedoaphakic.

Almost 82 % of eyes were given some kind of laser treatment, focal/grid/PRP during study period. Eyes with laser therapy had increased CMT when compared to eyes without laser treatment and this was statistically significant. But mean BCVA and macular volume did not differ significantly at final follow up between the two groups. This finding is supported by Diabetic retinopathy clinical research study, that combining photocoagulation with bevacizumab resulted inno apparent short-term benefit or adverse outcomes. The combination treatment did not yield better VA or macular thickness reduction at 6 months than bevacizumab injection alone

(Lee et al, 2011). But, focal or grid photocoagulation may be used to consolidate the results obtained with IVB injection and

may decrease the need of reinjection as recommended by Arevalo et al, 2009

Limitation of the present study is a shorter follow-up, which did not allow for an estimation of long-term efficacy and safety of this treatment. However, the results presented herein are promising, even though we have treated few patients with advanced stages of the disease, which underline the need for further investigations. Other limitations are the lack of a control group and the broad inclusion criteria, which were attributed to the off-label character of the treatment.

Conclusion

Intravitreal bevacizumab resulted in significant decrease in macular thickness, macular volume and improvement in visual acuity starting from first day post injection to maximum at 6 weeks. Though statistically significant the effect was somewhat blunted at 3 and 6 months with mean of 2.7 injection per eye. This slight reduction in improvement in visual acuity, CMT and macular volume at 3 months follow up suggests visual improvement and stable macular thickness can be maintained in the longer term with injection frequency of probably 6-12 weeks. Intravitreal bevacizumab showed equal efficacy both in eyes with or without previous DME treatment. Also, combining grid/focal photocoagulation resulted in no apparent short term benefit or adverse outcomes. Further prospective and randomized studies is needed to better determine which patients benefit the most and how often and which concentration the drug should be administered.

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