Original Article

Evaluation of the Effect of Intravitreal Bevacizumab (Avastin) in Patients with Diabetic Macular Edema

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Abstract

Introduction: Diabetic macular edema (DME) is the leading cause of visual impairment in patients with diabetes mellitus. The objectives of the study was to figure out the effect of intravitreal injection bevacizumab on visual acuity and retinal thickness in people with DME.

Materials and methods: We observed the case records of patients with DME requiring injection Avastin (Genentech Inc., San Francisco, CA, USA) intravitreal from January to July 2016 in Mechi Eye Hospital. The eighty seven eyes of 60 patients with DME were included in the study. Inclusion criteria were determined independently of the age, metabolic control, type of diabetes mellitus, visual acuity, leakage area size, retinal thickness as measured by optical coherence tomography. All the patients were treated with 0.05 ml injection containing 1.25 mg of Avastin (Genentech Inc., San Francisco, CA, USA) after written informed consent.

Results: The mean age group was 55.86 ± 9.61 years with 47 males and 13 females. At baseline the median BCVA was 1.00 (0.60-1.30) which improved to 0.78 (0.48- 1.00) at 6 weeks (p=0.001) which further improved to 0.78 (0.48-1.00) Log MAR (p value-0.005) at 12 weeks and 0.60 (0.43- 1.00) Log MAR at 18 weeks (p value= 0.006). Baseline mean central macular thickness (CMT) on OCT was 436.24 ± 142.2µm which decreased to 387.74±130.98µm at 6 weeks, 346.82 ±116.79 µm at 12 weeks and 307.1 ±105.49µm. Changes in VA and decrease in central subfield macular thickness during follow up visit was statistically significant (p<0.05).

Conclusion: In this study, intravitreal injection Avastin resulted in improvement in VA and decrease in retinal thickness in patients with DME.

Key words: Avastin, Diabetic macular edema, Central macular thickness, Visual acuity.

Introduction

Diabetic macular edema (DME) is the leading cause of decreased vision in diabetic patients. Raman R et al. noted the incidence of DME to be 2.6% among urban Indian population. In Nepal, about one fifth of the population with diabetic retinopathy had CSME in a hospital based study (Paudyal G et al., 2008).

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The multiple factors come into play in the pathogenesis of DME (Gundogan FC et al, 2016). The common pathway resulting in DME is disruption of blood retinal barrier (BRB) and increased vascular permeability which leads to accumulation of fluid within the intra-retinal layer of macula (Antcliff RJ et al, 1999). VEGF is a major factor involved in the disruption of BRB and induction of angiogenesis (Funatsu H et al, 2005). Chronic hypoxia and hyperglycemia leads to increased expression of VEGF. Vitreous fluid concentration of VEGF in patients with DME is known to be significantly increased compared to nondiabetic (Funatsu H et al., 2006). VEGF increases vascular permeability by causing phosphorylation of tight junction proteins (Antonetti DA et al, 1999) and increases angiogenesis by directly acting as a potent endothelial cell mitogen and indirectly by inhibiting activity of metalloprotease inhibitor (Pedro Romero-Aroca et al,2016). VEGF also increases expression of intercellular adhesion molecule-1 which increases retinal leukocytosis causing breakdown of BRB (Ishida S et al, 2003). Therefore the pharmacological agent that inhibits VEGF appears to be promising treatment for DME.

Focal photocoagulation used to be the gold standard in the treatment of DME. However 12% of laser treated eyes still lost 15 or more ETDRS letters at the 3 year follow-up interval. Approximately 40% of laser treated eyes had retinal thickening involving the fovea at 12 months follow up (ETDRS research group, 1985). Similarly Diabetic Retinopathy Clinical Research Network showed that approximately 20% of laser-treated eyes had VA worsen by ≥ 2 lines (DRCR.net, 2008). This suggests a distinct subgroup of DME patients exists, poorly responding to conventional laser therapy. With the introduction of anti VEGF, there is a paradigm shift in treatment of DME.

Recently many studies have shown better outcomes with anti VEGF therapy in patients with DME. Avastin is a recombinant, full length humanized antibody that binds VEGF isoform (Ishida S et al, 2003). It has been reported to be suitable and safe for intravitreal injection in various studies (Rajendram R et al, 2012; Wells JA et al, 2016). Avastin is used off level basis for DME because of cost benefit and efficacy comparable to other anti VEGF agents (Wells JA et aL 2016; Mukkamala L et al, 2017).

There have been only a few studies published (Vyas S et al, 2016) showing the effect of Avastin in Nepalese population with DME. No study has been done in eastern part of Nepal. This study was done to figure out the effect of intravitreal injection Avastin on retinal thickness and visual acuity in people of Eastern part of Nepal with DME.

Materials and methods

We retrospectively reviewed the case records of patients with DME attending the outpatient department of Mechi eye hospital requiring injection Avastin (Genentech Inc., San Francisco, CA, USA) intravitreal from January to July 2016. Patients with DME were included in this study irrespective of size of the leakage area, retinal thickness (as determined by spectral domain optical coherence tomography), visual acuity, age, metabolic control, type of diabetes mellitus. The patients with center involving DME with CMT >250 μm on OCT and VA ≤ 6/9 were considered for injection Avastin. The center involving DME is defined as retinal thickening or hard exudate involving center of the fovea (Raman R et al., 2015, Wilkinson C P et al, 2003).

The exclusion criteria of this study were patients with ocular disease like age related macular degeneration, retinal vascular occlusion, vasculitis apart from diabetic retinopathy, history of vitreoretinal surgery, cataract surgery

or intravitreal injection triamcinolone within 6 months or laser photocoagulation within 3 month before study.

At each follow up, patient underwent complete eye examination including measurement of visual acuity with Snellen testing chart, slit-lamp examination, intraocular pressure measurement, fundus examination with indirect ophthalmoscopy (90 D and 78D) and retinal thickness measurement by SD-OCT (Cirrus HD-OCT, model 500 Zeiss). Fundus fluorescein angiography and fundus photography of the macular area were performed whenever required.

A baseline OCT was performed in all patients. Central macular thickness (CMT) was measured in all scans using the caliper tool built within OCT software by SD-OCT (Cirrus HD-OCT, model 500 Zeiss). CMT was defined as the distance between the inner retinal surface (interface between the dark vitreous and bright reflection of the internal limiting membrane) and the outer retinal surface (inner surface of the bright retinal pigment epithelium/Bruch's membrane interface).

Injection Technique:

After diagnosis of DME, intravitreal injection of 1.25mg of Avastin using 30 gauge needles was given at 3.5 mm or 4 mm distance from limbus in pseudophakic or phakic respectively. Before injection, topical anesthesia was induced by applying eye drop proparacaine (1%). The bulbar conjunctiva, fornices and eyelid were rinsed using 5% povidone iodine. The lid speculum was inserted after sterile drape was applied. Then intravitreal injection bevacizumab was given as mentioned above. To prevent reflux sterile cotton applicator was used after removal of the needle. Topical antibiotic was prescribed for 1 week after injection.

Patients were examined 1 day before injection, reevaluated on day 1, 4-6 weeks after injection, and then every 4-6weeks thereafter. Further injections were given for patients with only limited response to the first injection in terms of decreasing retinal thickness or for patients with recurrent edema (≥50 μm) and associated deterioration of visual acuity during follow-up.

Written informed consent was obtained from all patients. Off-label character of drug and the potential risk of endophthalmitis and retinal detachment were explained.

Statistical Analysis: The data was collected and entered in Microsoft Excel and checked for validity and coded. It was then converted into SPSS 11.5 for further statistical analysis. Data was checked for normal distribution by Kolmogorov-Smirnov test. Descriptive analysis was done by calculating frequency and percentage (for categorical data), while mean and standard deviations were calculated for continuous data.

The changes in visual acuity and macular thickness from baseline to follow up period were shown in the line graph. Inferential analysis consisted of comparing the findings, using appropriate tests of significance. Wilcoxon Signed rank test was applied to compare the changes in visual acuity and macular thickness at different intervals. For all inferential analysis, p value of <0.05 was considered significant.

Results

The eighty seven eyes of 60 patients attending the outpatient department of Mechi Eye Hospital with DME were enrolled. The mean ± SD age was 55.86 ± 9.61 years with male preponderance (n-47). All eyes completed at least 6 weeks follow up, 71 (81.6%) eyes completed 12 weeks and 55 (63.2%) eyes completed 18 weeks follow-up. The baseline characteristics of the study population are presented in Table 1.

Table 1: Baseline characteristics of 60 patients (87 eyes) enrolled in this study

Characteristics	Frequency	Percentage (%)
Gender (n=60)		
Male	47	78.33
Female	13	21.67
Age in years (mean ± SD)	55.86± 9.61	
*Laterality (n=60)		
Right Eye	45	51.7
Left Eye	42	48.3
Grade of DR (n=87)		
Mild NPDR	4	4.6
Moderate NPDR	39	44.8
Severe NPDR	28	32.2
PDR	16	18.4
Systemic disease (n= 60)		
Hypertension	33	55
Nephropathy	5	8.3
Cardiac disease	2	3.3
Previous Intervention (n=87)		
PRP	12	13.8
Grid laser	6	6.9
Cataract Surgery	4	4.6
None	65	74.7

* 27(45%) patients have both eyes involvement

Table 2: Multiple linear regressions analysis of visual acuity at 18 weeks with ANOVA table for the model

Variables	Regression coefficient	SE	p-value
Intercept	0.25	0.18	-
Baseline BCVA	0.65	0.11	0.001
Baseline CMT	-0.06	0.01	0.59
Previous intervention	0.005	0.11	0.96

Visual acuity:

For assessing visual acuity, Snellen visual test was converted to LogMAR. The baseline median

BCVA was 1.00 (0.60-1.30) which improved to 0.78 (0.48- 1.00) at 6 weeks (p=0.001) which

further improved to 0.78 (0.48-1.00) Log MAR (p value- 0.005) at 12 weeks and 0.60 (0.43-

1.00) Log MAR at 18 weeks (p value= 0.006).

OCT:

The mean baseline CMT± SD in μm was 436.24 ± 142.2 measured by OCT. The mean ± SD CMT decreased to 387.74±130.98 μm after 1st injection of Avastin at 6 weeks which was statistically significant (P value-0.0001) and at 12 weeks mean ± SD CMT reduced to 346.82 ±116.79 μm (P value – 0.0001). After 18 weeks, the mean ± SD CMT was further reduced to 307.1 ±105.49 (Figure 2).

Multiple linear regression to determine the association between baseline BCVA, baseline CMT and previous intervention and LogMAR BCVA at 18 weeks demonstrated that baseline BCVA was significantly associated with the outcome LogMAR BCVA at 18 weeks $p < 0.05$. This suggests that patients with good vision at baseline show better outcomes. There was no significant association between previous intervention done and baseline CMT to determine the outcome respectively.

All cases (87eyes) received one dose of injection Avastin, 71 eyes required second dose injection and 50 eyes required 3 doses injection during the study period.

There were five cases with transient rise in IOP (>20 mmHg) in this study which was managed with topical anti-glaucoma medication. There were 4 eyes with vitreo-macular intersurface abnormality (one eye developed epiretinal membrane formation and 3 eyes vitreo-macular traction) during follow up in this study. No other injection related complications, such as endophthalmitis, uveitis or progression of cataract were noted during follow up.

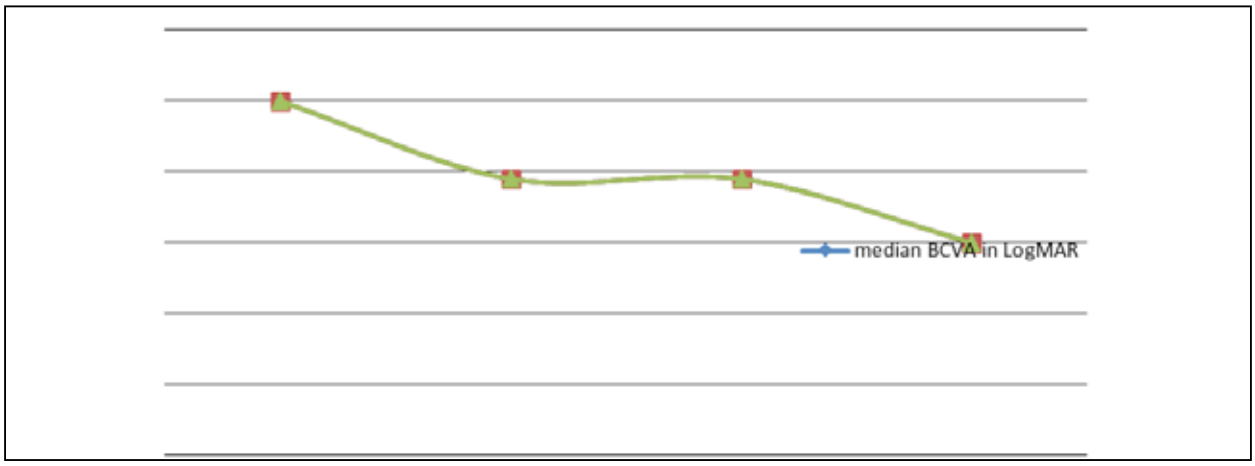


Figure 1: Graph showing changes in median BCVA following intravitreal injection of bevacizumab 1.25 mg.

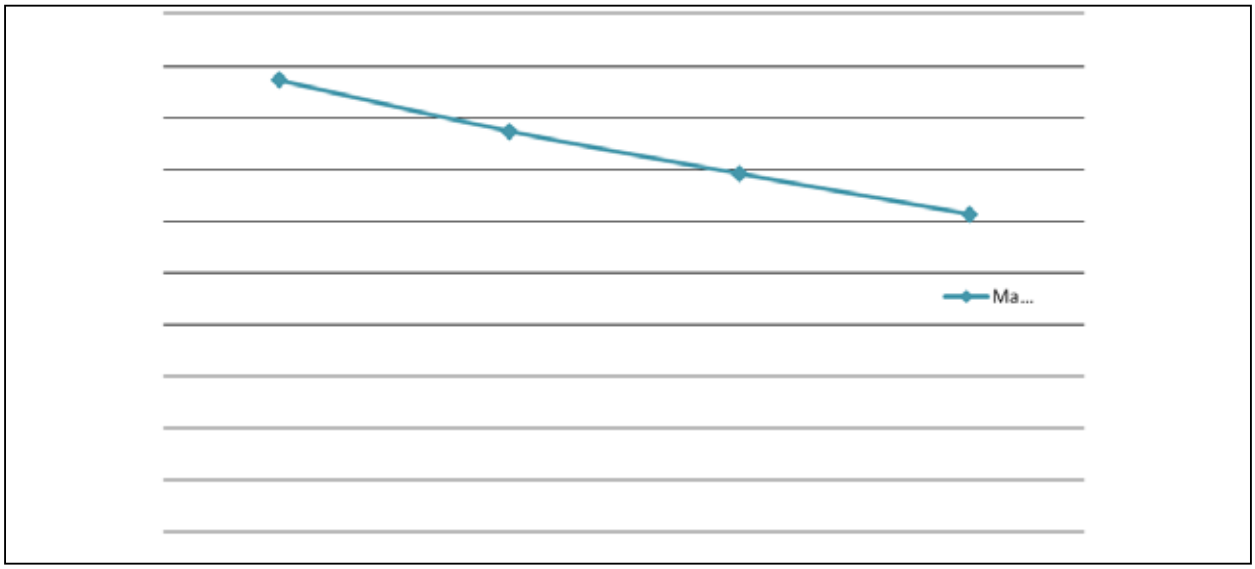
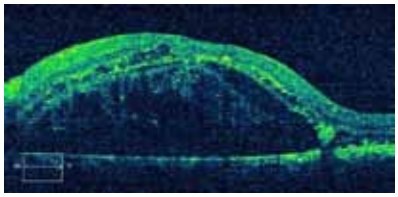
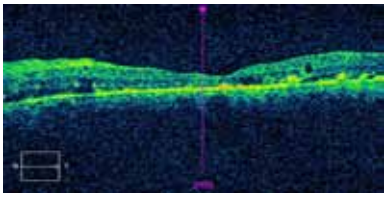


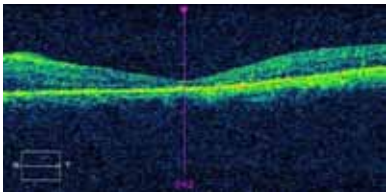
Figure 2: Figure shows changes in mean CMT measured by OCT following intravitreal injection Avastin.



Baseline BCVA 6/36 with CMT 670µm



BCVA improved to 6/18 with CMT 278µm at 6 weeks after 1st dose of injection Avastin



BCVA improved to 6/9 with CMT 234µm after 2nd dose of Avastin injection at 12 weeks

Figure 3: OCT showed decrement in macular edema with improvement in BCVA of a patient enrolled in this study following injection Avastin.

Discussion

DME is the major cause of diminution of vision in the working age group with diabetes mellitus. A third of diabetic patients have diabetic retinopathy of which 7% are affected by DME (Ding and Wong, 2012). Laser photocoagulation used to treat DME but is associated with potential side effects like laser scar expansion, paracentral scotoma, and subretinal fibrosis and secondary choroidal neovascularization formation which may develop two to eleven month after laser treatment (Han DP et al,1992; Guyer DR et al, 1992; Schatz H et al,1991). Anti-VEGF agents appeared to be safe and suitable treatment for DME (Rich RM et al,2006; Chakravarthy U et al, 2012).

In our study we observed improvement of median BCVA by 0.4 LogMAR at 18 weeks from baseline as compared to the study done by Vyas S et al (2016), Kumar A et al (2007) and Soheilin et al (2007) ,(mean 0.2, 0.24 and 0.24 LogMAR respectively) and the mean decrement of CMT by 129µm at 18 weeks from baseline is comparable to these study (123µm, 115µm and 97µm CMT respectively). Similarly Arevalo et al. (2007) showed an increase of mean BCVA by 0.27 and decrement of CMT by 105µm with bevacizumab injections of dose 1.25 mg at 3 months follow-up, which was comparable to our study.

The BOLT study showed better improvement in VA and greater reduction in CMT with Avastin in 2 years follow up study comparing bevacizumab to laser treatment. The median gain of 9 and 2.5 ETDRS letters (*P*=.005) with mean reduction in central macular thickness was 146µm and 118µm for bevacizumab arm and MLT arm respectively (Rajendram R et al, 2012).

Arevalo et al (2013) showed that primary intravitreal bevacizumab and combined intravitreal bevacizumab plus macular grid laser had a statistically significance from baseline BCVA at all points of 24 month follow up (P- 0.0001) and observed that primary IVB provides great reduction in CMT than GLP therapy or IVB plus GLP therapy (analysis of variance, P -0.001).

There were five cases (5.7%) with transient rise in IOP (>20mmHg) following injection Avastin in our study which was managed conservatively with topical anti-glaucoma medication. The DRCR.net study (2008) showed the probability of having sustained elevated intraocular pressure was 10% in the ranibizumab group (mean 15 injections) versus 3% in the sham group in 3 years of follow up study. The cause of transit rise in IOP may be temporary increase in vitreous volume.

In this study, 4 eyes developed vitreomacular

intersurface abnormality (one eye ERM and 3 eyes vitreo-macular traction) during follow up which may be due to natural disease process or may be due to use of anti-VEGF. Chang et al (2017) reported mean incidence of vitreomacular intersurface abnormality (VMIA) formation 6.43% per year in DME patients with intravitreal injection anti- VEGF treatment over a 40-month period. The angiofibrotic switch of VEGF and connective tissue growth factor (CTGF) may be the possible mechanism for vitreomacular intersurface abnormality. The level of unbound active VEGF reduced following anti-VEGF injection. This can lead to an increase in CTGF levels and thus promote a switch from angiogenesis to fibrosis (Kuiper EJ et al, 2008).

There was no injection related complication like endophthalmitis, uveitis or retinal detachment noted. There were no systemic side-effects like cardiovascular related accidents or increase in blood pressure noted during follow up.

Limitations

This is a non-randomized, uncontrolled, retrospective study with small sample size. As there is no control group so we cannot rule out the improvement in macular edema which may be secondary to improvement in general health conditions. Another limitation is shorter follow up which limits us to determine long term efficacy and safety of the treatment. Duration of the diabetes was not taken into account as data regarding duration was missing which could have influenced the result. The study has broad inclusion criteria which may be attributed to off label character of the drug.

Conclusion

In this study, intravitreal injection of Avastin 1.25mg resulted in significant improvement in BCVA with significant decrease in CMT in patients with DME in each follow up from baseline. Although our follow up period was short, results are encouraging for further multicenter prospective comparative study with longer follow up to determine efficacy and safety of the drug, and to better determine which patients benefit most.

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