

## Intravitreal Bevacizumab for Treatment of Diabetic Macular Edema

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To evaluate the effect of intravitreal bevacizumab on visual function and retinal thickness in patients with diabetic macular edema (DME) thirty eyes of twenty-eight patients (mean age, 57.9±13.8 years) with DME were included in this study. Complete ophthalmic examination, including determination of best corrected visual acuity (BCVA) and retinal thickness measurement by optical coherence tomography (OCT) was done at baseline and at each follow-up visit. All patients were treated with a 0.05 ml intravitreal injection containing 1.25 mg of bevacizumab. All patients completed 3 months of follow-up with a mean follow-up period of 5.26±2.39 months. The mean BCVA at baseline was 0.73±0.36 log MAR, which significantly improved to 0.63±0.41 ( $p=0.02$ ), 0.58±0.36 ( $p=0.003$ ), and 0.61±0.40 log MAR ( $p=0.006$ ) at 1 week, 1 month and 3 months. Final BCVA analysis demonstrated that 15 eyes (50%) remained stable and 12 (40%) improved  $\geq 2$  lines on BCVA. The mean central retinal thickness was 498.96±123.99  $\mu\text{m}$  at baseline and decreased to 359.06±105.97 ( $p<0.001$ ), 334.40±121.76 ( $p<0.001$ ), 421.40±192.76  $\mu\text{m}$  ( $p=0.035$ ) at 1 week, 1 month and 3 months. No ocular toxicity or adverse effects were observed. Intravitreal bevacizumab injection resulted in significant improvement in BCVA and central retinal thickness as early as 1 week after injection in patients with DME, and this beneficial effect persisted for up to 3 months. However, the slight reduction in this improvement at 3 months suggests that repeated bevacizumab injections might be necessary. To evaluate the long-term safety and efficacy, further prospective randomized controlled clinical trials will be needed.

[Dinajpur Med Col J 2017 Jan; 10 (1):18-24]

**Key words:** Diabetic macular edema, intravitreal bevacizumab injection

### Introduction

**D** iabetic macular edema (DME) is the leading cause of visual loss in patients with diabetes mellitus, and it frequently leads to irreversible changes in visual acuity.<sup>1</sup> DME is caused by excessive vascular permeability, which leads to leakage of fluid and plasma constituents, such as lipoproteins, into the retina. This then causes retinal thickening. The Early Treatment Diabetic Retinopathy Study (ETDRS) showed that focal laser photocoagulation is beneficial in the treatment of clinically significant

macular edema, reducing the rate of moderate visual loss by 50%.<sup>2</sup> However, only 3% of patients improved by  $\geq 3$  lines of vision by the end of the study. Intravitreal triamcinolone acetonide (IVTA) injection has proven effective in improving vision and reducing macular thickness in DME, both as an initial treatment and as a second line therapy after unsuccessful laser therapy.<sup>3,4</sup> However, its effect is temporary, and a number of side effects have been reported.<sup>5,6</sup> Consequently, its therapeutic value remains unclear.

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Vascular endothelial growth factor (VEGF) has been implicated as an important factor in the breakdown of the blood-retina barrier, with increased vascular permeability resulting in retinal edema in diabetic patients through affecting endothelial tight junction proteins.<sup>7</sup> While the normal human retina contains VEGF, hypoxia stimulates the secretion of VEGF from retinal pigment epithelial cells.<sup>8,9</sup> VEGF levels are significantly elevated in eyes with DME.<sup>10,11</sup> In addition, VEGF concentrations are significantly higher in eyes with extensive macular leakage when compared to eyes with minimal leakage.<sup>11</sup> Therefore anti-VEGF treatments have been proposed as an alternative adjunctive treatment for DME.<sup>12</sup> Bevacizumab is a complete full-length humanized antibody that binds to all subtypes of VEGF; it has been used successfully as a systemic drug in tumor therapy.<sup>13</sup> Recent studies have demonstrated the usefulness of intravitreal injections of Bevacizumab in the reduction of macular edema secondary to central retinal vein occlusion, vascular permeability, fibrovascular proliferation in retinal neovascularization secondary to proliferative diabetic retinopathy (PDR), and choroidal neovascularization secondary to age-related macular degeneration (AMD).<sup>14-17</sup>

The purpose of this prospective study was to evaluate the effect of intravitreal bevacizumab on visual function and retinal thickness in patients with DME.

### Methods

The present study was designed as a prospective, consecutive case series study of eyes with DME treated with intravitreal bevacizumab between January 2014 and July 2015. We reviewed the clinical records of 28 consecutive patients (30 eyes) with DME treated with at least one intravitreal injection of 1.25 mg of bevacizumab. Because there are no evidence-based indications for the

treatment of DME with bevacizumab, we included a wide range of patients with diffuse, clinically significant DME who did not respond to other treatments such as photocoagulation, intravitreal triamcinolone injection, or pars plana vitrectomy. The inclusion criteria for the study eye included (1) best-corrected visual acuity (BCVA)  $\leq 20/40$ , (2) clinically definite retinal thickening due to DME involving the center of the macula (3) optical coherence tomography (OCT) central retinal thickness  $\geq 275 \mu\text{m}$ , and (4) no history of treatment for DME within the prior 3 months. Exclusion criteria included macular edema due to a cause other than diabetes, other ocular condition that might affect macular edema or alter visual acuity, and evidence of external ocular infection.

Each patient underwent a complete eye examination, including determination of BCVA, slit-lamp examination, intraocular pressure (IOP) measurement, stereoscopic biomicroscopy of the retina using a 90-diopter lens and retinal thickness measurement by OCT at baseline and at each visit. Patients were examined at week and 1 month after injection, and then at 1 or 2 month intervals at the discretion of the investigator. Each patient's BCVA was transferred from his or her records and converted to a logarithm of the minimum angle of resolution (logMAR) scale for analysis.

Topical anesthesia was induced by applying proparacaine (0.5%) eye drops before injection. The conjunctiva bulbi and the fornices were repeatedly rinsed with povidone-iodine, which was also applied to the eyelid margins and the lashes. After application of sterile drape a 27 gauge needle on a 1 cc syringe was used to inject bevacizumab intravitreally through the pars

plana 3.5 to 4.0 mm posterior to the limbus at a dose of 1.25 mg in 0.05ml.

The needle was carefully removed using a sterile cotton applicator to prevent reflux. After injection, antibiotic eye drops were applied four times per day for 3 days. 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. The paired *t*-test was used for comparison of preoperative and postoperative BCVA and central retinal thickness. The multiple regression analysis was performed to evaluate the associated factors influencing treatment success. For all statistical tests, a *p* value <0.05 was considered statistically significant. The data was analyzed using statistical software (SPSS, version 12.0, SPSS Inc, Chicago, Illinois, USA).

## Results

Table I: Baseline Characteristics of the study eyes

Variables	Values
Gender, male: female	18:12
Age (years)	57.9±13.8
Diabetes type 1:2	5:25
Duration (years)	15.9±7.6
Hypertension	10
Stage of retinopathy, severe NPDR*:PDR	12:18
Mean follow-up period (months)	5.26±2.39
Baseline visual acuity (logMAR)	0.73±0.36
Baseline central retinal thickness (µm)	498.96±123.99

- NPDR= nonproliferative diabetic retinopathy;  
\*PDR=proliferative diabetic retinopathy

Table II: Best-corrected visual acuity (BCVA) analysis

	First Week		First Month		Third Month	
	No	%	No	%	No	%
Decreased $\geq 2$ lines of BCVA	2	7%	1	3%	3	10%
Remained stable	17	57%	16	53%	15	50%
Improved $\geq 2$ lines of BCVA	11	%	13	%	12	40%
			37	43%		

Thirty eyes (28 patients) with a minimum of 3 months follow-up were included for analysis. The mean patient age was 57.9±13.8 years and 60% were male (18 men, 12 women). All patients completed 3 months of follow-up, with a mean follow-up period of 5.26±2.39 months (range, 3-11 months). Type 2 diabetes was present in 83.3% of patients, and type 1 diabetes was present in 16.7% of patients. Eighteen eyes (60%) exhibited PDR, and twelve exhibited severe nonproliferative diabetic retinopathy (NPDR).

Improvements in visual acuity were noted from 1 week after intravitreal bevacizumab injection, and these statistically significant changes continued throughout the 3 month follow-up visit. At baseline, the mean BCVA was 0.73±0.36 logMAR. This improved significantly to 0.63±0.41 (*p*=0.02), 0.58±0.36 (*p*=0.003), and 0.61±0.40 logMAR (*p*=0.006) at 1 week, 1 month, and 3 months, respectively. At 3 month follow-up, the BCVA was slightly decreased, but there was no significant difference in the mean BCVA between the 1 and 3 month follow-up visits (*p*=0.536). Final BCVA analysis by subgroup demonstrated that 15 (50%) of 30 eyes remained stable, 12 (40%) improved  $\geq 2$  lines on BCVA, and 3 (10%) deteriorated  $\geq 2$  lines on BCVA (Table II).

Mean central retinal thickness was 498.96±123.99 µm (range, 275-733 µm) at baseline by OCT. At 1 week post operatively, the mean central retinal thickness

measurement decreased to  $359.06 \pm 105.97 \mu\text{m}$  ( $p < 0.001$ ), and this significant improvement of retinal thickening continued through the 1 and 3 month follow-up visits ( $p < 0.001$  and  $p = 0.035$ , respectively). However, at 3 month follow-up, mean central retinal thickness significantly increased to  $421.40 \pm 192.76 \mu\text{m}$ , compared with 1 month follow-up ( $334.40 \pm 121.76 \mu\text{m}$ ,  $p = 0.044$ ).

There were no cases of endophthalmitis, uveitis, IOP increase, or severe decrease in vision immediately after injection. At 3 months, no ocular or systemic adverse events were reported.

### Discussion

DME is a manifestation of diabetic retinopathy that produces severe visual impairment. Although several treatment modalities are under investigation, the only demonstrated means to reduce the risk of vision loss from DME are laser photocoagulation, as demonstrated by the ETDRS,<sup>2</sup> intensive glycemic control, as demonstrated by the Diabetes Control and Complications Trial and the United Kingdom Prospective Diabetes Study; and blood pressure control, as demonstrated by the United Kingdom Prospective Diabetes Study.<sup>18,19</sup> However, there has been interest in other treatment modalities, such as pharmacologic therapy with oral protein kinase C inhibitors and the use of intravitreal corticosteroids because most laser-treated DME eyes do not exhibit satisfactory improvements in VA.<sup>20,21</sup> Antibodies targeted to VEGF have also generated considerable interest and are being investigated.

VEGF is an endothelial cell-specific mitogen and angiogenic inducer in a variety of *in vitro* and *in vivo* models.<sup>22</sup> It is upregulated by hypoxia, and it plays a role in DME and contributes to the excessive vascular permeability that leads to macular edema in

diabetic patients. Bevacizumab is a full-length humanized monoclonal antibody that binds and inhibits all biologically active isoforms of VEGF. Although preclinical experimental data from primates suggested that the full-length antibody might not penetrate the internal limiting membrane of the retina, recent studies have shown full-thickness penetration of the retina within 24 hours.<sup>23,24</sup> To our knowledge, all clinical and experimental studies presented thus far have not noted drug-related toxic effects in any retinal structure.<sup>14-17,25-30</sup> Intravitreal injection of bevacizumab appears to have good efficacy in the treatment of wet AMD as a new treatment option. Injection of bevacizumab into the vitreous cavity, as is presently done mostly for patients with AMD, is based on the results of clinical reports clearly indicating an increase in visual acuity and a decrease in retinal thickness.<sup>15,16,27</sup> In addition, other VEGF inhibitors, such as pegaptanib sodium (Macugen) - which binds to one VEGF isoform - have also been successfully used to treat DME in a published randomized, controlled double-masked phase II multicenter trial. Subjects treated with pegaptanib had better visual acuity outcomes, were more likely to have reduction in central retinal thickness, and were less likely to need additional photocoagulation therapy at follow-up.<sup>12</sup> In light of this information, intravitreal bevacizumab injection is expected to have good efficacy in the treatment of DME.

Recently, Haritoglou et al.<sup>28</sup> published a prospective, noncomparative case series of patients with DME treated with 1.25 mg bevacizumab. There was a significant reduction in macular thickness at 2 weeks ( $p = 0.002$ ) and although mean visual acuity improved significantly at 6 weeks ( $p = 0.02$ ), this was not sustained at 12 weeks. In the present investigation, however, we found that significant improvement in both visual acuity

and retinal thickness was achieved soon after intravitreal bevacizumab injection, and the beneficial effects lasted for 3 months. The mean BCVA improved from  $0.73 \pm 0.36$  logMAR at baseline to  $0.63 \pm 0.41$  logMAR at 1 week follow-up ( $p=0.02$ ), and the mean central retinal thickness as measured by OCT also decreased significantly from  $498.96 \pm 123.99 \mu\text{m}$  at baseline to  $359.06 \pm 105.97 \mu\text{m}$  at 1 week follow-up ( $p < 0.001$ ). At 1 month after the injection of bevacizumab, this beneficial effect on BCVA and central retinal thickness appeared to be most prominent in the current study. Thirteen (43%) of 30 eyes showed an improvement in BCVA by 2 or more lines, and only 1 eye (3%) decreased  $\geq 2$  lines on BCVA at 1 month follow-up. In addition, the central retinal thickness showed a considerable reduction (33%): from  $498.96 \pm 123.99 \mu\text{m}$  at baseline to  $334.40 \pm 121.76 \mu\text{m}$  at 1 month. Although the duration of action of intravitreal bevacizumab is unknown, recent electrophysiologic and retinal penetration studies have reported that full thickness retinal penetration is present at 24 hours.<sup>24</sup> This may explain the earlier clinical effects of intravitreal bevacizumab observed in the current study.

A recent report from the Pan-American Collaborative Retina Study Group showed a significant decrease of DME one month after intravitreal injection of bevacizumab, and those decreased levels were kept for up to six months.<sup>29</sup> In our study, the reduction of central retinal thickness and the improvement of BCVA were observed at 1 week, and these results were maintained for up to 3 months. However, at 3 month follow-up, a slight decrease in visual acuity and an increase in retinal thickness were observed as compared with the 1 month follow-up. The central retinal thickness increased significantly from  $334.40 \pm 121.76 \mu\text{m}$  at 1 month to  $421.40 \pm 192.76 \mu\text{m}$  at 3 months ( $p=0.044$ ). This slight reduction in the improvement of

visual acuity and central retinal thickness at 3 month follow-up suggests that repeated intravitreal bevacizumab injections may be necessary within 3 months to maintain a beneficial effect.

The breakdown of endothelial tight junctions and loss of the blood-retina barrier that lead to DME can be associated with both nonproliferative diabetic retinopathy and PDR. The present study demonstrates a comparable population of PDR and NPDR patients with macular edema. The results of the present study indicate that intravitreal bevacizumab injections may have a beneficial effect on retinal thickness and visual acuity, independent of the type of diabetic retinopathy.

In conclusion, intravitreal bevacizumab injection appears to result in significant improvement in BCVA and reduction in central retinal thickness as early as 1 week after injection and this beneficial effect was shown to persist for up to 3 months. However, the slight reduction in improvement in visual acuity and central retinal thickness at 3 month follow-up suggests that repeated bevacizumab injections might be necessary within 3 months to maintain its effect, as the drug is well tolerated and there are no safety concerns. To evaluate the long term safety and efficacy of this new treatment further prospective randomized controlled clinical trials will be needed, with scheduled re-injection and longer follow-up.

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