Treatment of Refractory Diffuse Diabetic Macular Edema with Intravitreal Bevacizumab

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Abstract:
Purpose: To analyze the short term visual acuity and anatomic response after a single dose of off-label intravitreal injection of bevacizumab in diffuse diabetic macular edema (DME) not responding to conventional laser photocoagulation.

Patients and Methods: Prospective analysis of consecutive case series of 45 eyes of 38 patients with refractory diffuse DME who had one intra-vitreal injection of 1.25 mg of bevacizumab (Avastin) and followed up for 3 months. All patients passed at least six months since their last laser treatment before inclusion in the study. Patients underwent best corrected visual acuity determination, intraocular pressure measurement, stereoscopic biomicroscopy of the macula and measurement of the retinal thickness by optical coherence tomography (OCT) at base line and follow up visits.

Results: At 1 month post-injection, visual acuity improved by 1 line in 7 eyes, unchanged from the pre-injection levels in 24 eyes and deteriorated in 14 eyes. At 3 months post injection, visual acuity improved in 18 eyes, it remained unchanged in 13 eyes and deteriorated in 14 eyes. The mean logMAR visual acuities were 0.60 (SD ± 0.34), 0.64 (SD ± 0.31) and 0.61 (SD ± 0.32) at pre-injection, at 1 month post-injection and at 3 months post-injection respectively; but this mean decrease in vision was statistically not significant (P value = 0.099). The foveal thickness on optical coherence tomography had decreased in 27 eyes and it increased in 18 eyes at 1 month post-injection. At 3 months following injection, foveal thickness was reduced in 34 eyes, but was increased in 11 eyes. The mean foveal thicknesses were 444.95 µ (SD ± 127.36), 394.95 µ (SD ± 138.03) and 378.32 µ (SD ± 112.01) at pre-injection, 1 month post-injection and 3 months post-injection respectively. This decrease in the foveal thickness was statistically significant (P value < 0.001).

Conclusions: Intravitreal bevacizumab is effective in patients with diffuse DME which is refractory to treatment with conventional macular laser photocoagulation.

Key words: bevacizumab, intravitreal, diffuse diabetic macular edema

Introduction:
Diabetic retinopathy is one of many micro-vascular complications seen in patients with diabetes mellitus. Diabetic macular edema (DME) is a common cause of central visual impairment in patients with diabetic retinopathy. DME results from excessive retinal vascular permeability, leading to the egress of blood and plasma constituents into the retina in the macular area, leading to increased macular thickness. DME is clinically differentiated into focal and diffuse types. Focal type of DME has been reported to be more common than diffuse type of DME. Focal DME has also been associated with lesser increase in the macular thickening and better visual acuity. On the other hand, diffuse DME is characterized by diffuse and more increase in the macular thickening and is suspected to be carrying poorer prognosis for visual acuity.

In addition to the intensive glycemic control, as proven by the Diabetic Control and Complications Trail Research Group (DCCT), and good blood pressure control, as shown by the UK Prospective Diabetes Study Group (UKPDS), the only other proven means to reduce the risk of visual loss from DME is by laser photocoagulation, as demonstrated by the Early Treatment Diabetic Retinopathy Study Research Group (ETDRS). The ETDRS showed that early laser photocoagulation was beneficial for eyes with clinically significant macular edema (CSME) by reducing the moderate visual loss by 50%; and only 3% of laser treated eyes experienced a gain of ≥3 lines of visual acuity. This suggests that a distinct sub-group of eyes with DME still exists which do not respond to laser photocoagulation. Some studies have also suggested that eyes with diffuse DME carry poor prognosis in spite of laser photocoagulation. This limitation of laser treatment has lead to the increased interest in other treatment modalities with alternative or adjunctive pharmacologic...
therapies for DME especially the diffuse type.

Many theories have been proposed to explain the clinico-pathological findings in diabetic retinopathy and DME, including biochemical, hemodynamic, endocrine, growth factors and inflammatory theories. Vascular endothelial growth factors (VEGF), which are up-regulated by hypoxia,\(^9\) play significant role in the pathogenesis and development of DME. VEGF, in addition to being an angiogenic inducer, increases retinal vascular permeability. All variants of VEGF have been implicated in the causation of DME. Hence, the use of antibodies targeted at VEGF has emerged as another potential therapeutic modality for managing DME.\(^{10-13}\)

The anti-VEGF therapy has generated considerable interest recently and is being investigated extensively in managing diverse retinal pathologies. The success of anti-VEGF therapy in age related macular degeneration\(^{14,15}\) has led researchers to use it in DME in instances when other therapies are inappropriate or do not work. However, all of these studies are preliminary, and no anti-VEGF agent has been approved by Food and Drug Administration (of USA) for DME till date. Currently, most research on anti-VEGF therapy in DME consists of pilot studies, but a few randomized, placebo-controlled trials are being performed and suggest promise. The common anti-VEGF drugs being used in DME are: pegaptanib, ranibizumab and bevacizumab.\(^{10-13}\)

We present herewith our experience with bevacizumab in patients with diffuse DME not responding to conventional laser photocoagulation.

**Patients and Methods:**

We conducted this prospective, consecutive and a non-comparative interventional study between February and August 2007. The aim of this study was to analyze the short term best corrected visual acuity and anatomic response after a single dose of off-label intravitreal bevacizumab (Avastin, Genentech Inc, San Francisco, California, USA) in the dosage of 1.25 mg (0.05 ml) in patients with persistent diffuse DME. The off-label use of the drug along with the potential benefits and risks were discussed extensively with each patient and an informed consent was obtained to participate in the study.

The main inclusion criteria were: patients with persistent diffuse DME, not responding to the conventional macular laser photocoagulation and passed six months after their last laser session before inclusion in the study. The main exclusion criteria were: any other co-existent ocular pathology (e.g., significant cataract, glaucoma, corneal pathology or age related macular degeneration), patients with macular ischemia on fundus fluorescein angiography, epiretinal membrane, vitreomacular traction syndrome and any other combined surgical procedure (e.g., phaco/IOL/vitrectomy). Patients with uncontrolled hypertension, high HbA1c levels (≥7%) and any recent thromboembolic episodes (i.e. stroke, myocardial infarc-

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**Results:**

Forty five eyes of 38 patients who completed 3 months of follow-up were included for analysis. 31 patients had injections in one eye and 7 patients had injections in both eyes at an interval of 1 to 2 weeks (mean: 1.4 weeks). The mean age of our patients was 57.5 years (Range: 35 - 77 years). There were 22 males (57.9%) and 16 (42.1%) females. Of the 45 eyes, 24 were right eyes and 21 were left eyes. All eyes had diffuse DME which was refractory to treatment with conventional macular laser photocoagulation which was carried out ≤ 6 months prior to the injection. 23 eyes had non-proliferative stage of diabetic retinopathy and 22 eyes had proliferative stage of diabetic retinopathy. All eyes with proliferative diabetic retinopathy were stabilized by...
the prior panretinal photocoagulation performed at least 6 months earlier.

At 1 month follow up, one Snellen line improvement was seen in 7 eyes (15.56%), the visual acuity remained at the same level in 24 eyes (53.33%), but 1-to-2 line deterioration was seen in 14 eyes (31.11%). By 3 months, 1 to 2 line improvement was seen in 18 eyes (40%), and the Snellen visual acuity remained unchanged in 13 eyes (28.89%) and it got deteriorated by 1-to-2 lines in 14 eyes (31.11%). On statistical analysis, the mean pre-injection logMAR vision was 0.60 (SD ± 0.34). This decreased to 0.64 (SD ± 0.31) at 1 month post injection, and then showed mild improvement to 0.61 (SD ± 0.32) as shown in Table 1 and Figure 1. At 1 month and 3 month follow-ups, the mean BCVA though showed marginal deterioration, it was statistically not significant (p value = 0.099) (Table 1).

The foveal thickness, evaluated by optical coherence tomography, was available in all 45 eyes. At 1 month follow-up, the foveal thickness had decreased in 27 eyes (60%) and it increased in 18 eyes (40%). At the 3rd month follow up visit, the foveal thickness was reduced in 34 eyes (75.56%), but was increased in 11 eyes (24.44%). The mean pre-injection foveal thickness was 444.95 μ (SD ± 127.36). This mean foveal thickness got reduced to 394.95 μ (SD ± 138.03) by 1 month; and at 3 months follow up visit, the mean foveal thickness was 378.32 μ (SD ± 112.01) (Table 2, Figure 1, 2 and Figures 3A-C). This decrease in the foveal thickness was statistically significant (P value < 0.001) as shown in Table 2. One eye developed vitreous haemorrhage during the 3 months of follow-up period, which was thought to be related to the progression of proliferative diabetic retinopathy. None of the eyes showed increased intraocular pressures during the follow-up period. We did not notice any post-injection uveitis or endophthalmitis in this case series, neither had we seen any systemic thromboembolic episodes in our patients during this period.

**Discussion:**

Diabetic macular edema (DME) commonly leads to central visual impairment in patients with diabetes mel- litus. The severity of visual impairment due to DME may range from mild and asymptomatic to profound loss of vision. All patients with diabetes are at risk of developing DME. In Wisconsin epidemiological study on diabetic retinopathy, the incidence of DME over a 10 year period ranged from 13.9% in adult-onset diabetics not taking insulin to 25.4% in adult-onset diabetics taking insulin.(16) DME is a general term defined as retinal thickening within two disc diameters of the foveal center. Clinically significant macular edema (CSME) is a form of DME that was precisely defined by the ETDRS.(6) DME occurs due to the breakdown in the blood-retinal barrier resulting in leakage of fluid from microaneurisms and abnormal retinal capillaries into the retina. Development of DME

![Figure 1:](image1)

![Figure 2:](image2)

<table>
<thead>
<tr>
<th>LogMAR</th>
<th>Pre-injection</th>
<th>1 month post injection</th>
<th>3 months post injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD</td>
<td>0.60 ± 0.34</td>
<td>0.64 ± 0.31</td>
<td>0.61 ± 0.32</td>
</tr>
<tr>
<td>95% CI for Mean</td>
<td>0.50 - 0.70</td>
<td>0.54 - 0.73</td>
<td>0.51 - 0.71</td>
</tr>
<tr>
<td>Median</td>
<td>0.60</td>
<td>0.60</td>
<td>0.60</td>
</tr>
</tbody>
</table>

Friedman Test (X²=4.617, df=2, p-value=0.099)

Table 1:

<table>
<thead>
<tr>
<th>Foveal Thickness</th>
<th>Pre-injection</th>
<th>1 month post injection</th>
<th>3 months post injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD</td>
<td>444.95 ± 127.36</td>
<td>394.95 ± 138.03</td>
<td>378.32 ± 112.01</td>
</tr>
<tr>
<td>95% CI for Mean</td>
<td>404.23 - 483.67</td>
<td>352.99 - 436.92</td>
<td>344.27 - 412.37</td>
</tr>
<tr>
<td>Median</td>
<td>434.50</td>
<td>395.00</td>
<td>372.50</td>
</tr>
<tr>
<td>Range</td>
<td>234 - 840</td>
<td>202 - 1084</td>
<td>183 - 732</td>
</tr>
</tbody>
</table>

Friedman Test (X²=15.318, df=2, p-value=0.001)

Table 2:
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Figure 3A: Pre-injection OCT

Figure 3B: OCT at 1 month after injection

is a highly complex process requiring the coordinated action and interplay of multiple biochemical messengers and permeability factors such as (VEGF, interleukin-6 and histamine), tissue hypoxia and chronic inflammation.\(^{(17)}\)

Laser photocoagulation became the standard of care in the treatment of DME primarily as a result of the findings of the ETDRS.\(^{(6)}\) However, only 50% of the eyes with CSME were stabilized with laser at 3 years; and 12% of the treated eyes still lost ≥15 letters at 3 years, according to the ETDRS. This failure of laser in substantial subgroup of patients of DME has promoted interest in other treatment modalities.

Unlike the focal type of DME which is often associated with circinate rings of hard exudates resulting from leakage from microaneurysms, diffuse edema represents more extensive breakdown of the blood-retinal barrier,
with leakage from both microaneurysms and retinal capillaries throughout the posterior pole. Hence, some authors have claimed that diffuse type DME is refractory to laser photocoagulation and it is a prognostic factor for poorer visual acuity at follow-up. This has led many researchers to try other options of therapy in patients with diffuse DME. Some have tried intravitreal triamcinolone injection and have found out that diffuse DME responds better to intravitreal triamcinolone. Others have used intravitreal bevacizumab when photocoagulations, intravitreal injection of triamcinolone, or vitrectomy have failed to treat diffuse DME. We wanted to evaluate the role of the intravitreal anti-VEGF agent in patients with persistent and diffuse DME refractory to conventional macular laser photocoagulation.

In the pathophysiologic cascade which leads to the DME, chronic hyperglycemia leads to ischemia which results in overexpression of a number of growth factors, including VEGF. Blockade of all involved growth factors will likely be necessary to completely suppress the detrimental effects of ischemia, but even isolated blockade of all isoforms of VEGF may have beneficial effects on DME. VEGF increases vascular permeability by relaxing endothelial cell junctions, which increases permeability and leakage. Inhibition of VEGF blocks this effect to some extent, as demonstrated in several recent clinical trials and case series involving the anti-VEGF molecules e.g. pegaptanib, ranibizumab, and bevacizumab.

In this study, bavacizumab (Avastin, Genentech, CA, USA) as the anti-VEGF agent was used to evaluate its effect when the conventional laser photocoagulation failed in resolving the diffuse type of diabetic macular edema. We chose bevacizumab as the anti-VEGF agent since it blocks all isoforms of VEGF. We chose the widely used intra-vitreal concentration of bevacizumab (i.e. 1.25 mg). Since, the effectiveness of intravitreal bevacizumab has been reported to last from a minimum of 6 weeks to a maximum of 12 weeks, we decided to follow up our patients for a period of 3 months following the injection.

In this study we found that, at 1 month following the intra-vitreal injection of bevacizumab in eyes with refractory diffuse DME, the visual improvement was seen in 15.56% of eyes; visual stabilization was seen in 53.33% of eyes; and visual acuity decreased in 31.11% of eyes. But, at 3 months following injection, the visual acuity improved in 40% of eyes, it remained at pre-injection levels in 28.89% of eyes; and it remained decreased in 31.11% of eyes. The Macugen Diabetic Retinopathy Study Group reported gains in visual acuity of 10 letters in 34% of eyes; visual stabilization was seen in 53.33% of eyes; and visual acuity decreased in 31.11% of eyes. The Pan-American Collaborative Retina Study Group reported that 41.1% eyes remained stable, 55.1% improved >2 lines, 3.8% decreased 2 or more lines at 6 months follow-up.

In this study, the anatomic results (i.e. the reduction in the foveal thickness on OCT) were better when compared to the functional results in terms of the gain in the BCVA. But Soheilian et al reported that the reduction in the central macular thickness following intravitreal injection of bevacizumab was not as prominent as visual acuity improvement. We saw the decrease in foveal thickness.
in 60% of eyes and its increase in 40% of eyes 1 month post-injection. However at 3 months, foveal thickness had decreased in 75.56% of eyes though it remained increased in 24.44% of treated eyes. The Macugen Diabetic Retinopathy Study Group reported a reduction of mean central retinal thickness by 68 μ following the macugen therapy.\(^{(11)}\) Chun DW, et al. found in their study on ranibizumab that the mean central retinal thickness was reduced by 45.3 μ in 0.3 mg group; by 197.8μ in 0.5 mg group.\(^{(11)}\) The Pan-American Collaborative Retina Study Group reported in their study a mean decrease of 112μ following primary intravitreal therapy with bevaciuzumb in eyes with DME.\(^{(24)}\) We found in this study that the mean central macular thickness got reduced by 66 μ following intravitreal bevacizumab therapy in eyes with refractory and diffuse DME.

In our study, the visual acuity improvement as well as the reduction in the foveal thickness was maximum at 3 months following the injection. However other reports showed that the reduction in the retinal thickness associated with bevaciuzumb at 3 weeks tends to decrease or plateau between 3–6 weeks post injection.\(^{(24)}\) This difference in the duration of effectiveness is important when considering the optimal time of injection interval.

Systemic adverse side effect due to the use of bevacizumab or major intravitreal injection related-complications did not occur in this case series. Chun, et al. reported the occurrence of 5 cases of mild-moderate ocular inflammation but no cases of systemic side effects after intravitreal injection of ranibizumab.\(^{(11)}\)

Limitations of our study are it is a short term, non-randomised and non-comparative study involving a small patient group. In addition, it is quite possible that the therapeutic response to intravitreal bevacizumab in patients with refractory DME would depend on their systemic factors including the tightness of glycemic control and other coexistent diseases like hyper-lipidemia, anemia and hypo-proteinemia which we did not analyze in our study. However, our results are quite encouraging and need further investigations in patients with refractory diffuse diabetic macular edema.

To conclude, intravitreal bevacizumab shows promise in managing the diffuse DME not responding to conventional laser photocoagulation. We recommend larger studies with longer follow-ups which determine the duration of treatment and the optimal injection frequency.

References: