Visual Outcome after Intravitreal Avastin (Bevacizumab) for Persistent Diabetic Macular Edema

Tehmina Jahangir, Samina Jahangir, Haroon Tayyab, Uzma Hamza

Purpose: To determine the effect of intravitreal bevacizumab (Avastin) on visual acuity in patients with persistent diabetic macular edema.

Material and Methods: A prospective, hospital based study conducted at Department of Ophthalmology, Jinnah Hospital Lahore from May 2010 to October 2010. Twenty eyes of 20 patients received a single intravitreal injection of Bevacizumab in a dose of 1.25mg / 0.05ml. The visual acuity was measured pre-injection and at 1, 4 and 12 weeks post-injection using Snellen’s visual acuity chart.

Results: Prior to injection, there was 1 (5%) eye with best-corrected visual acuity (BCVA) better than or equal to 6/18, 10 eyes (50%) with VA between 6/24 and 6/60 and 9 (45%) with VA below 6/60. At 12 weeks post-injection, 2 (10%) eyes had BCVA better than or equal to 6/18; the number of eyes with BCVA between 6/24 and 6/60 were 12(60%), while 6(30%) eyes had BCVA below 6/60. The results are statistically significant (for each, p value is less than 0.05).

Conclusion: This study revealed that intravitreal Bevacizumab (1.25mg/0.05ml) resulted in improvement of visual acuity in patients with persistent diffuse diabetic macular edema unresponsive to previous grid laser photocoagulation. The follow-up period was however too short to provide specific treatment recommendations, the short term results encourage further prospective studies with different treatment groups and longer follow-up.

Retinal edema threatening or involving the macula is an important visual consequence of abnormal retinal vascular permeability in diabetic retinopathy. Focal/grid photocoagulation has been the mainstay of treatment since its benefit was demonstrated in the Early Treatment Diabetic Retinopathy Study (ETDRS) in 1985. However, especially in macular edema laser treatment is not always beneficial. Most of the retinal damage that characterizes the disease is believed to result from breakdown of the inner blood retinal barrier mediated by numerous growth factors such as vascular endothelial growth factor (VEGF). Based on these facts anti-VEGF agents like Pegaptanib sodium and Ranibzumab have been evaluated for diabetic macular edema in Phase II randomized trials. One such VEGF inhibitor is Bevacizumab (Avastin; Genentech, Inc., South San Francisco, CA), a US Food and Drug Administration approved full-length humanized monoclonal antibody that until recently was used for the treatment of metastatic colorectal cancer. As compared to Pegaptanib, which is a selective inhibitor of VEGF 165, Bevacizumab inhibits all active isoforms of VEGF. Intravitreal Bevacizumab is currently being evaluated for use in macular edema following central retinal vein occlusion (CRVO), wet age-related macular degeneration (ARMD), rubeosis iridis and proliferative diabetic retinopathy (PDR). It seems reasonable to assume that VEGF inhibitors will also be beneficial in diabetic macular edema. Although
intravitreal use of Bevacizumab is an off-label option, its use has risen exponentially in the recent past due to its efficacy and economic feasibility. However, there are very few studies to-date showing the beneficial effect of intravitreal Bevacizumab for persistent diffuse diabetic macular edema. The purpose of this study was to evaluate the beneficial effect of intravitreal injection of Bevacizumab on visual acuity in diabetic macular edema.

MATERIAL AND METHODS

This was a prospective, interventional, non-comparative case series carried out at the Department of Ophthalmology, Jinnah Hospital Lahore. The study was carried out over a period of six months from May 2010 to October 2010. Twenty eyes of twenty patients were included. The sampling technique was non-probability convenience sampling. We included diabetic patients of all ages and both sexes having non-proliferative diabetic retinopathy with diffuse, clinically significant diabetic macular edema, which was previously treated with grid laser (more than six months ago). However, the following patients were excluded: those having only focal macular edema attributable to focal leaks from microaneurysm; patients with any other macular pathology like ARMD or any vascular occlusive disease affecting the macula; those previously treated with pan retinal photocoagulation (PRP) and grid laser within last six months; those with angiographic evidence of widening or irregularity of the foveal avascular zone suggestive of ischemic maculopathy; and patients with uncontrolled diabetes, hypertension and/or chronic renal failure.

Injection Technique: All intravitreal injections were performed under topical anesthesia. Intravitreal Bevacizumab injection was prepared and dispensed by the pharmacy at Shaukat Khanum Memorial Cancer Hospital, Lahore at the concentration of 1.25mg/0.05ml. The lid was prepared with 5% povidone-iodine applied directly to the eye, and Bevacizumab was injected into the mid-vitreous 3.5mm posterior to the limbus in pseudophakic eyes and 4.0 mm posterior to the limbus in phakic eyes with a tuberculin syringe and 27-gauge needle. Topical ciprofloxacin eye drops were applied four times daily for one week.

Follow-up visits were at 1 week after injection, and then at 1 month and 3 months.

Only one eye per subject was treated. All data were analyzed using SPSS 13.0 for windows. The paired t-test was used for comparison of preoperative and postoperative BCVA. For all statistical tests a p value of <0.05 was considered statistically significant.

RESULTS

In this study, 20 eyes of 20 patients with diabetic macular edema were studied. Of these 12 (60%) were males and 8 (40%) females. The age range was from 45 to 67 years with a mean of 59.2 ± 6.0 years. (Table 1) All patients had diffuse, clinically significant diabetic macular edema at baseline for which they had received grid laser photocoagulation at least 6 months before injection. All patients completed 12 weeks of follow-up.

The glycosylated hemoglobin (HbA1c) averaged 6.0 ± 1.3 before starting the study.

Pre-injection, there was 1 (5%) eye with best-corrected visual acuity (BCVA) better than or equal to 6/18, 10 eyes (50%) with VA between 6/24 and 6/60 and 9 (45%) with VA below 6/60.

At the first post-injection week, no changes were observed in the BCVA.

At first post-injection month, 2 (10%) eyes had BCVA better than or equal to 6/18; 15 (75%) between 6/24 and 6/60 and 3 (15%) eyes had BCVA worse than 6/60.

Three months after the injection, again 2 (10%) eyes had BCVA better than or equal to 6/18. However, the number of eyes with BCVA between 6/24 and 6/60 were 12 (60%), while 6 (30%) eyes had BCVA worse than 6/60. Thus twelve weeks after the injection, some regression of the increase in visual acuity was noted (Fig. 1).
**Table 1:** Clinical characteristics patients with diabetic macular edema at baseline n = 20

<table>
<thead>
<tr>
<th>Gender</th>
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</thead>
<tbody>
<tr>
<td>Male</td>
<td>12</td>
</tr>
<tr>
<td>Female</td>
<td>8</td>
</tr>
<tr>
<td>Age (years), Mean ± SD</td>
<td>59.2 ± 6</td>
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<tr>
<td>Glycosylated hemoglobin (HbA1c, %)</td>
<td>6.2 ± 1.3</td>
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</table>

**Table 2:** Mean intraocular pressures of patients before and after intravitreal bevacizumab injection n = 20

<table>
<thead>
<tr>
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<th>Mean IOP (mmHg)</th>
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<tbody>
<tr>
<td>Pre-injection</td>
<td>16.2 ± 2.6</td>
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<tr>
<td>One week</td>
<td>15.8 ± 2.2</td>
</tr>
<tr>
<td>One month</td>
<td>16 ± 2.3</td>
</tr>
<tr>
<td>Three months</td>
<td>16.1 ± 2.2</td>
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**Fig. 1:** Graphical representation of pre and post-injection visual acuities

There was statistically significant difference in the pre and post injection visual acuity of the patients. Thus, in comparing the visual acuities at one month and 3 months the p value is less than 0.05.

No significant increase of IOP was observed throughout the study (Table 2).

Mild anterior chamber cellular reaction was observed in 3 eyes (10%), however the inflammation resolved within a week with topical corticosteroid. Other injection related adverse events such as endophthalmitis, vitreous hemorrhage and retinal detachment were not observed.

**DISCUSSION**

Diabetic retinopathy is the leading cause of blindness in patients aged more than 50 years in our country. The intravitreal injection of Bevacizumab has been met with great enthusiasm especially for patients with neovascular age-related macular degeneration. A significant improvement has also been reported in macular edema secondary to other conditions such as CRVO. It was also found that the concentration of VEGF increased and correlated with the severity of macular edema in patients with DME.

In light of this information we decided to conduct a prospective, hospital-based study to investigate the visual outcome after intravitreal Bevacizumab injection in patients with chronic diffuse diabetic macular edema unresponsive to previous grid laser photocoagulation. Bevacizumab has attracted interest because of its low cost; however systemic safety is of concern.

The results of our study showed that intravitreal Bevacizumab is useful in increasing visual acuity in patients with diffuse diabetic macular edema. There was a statistically significant increase in the VA at 4 and 12 weeks after the injection. Our results are comparable with those of Haritoglou et al.

The observed slight reduction of the increase in visual acuity at the limited 12-week follow-up is also consistent with the findings of Haritoglou. This decrease also hints that repeated Bevacizumab injections may be necessary.

Many clinical investigators have found that an intravitreal injection of Triamcinolone (TA) may reduce macular edema. However, the intravitreal use of TA may lead to complications such as increased IOP, progression of cataract and endophthalmitis. However unlike the eyes treated with triamcinolone, there was no significant rise in the IOP. These results are comparable to those of Toshihiko and associates.

A limitation of the present investigation is the short follow-up, due to which the long-term safety and efficacy of the treatment could not be assessed. Other limitations are the lack of a control group, but it can be argued that the enrolled eyes served as their own controls because the pre and post-injection visual acuities of patients were compared. Thirdly, the visual acuity was measured on a Snellen’s chart as opposed to the more standardized and accepted ETDRS chart. However, all eyes were tested with the same correction throughout the follow-up period. The strengths are prospective design and careful follow-up.

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up. Most of the studies on the intravitreal injection of Bevacizumab were designed as retrospective analysis\textsuperscript{14}.

Many clinical investigators have found that an intravitreal injection of TA may reduce macular edema. However, the intravitreal use of TA may lead to complications such as increased IOP, progression of cataract and endophthalmitis\textsuperscript{16,20}.

Recent studies have shown that the combination of laser photocoagulation with intravitreal Bevacizumab may improve BCVA and retinal thickness more than laser photocoagulation alone or intravitreal Bevacizumab alone for DME\textsuperscript{21,22}.

CONCLUSION

The positive results of this prospective, non-randomized study are quite promising and suggest the need for a longer, prospective randomized studies to evaluate the long-term safety and efficacy of intravitreal Bevacizumab.

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REFERENCE