World Journal of Medical and Surgical Ophthalmology

Intravitreal Bevacizumab as a Treatment of Diabetic Macular Edema in Patients Refractory to Laser Photocoagulation Therapy

Abhisek mondal, Ishan yadav, Sujit deshmukh, Arnub majumdar
*Department of Ophthalmology, Bharat Sevashram Sangha Hospital, Kolkata.
** Department of Ophthalmology, IMS, BHU, Varanasi, India

Abstract

Aim: To evaluate the effectiveness of intravitreal bevacizumab injection as treatment of diabetic macular edema in patients who are not responding to previous photocoagulation.

Patients and Methods: 40 eyes of 40 diabetic patients were treated with 1.25 mg of intravitreal bevacizumab injection as the primary therapy for diabetic macular edema. The main outcome measures included best-corrected visual acuity, fundus fluorescein angiography, and macular edema map values of optical coherence tomography before and after intravitreal injections.

Results: All the eyes had received some form of laser photocoagulation before (not less than six months ago), but all of these patients had persistent diffuse macular edema with no improvement in visual acuity. The visual acuity increased in 30 of 40 eyes (75%) during a mean follow-up time of 5.6 months. The mean baseline best-corrected Log MAR value for visual acuities of the patients before intravitreal bevacizumab injection was 1.09 ± 0.23. After treatment, it was 0.90 ± 0.17 at the 1-month, 0.81 ±0.24, at 3-month, and 0.77 ± 0.26 at the last visit examination and the differences were significant when compared with baseline values (for each, $P<0.001$). The mean edema map values significantly decreased by 33.3% at the last visit examination when compared with preinjection values ($P<0.001$). No adverse events were observed, including endophthalmitis, inflammation and increased intraocular pressure or thromboembolic events in any patient. Mild anterior chamber inflammation was observed in four eyes (10%), which resolved in a week with topical corticosteroid. No other injection- or drug-related complications were observed.

Conclusions: Initial treatment results of patients with diffuse diabetic macular edema not responding to previous photocoagulation did not reveal any short-term safety concern. Intravitreal bevacizumab application provides significant improvement in visual acuity of diabetic patients and clinical course of macular edema, and may therefore be a promising approach in the primary treatment of diabetic macular edema.

Introduction

Diabetic macular edema (DME) continues to be the paramount cause of visual loss in diabetic patients. The visual impairment from untreated macular edema often leads to legal blindness and has a significant detrimental effect on the quality of life. In our country alone we have a staggering 31.7 million diabetics with a rising incidence, of which nearly 30% have some degree of retinopathy [1].

Address for correspondence and reprint requests to:
Department of Ophthalmology, IMS, BHU, Varanasi
ishanu13@gmail.com

 Submitted Friday, January 2, 2015; Accepted Tuesday, February 24, 2015; Published Sunday, March 01, 2015

Apart from laser photocoagulation, which is the primary treatment modality, intravitreal triamcinolone acetonide (IVTA) is being used commonly for the various forms of DME. [2, 3] It has been well established that vascular endothelial growth factor (VEGF) plays a vital role in promoting neovascularization and increased vascular permeability in diabetic eyes. Levels of ocular VEGF are correlated with both the growth and permeability of new vessels [4]. Furthermore, introduction of VEGF into normal primate eyes induces the same pathological processes as seen in diabetic retinopathy, namely micro aneurysm formation and increased vascular permeability. Also, studies have shown vitreous samples from patients with DME contain elevated VEGF levels [5]. Based on these facts anti-VEGF agents like Pegaptanib sodium and Ranibizumab have been evaluated for DME. Compared to Pegaptanib which is a modified 28-base ribonucleic acid aptamer that selectively binds VEGF 165, Bevacizumab is a humanized monoclonal antibody that inhibits all active isoforms of VEGF. Intravitreal bevacizumab is a new treatment modality which is currently being tried out for use in macular edema following central retinal vein occlusion (CRVO), wet age-related macular degeneration (ARMD), rubeosis irides, proliferative diabetic retinopathy (PDR) and retinopathy of prematurity [6-9]. Although intravitreal use of bevacizumab is an off-label option its use has risen exponentially in the last few months mainly due to its efficacy and economic considerations.

Based on these observations we evaluated intravitreal bevacizumab in DME in which VEGF is known to play a key role in increasing vascular permeability and breaking down the blood retinal barrier.

Patients and methods

A total of 40 eyes of 40 diabetic patients who underwent intravitreal bevacizumab injection as the primary treatment for DME were included in this study. There were 23 women and 17 men, and the mean age of the patients was 59.1 ± 8.9 years (range, 40-75 years). All patients had macular edema with hyperfluorescent leakage on fundus fluorescein angiography. The mean duration of DME was 7.4 ± 3.9 months (range 3-16 months). A detailed history of medication was obtained, and the patients were excluded from the study if they had uncontrolled systemic hypertension, thromboembolic events, severe renal dysfunction, nephrotic syndrome, and dysproteinemias or receiving vasoactive drugs or antioxidant.

Before intravitreal bevacizumab injection, all eyes had received peripheral scatter laser photocoagulation to ablate ischemic areas or neovascularization, but no eyes received any treatment for DME. Intravitreal injection of bevacizumab (1.25 mg/0.05 ml) was offered as the first treatment of DME. All patients were fully informed about the experimental character of the treatment and informed consent was obtained from each patient.

Baseline parameters were documented including best-corrected visual acuity (BCVA), edema map values of OCT, fundus fluorescein angiography (FFA) findings, and IOP. BCVA for each eye was ascertained using Snellen chart, which was situated 20 ft (approximately 6 m) away from the patient before intravitreal applications, and then all eyes were tested with the same

Table 1. Mean LogMAR Value for the Visual Acuities, EM Values, and IOPs of Patients Before and After Intravitreal Bevacizumab Injection.

	LogMAR value	EM value	IOPs (mmHg)
PI	1.09±0.23	2.4±0.6	15.0±2.3
1 month	0.90±0.17	1.7±0.5	14.8±2.5
3 months	0.81±0.24	1.7±0.4	15.1±2.4
LV	0.77±0.26	1.6±0.4	14.9±2.5

EM=Edema map; IOP=intraocular pressure; LV=last visit; PI=preinjection

correction throughout the follow-up period. The proper average VA was computed by converting the value to the LogMAR equivalent. Statistical calculations were performed using LogMAR values for VA.

All intravitreal injections were performed by the same surgeon (AM) under topical anesthesia. The drug was drawn under sterile conditions from a bevacizumab infusion bottle. The lid was prepared with povidone-iodine 5% applied directly to the eye, and bevacizumab was injected into the anterior vitreous 3.5 mm 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. A cotton-tipped applicator was applied at the injection site immediately after the removal of the needle to prevent reflux. Indirect ophthalmoscopy was used to confirm the central retinal artery perfusion. Topical Ciprofloxacin drops were applied four times daily for 1 week.

The eyes were examined after 1 week and every 4 weeks. Response to the treatment was monitored by VA assessment, FFA, and OCT. Potential drug or injection-related complications were also recorded, if present. Patients received reinjection when there was a recurrence of DME, and the recurrence was considered when there was a decrease in BCVA associated with an increase of intraretinal fluid due to macular edema on FFA and/or OCT.

The analysis of macular edema was performed using the OCT Macular edema module. Edema map value of OCT was used to evaluate the changes at the macula after bevacizumab injection.

Statistical Analysis

Results are presented as means ± SD. Statistical evaluation of the data was performed with two-way ANOVA. The difference was considered statistically significant when *P*-value was lower than 0.05.

Results

All patients had clinically significant macular edema according to the ETDRS classification at the baseline examination and completed 12 weeks of follow-up. All these patients had had prior scatter photocoagulation at least 6 months before injection. Twenty cases received a second (50%) intravitreal injection of bevacizumab, and four (10%) needed a third injection. The mean VAs, edema map values, and intraocular pressures (IOPs) of the patients before and after intravitreal bevacizumab injection are presented in Table 1. There were statistically significant differences in VA after bevacizumab injection when compared with pretreatment values (for each, $P<0.001$). After a mean follow-up period of 5.6 months, VA increased in 30 of 40 eyes with a mean of 2.4±1.6, 2.7±1.9 and 2.8±2.0 Snellen lines at the 1-, 3-month, and last visit follow-up intervals, respectively. VA remained unchanged in five eyes, and decreased in one eye and showed increased fluorescein leakage on FFA.

Twenty-seven eyes showed a reduction in macular edema map value after intravitreal bevacizumab injection. Mean edema map value decreased from a baseline value of 2.4 ± 0.6 to a value of 1.6 ± 0.4 at the last visit control examinations. Mean reduction of edema map values at 1-, 3-month, and last visit was 29.1, 29.1, and 33.3%, respectively and the differences were statistically significant when compared with preinjection values (for each, $P<0.001$).

Average IOP values at 1-, 3-month, and last visit were not statistically significant when compared with preinjection values. Mild anterior chamber cellular reaction was observed in four eyes (13.3%), but the inflammation resolved within a week with topical corticosteroid. No other injection- or drug-related complications were observed.

Discussion

DME is the most important cause of VA impairment in patients with diabetes mellitus and may be localized or diffused. The prognosis of diffused macular edema is poorer when compared with focal edema. Although the exact pathophysiologic mechanism responsible for DME remain uncertain, the disruption of the inner blood-retinal barrier is known to be associated with metabolic alterations affecting the retinal epithelium or retinal vascular endothelium [10, 11]. The ETDRS demonstrated the beneficial effect of laser photocoagulation on preventing visual loss in eyes with diffuse DME. However, macular edema may persist in some eyes despite laser treatment. Reported injection-related complications include endophthalmitis, lens injuries, vitreous hemorrhage, and retinal detachment [12-15].

VEGF plays an important role in breakdown of the blood-retina barrier with increased vascular permeability resulting in retinal edema. Therefore, anti-VEGF therapy may be a promising treatment option for ocular neovascularization and DME. Intravitreal injection of pegaptanib (anti-VEGF aptamer) has recently demonstrated promising results for DME. Cunningham *et al* reported that patients who had underwent intravitreal injection of pegaptanib had better VA outcomes with reduction in central retinal thickness and less additional therapy with laser photocoagulation [16]. More recently, intravitreal bevacizumab has been used to reduce the breakdown of the inner blood-retinal barrier, extravasation from leaking blood vessels, and inhibition of neovascularization. They inhibit the release of VEGF, contribute to the integrity of the inner blood-retinal barrier, reduce extravasation from leaking blood vessels, and have beneficial effect in the prevention and treatment of macular edema. The safety of intravitreal bevacizumab has been confirmed by previous animal studies and human trials, and intravitreal injection of bevacizumab has recently been reported to be effective in macular edema of various etiologies [17-19].

Results of our study suggest that intravitreal bevacizumab injection appears to be effective in the primary treatment of DME. In our study, 30 eyes showed an improvement in VA with a decrease in fluorescein leakage on FFA. Edema map values of OCT showed a reduction in 27 eyes. The results of our study confirm previous reports showing the beneficial effect of intravitreal bevacizumab in the treatment of DME. In a recent study with an intravitreal injection of 1.25 mg

bevacizumab, Haritoglou *et al.,* [20] reported an improvement in VA from a baseline value of 0.86 logMAR to a value of 0.75 logMAR after 6 weeks of injection in patients with DME who did not respond to other treatments such as photocoagulation, IVTA injection, or vitrectomy. An increase in VA of at least three lines was observed in 15 of 51 eyes at a 6-week follow-up, and in 6 of 23 eyes completing 12 weeks of follow-up. Mean reduction in central macular thickness was 16.9% at 6 weeks, 24.75% at 12 weeks after the injection. In this study, VA increased with a mean of 2.4, 2.7, and 2.8 Snellen lines at 1-, 3-month, and last visit follow-up intervals, respectively. This high success in our study may be explained by performing intravitreal bevacizumab injection as the primary treatment of DME or a short duration of DME in our patients or using of 2.5 mg of bevacizumab.

After intravitreal bevacizumab injection, complications such as anterior chamber inflammation, endophthalmitis, vitreous hemorrhage, subconjunctival hemorrhage, and retinal detachment may occur. In our study, four eyes developed mild anterior segment inflammation, which completely resolved in a week after topical application of corticosteroids. No other complications were observed during the follow-up period.

This study has some differences from previous studies. Macular edema was evaluated by OCT before and after bevacizumab injection, and reduction in edema map values was demonstrated as the effectiveness of bevacizumab application. This study has several limitations. First, the follow-up time was relatively short, but visual and anatomical responses were apparent during the follow-up time. Second, there is no control group in this study, but it can be argued that the enrolled eyes serve as their own controls because the pre-and post-treatment VAs and edema map values of the same patients were compared. Third, VA was measured on a Snellen 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.

In conclusion, this study demonstrated that intravitreal bevacizumab application is an effective approach with promising results for the primary treatment of DME. Intravitreal bevacizumab provides significant resolution of macular edema and improvement in VA. However, further studies are needed to obtain the long-term results of such application.

Conflict of Interest

The authors declare that there are no conflict of interests.

Authors' Contribution

IY: collected, interpreted and analysed clinical data.

AM: Performed literature search, carried out the study and prepared draft and manuscript.

SD: designed the study, helped with analysis and interpretation of the data.

AM: collection, interpretation and evaluation of pathological data.

Ethical Considerations

The study was approved by the Institute Ethics Committee and written informed consent was taken from all patients.

Funding

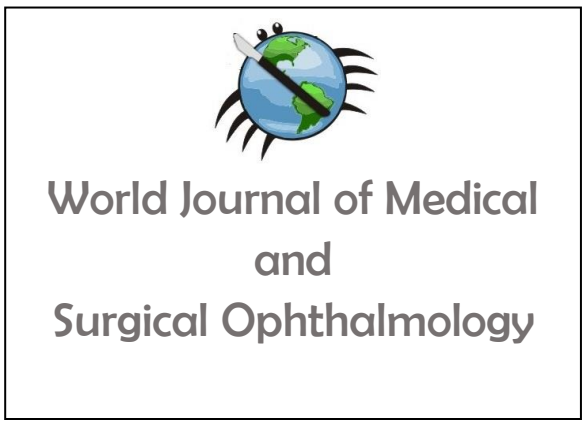
None declared

References

1. Pelzek C, Lim JI. Diabetic macular edema: review and update. *Ophthalmol Clin North Am* 2002; 15: 555-563.[Pubmed]
2. Antcliff RJ, Marshall J. The pathogenesis of edema in diabetic maculopathy. *Semin Ophthalmol* 1999; 14: 223-232.[Pubmed]
3. Ciulla TA, Amador AG, Zinman B. Diabetic retinopathy and diabetic macular edema: pathophysiology, screening, and novel therapies. *Diabetes Care* 2003; 26: 2653-2664.[Pubmed]
4. Ozkiris A, Evereklioglu C, Oner A, Erkilic K. Pattern electroretinogram for monitoring the efficacy of intravitreal triamcinolone injection in diabetic macular edema. *Doc Ophthalmol* 2004; 109: 139-145.[Pubmed]
5. Ozkiris A, Evereklioglu C, Erkilic K, Tamcelik N, Mirza E. Intravitreal triamcinolone acetonide injection as primary treatment for diabetic macular edema. *Eur J Ophthalmol* 2004; 14: 543-549.[Pubmed]
6. Ozkiris A, Erkilic K, Koc A, Mistik S. Effect of atorvastatin on ocular blood flow velocities in patients with diabetic retinopathy. *Br J Ophthalmol* 2007; 91: 69-73.[Pubmed]
7. Early Treatment Diabetic Retinopathy Study Research Group. Treatment techniques and clinical guidelines for photocoagulation of diabetic macular edema. Early Treatment Diabetic Retinopathy Study Report Number 2. *Ophthalmology* 1987; 94: 761-774.[Pubmed]
8. Jonas JB, Kamppeter BA, Harder B, Vossmerbaeumer U, Sauder G, Spandau UH. Intravitreal triamcinolone acetonide for diabetic macular edema: a prospective, randomized study. *J Ocul Pharmacol Ther* 2006; 22: 200-207.[Pubmed]
9. Martidis A, Duker JS, Greenberg PB, Rogers AH, Puliafito CA, Reichel E *et al*. Intravitreal triamcinolone for refractory diabetic macular edema. *Ophthalmology* 2002; 109: 920-927.[Pubmed]
10. Otani T, Kishi S. A controlled study of vitrectomy for diabetic macular edema. *Am J Ophthalmol* 2002; 134: 214-229?[Pubmed]
11. Yamamoto T, Akabane N, Takeuchi S. Vitrectomy for diabetic macular edema: the role of posterior vitreous detachment and epimacular membrane. *Am J Ophthalmol* 2001; 132: 369-377.[Pubmed]
12. Aiello LP. The potential role of PKC beta in diabetic retinopathy and macular edema. *Surv Ophthalmol* 2002; 47: S263-S269.[Pubmed]
13. Nguyen QD, Tatlipinar S, Shah SM, Haller JA, Quinlan E, Sung J *et al*. Vascular endothelial growth factor is a critical stimulus for diabetic macular edema. *Am J Ophthalmol* 2006; 142: 961-969.[Pubmed]
14. Presta LG, Chen H, O'Connor SJ, Chisholm V, Meng YG, Krummen L *et al*. Humanization of an anti-vascular endothelial growth factor monoclonal antibody for the therapy of solid tumors and other disorders. *Cancer Res* 1997; 57: 4593-4599.[Pubmed]
15. Chen Y, Wiesmann C, Fuh G, Li B, Christinger HW, McKay P *et al*. Selection and analysis of an optimized anti-VEGF antibody: crystal structure of an affinity-matured Fab in complex with antigen. *J Mol Biol* 1999; 293: 865-881.[Pubmed]
16. Yoganathan P, Deramo VA, Lai JC, Tibrewala RK, Fastenberg DM. Visual improvement following intravitreal bevacizumab (Avastin) in exudative age-related macular degeneration. *Retina* 2006; 26: 994-998.[Pubmed]
17. Iliev ME, Domig D, Wolf-Schnurrbursch U, Wolf S, Sarra GM. Intravitreal bevacizumab (Avastin) in the treatment of neovascular glaucoma. *Am J Ophthalmol* 2006; 142: 1054-1056.[Pubmed]
18. Oshima Y, Sakaguchi H, Gomi F, Tano Y. Regression of iris neovascularization after intravitreal injection of bevacizumab in patients with proliferative diabetic retinopathy. *Am J Ophthalmol* 2006; 142: 155-158.[Pubmed]

19. Jorge R, Costa RA, Calucci D, Cintra LP, Scott IU. Intravitreal bevacizumab (Avastin) for persistent new vessels in diabetic retinopathy (IBEPE study). *Retina* 2006; 26: 1006-1013.

20. Haritoglou C, Kook D, Neubauer A, Wolf A, Priglinger S, Strauss R *et al*. Intravitreal bevacizumab (Avastin) therapy for persistent diffuse diabetic macular edema. *Retina* 2006; 26: 999-1005.[Pubmed]



Published by Narain Publishers Pvt. Ltd. (NPPL)