Original Article

Intravitreal Bevacizumab (Avastin) for Primary Treatment of Diffuse Diabetic Macular Oedema

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Objective: To evaluate the effect of intravitreal Bevacizumab injection on visual acuity in diffuse diabetic macular oedema.

Material & Methods: 25 eyes of 25 diabetic patients were treated with 1.5 mg/0.1 ml of intravitreal bevacizumab injection as the primary therapy for diffuse diabetic macular oedema. This prospective study was conducted in Eye Unit I, SIMS/Services Hospital, Lahore over 6 months from November 2008 to April 2009. 17 patients were male and 08 were female, age ranged between 35 to 52 years. All patients were completely evaluated in out patient department of Eye Unit - I. Every patient underwent complete ophthalmological evaluation including history, record of visual acuity and IOP, slit lamp bi-microscopic examination, fundi assessment with 78 lens and indirect ophthalmoscope. Fundus fluorescein angiogram was done to exclude macular ischaemia and optical coherence tomography was done to evaluate the macular oedema. Intravitreal Avastin 1.5 mg/ 0.1 ml injection was given to these patients under complete aseptic techniques in operation theater after explaining the advantages and disadvantages of the intravitreal injection to the patients.

Results: Visual Acuity increased in 25 eyes during follow up time of six month; the mean best corrected log MAR value of visual acuities of the patients before intravitreal bevacizumab injection was 0.275 and it improved to 0.642 after intravitreal Bevacizumab injection. Diffuse macular oedema remarkably settled in these eyes. Intravitreal injection of Avastin was repeated in 10 patients; only one patient developed acute endophthalmitis which was treated with intravitreal antibiotic and pars plana vitrectomy with lensectomy.

Conclusion: Intravitreal bevacizumab injection provides significant improvement in visual acuity of diabetic patients and clinical course of diffuse macular oedema.

Keywords: Diabetic macular oedema, intravitreal bevacizumab; acute endophthalmitis; pars plana vitrectomy; visual acuity.

Introduction

Diabetic retinopathy remains a major threat to the vision in the working age population. It is increasing as a major cause of blindness in all parts of the world and macular oedema is the most common cause of visual impairment in diabetic patients. The exact pathogenesis of diabetic macular edema (DME) has not been elucidated, although a breakdown of the inner blood-retinal barrier seems to be a reasonable explanation. The important pathophysiology of DME is the loss of retinal capillary pericytes, resulting in increased vascular permeability.[1-3] The 3 year risk of moderate visual loss due to macular edema was 32% in the early treatment diabetic retinopathy study (ETDRS). Focal macular laser photocoagulation has been shown to be effective in the treatment of diffuse diabetic macular edema in a large prospective multicenter randomized clinical trail of ETDRS.[4] However, some treated eyes may be resistant to laser photocoagulation or efficient laser treatment could not be performed due to diffuse macular edema. Therefore, the failure of laser photocoagulation in these eyes has prompted interest in other treatment modalities, such as intravitreal triamcinolone acetonide (IVTA) injection,[4,5] pars plana vitrectomy, or treatment with protein kinase C inhibitors.[6]

Retinal hypoxia is the primary cause of diabetic retinopathy, which increases expression of vascular endothelial growth factor (VEGF). As known, VEGF is a potent inducer of vascular permeability that has been shown to cause leakage from retinal vessels and contribute to DME. Bevacizumab (Avastin, Genentech Inc., South San Francisco, CA, USA), a full length, humanized monoclonal antibody against VEGF also binds and inhibits all the biologically active forms of VEGF, and approved by the Food and Drug Administration for the treatment

of metastatic colorectal cancer.[7] Bevacizumab has been used for intravitreal injection in patients with choroidal and iris neovascularization, vitreous haemorrhage, and macular edema and shown to provide beneficial effects in such patients.[8]

Patients and Methods

This prospective study was conducted in Eye Unit I, Services Hospital, Lahore for the duration of six months from November 2008 to April 2009. During this period 25 patients were enrolled in this study, 17 were male and 8 females; the age ranged between 35-52 years. Their complete evaluation was done in out patient department including history, record of V/A and IOP measurement, slit lamp bimicroscopy, fundi examination with lens (78D) indirect ophthalmoscopy, optical coherence tomography (OCT). Fluorescein angiography was done to confirm the macular ischemia. Intravitreal Avastin injection 1.5 mg was given in 25 eyes using antiseptic technique in operation theater. On fluorescein angiography, all patients had diffuse macular edema with hyperfluorescent leakage.

Before intravitreal bevacizumab injection, 8 eyes had received peripheral scatter laser photocoagulation to ablate ischemic areas of neovascularization, but no eyes received any medical treatment for diffuse diabetic macular edema (DME). Intravitreal injection of bevacizumab 1.5 mg/0.1 ml was offered as the first treatment of DME and informed consent was obtained from each patient. Baseline parameters were documented including best corrected visual acuity (BCVA) using Snellen chart, fundus fluorescein angiography (FFA) and optical coherence tomography (OCT). The eyes were examined after 1 week and then every 4 weeks. Response to the treatment was monitored by V/A assessment, direct fundi examination, fundus fluorescein angiography and optical coherence tomography. Patients received re-injection when there was a recurrence of DME and recurrence was considered when there was a decrease in BCVA associated with an increase of intra-retinal fluid due to macular edema on fundus fluorescein angiography. Repeated injection of Avastin was given in 10 patients.

Results

Diabetic retinopathy is quite common problem in our population present study was planned to see the effects of treatment with intravitreal Bevacizumab injection in DME.

All patients had clinically significant macular edema according to the ETDRS classification at the baseline examination and completed 06 months of follow up. Age range was 46 to 65 years. Visual acuity was shown as log MAR value; before injection was given it was 0.1 to 0.3 (mean = 0.275) and after injection it was 0.25 to 0.5 (mean = 0.642). Eight patients had PDR, and all of these patients had prior scattered photo coagulation at least 3 months before injection. 05 eyes received a second intravitreal injection of bevacizumab and 5 needed a third injection.

Table-1: V/A before and after intravitreal Avastin injection in DME

Gender	Age	V/A before avastin injection	V/A after avastin injection
Male	45	0.1	0.3
Male	50	0.1	0.3
Male	45	0.1	0.3
Male	47	0.1	0.3
Female	52	0.1	0.3
Female	35	0.1	0.3
Female	37	0.1	0.25
Male	51	0.1	0.25
Male	40	0.1	0.25
Male	48	0.1	0.25
Female	50	0.1	0.25
Female	38	0.1	0.25

Male	40	0.1	0.25
Male	45	0.1	0.25
Male	43	0.1	0.25
Female	52	0.1	0.25
Male	46	0.1	0.25
Male	50	0.1	0.25
Female	45	0.3	0.25
Female	43	0.3	0.25
Male	48	0.3	0.5
Male	48	0.3	0.5
Male	45	0.3	0.5
Male	42	0.3	0.5
Male	49	0.3	0.5

V/A Visual Acuity

Discussion

Diabetic macular edema is the most important cause of VA impairment in patients with diabetes mellitus. It may be localized or diffused. The prognosis of diffused macular edema is poorer when compared with focal edema. Although the exact patho-physiologic mechanism responsible for DME remains 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.[1-2] The ETDRS[4] demonstrated the beneficial effects of laser photocoagulation on preventing visual loss in eyes with diffuse DME. However, macular edema may persist in some eyes in spite of laser treatment and IVTA injection. The treatment is not without risks, and complications can be attributed to the injection procedure or to the corticosteroid suspension. Reported injection-related complications include endophthalmitis, lens injuries, vitreous hemorrhage, and retinal detachment. Corticosteroid-associated adverse events include IOP elevation, cataract progression, pseudo-endophthalmitis, and pseudo-hypopyon. Moreover, the efficacy of IVTA is transient and repeated injections are required.[9]

VEGF plays an important role in breakdown of the blood-retinal barrier with increased vascular permeability resulting in retinal edema. Therefore, anti-VEGF therapy may be a promising treatment option for ocular neo-vascularization and DME. Intravitreal injection of pegaptanib (anti-VEGF aptamer) has recently demonstrated promising results for DME. Cunningham et al[10] 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 photo coagulation. 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 neo-vascularization. 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 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.[11]

Results of our study suggest that intravitreal bevacizumab injection appears to be effective in the primary treatment of DME. In our study, all the eyes showed an improvement in VA with a decrease in fluorescein leakage of FFA. The results of our study are consistent with previous reports showing the beneficial effects of intravitreal bevacizumab in the treatment of DME.[12] In a recent study with an intravitreal injection of 1.25mg bevacizumab, reported an improvement in VA from a baseline value of 0.86 log MAR to a value of 0.75 log MAR after 6 weeks of injection in patients with DME who did not

respond to other treatments such as photocoagulation, IVTA injection or vitrectomy. 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 1.5mg/0.1ml of bevacizumab. After intravitreal bevacizumab injection, only one patient developed acute endophthalmitis which was treated with intravitreal antibiotics and pars plana vitrectomy with lensectomy.

Conclusion

In conclusion, this study demonstrated that intravitreal bevacizumab application is an effective approach with good 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.

Intravitreal bevacizumab injection provides significant improvement in visual acuity of diabetic patients and clinical course of diffuse macular edema.

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