Original article

Evaluation of intravitreal injection of bevacizumab (Avastin) in treatment of diabetic macular edema

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BACKGROUND: Diabetic macular edema (DME) is the most common cause of reduced vision in diabetic patients. With regards to its prevalence and its severe morbidity, attention to new methods of treatment like anti-vascular endothelial growth factor (VEGF) therapy is of great importance. Therefore, this study aimed to evaluate the efficacy of intravitreal injection of bevacizumab (Avastin) in the treatment of diabetic macular edema. **METHODS:** This prospective clinical trial was conducted on patients with DME who referred to Feiz Hospital, Isfahan, Iran, during 2007-8. The subjects were selected using simple sampling method. Eligible patients underwent a complete ophthalmic examination including optical coherence tomography (OCT) before injection. The treatment was performed through 3 intravitreal injections of 1.25 mg Avastin. There was a 1-month interval between very two injections. A second OCT was obtained 4 weeks after the last injection and the changes in macular thickness were compared using statistical analyses. **RESULTS:** This study was conducted on 52 eyes of 28 patients (17 men and 11 women) with the mean age of 62.60 ± 7.80 years (range: 45-80 years). The mean macular thickness increased from 259.19 ± 75.9 microns before injections to 265.94 ± 109.40 after 3 injections (p = 0.48). In case to case comparisons, macular thickness reductions were observed in 31 cases from 2 to 74 microns (mean: 24.60 ± 20.85). In 21 cases on the other hand, macular thickness increased from 1 to 324 microns (mean: 52 ± 88.20). Macular thickness before injection was 261.22 ± 77.79 microns in men and 255.95 ± 74.67 in women (p = 0.81). After injections, the values changed to 276.44 ± 122.79 microns in men and 249.15 ± 83.94 in women (p = 0.34). **CONCLUSIONS:** Intravitreal Avastin is not effective in reducing macular thickness after 4 weeks of injection. In contrast, according to other studies, it seems to be temporarily effective. Therefore, it is better to be combined with other routes of therapy, e.g. laser and intravitreal steroid, in the management of DME.

KEYWORDS: Avastin, Bevacizumab, Intravitreal Injection, Diabetes Mellitus, Diabetic Macular Edema, Optical Coherence ToMography

BACKGROUND

Diabetic macular edema (DME) is the most common cause of visual impairment in patients with diabetes mellitus. It affects approximately 75,000 new patients in the United States every year.[1] Several features of vascular endothelial growth factor (VEGF) make it a plausible mediator of retinal neovascularization and vascular permeability in ocular ischemic conditions. It is produced by numerous types of ocular cells. On the other hand, retinal endothelial cells express abundant VEGF receptors. In addition, VEGF expression is markedly increased in response to hypoxia, and VEGF is a potent inducer of vascular permeability. Furthermore, VEGF levels correlate closely with active intraocular neovascularization and very high intraocular levels in patients with proliferative diabetic retinopathy decline after successful laser photocoagulation.[2] These observations have led to the hypothesis that antiangiogenic agents could be used to inhibit the development of proliferative retinopathy, much like their use in cancer, which was originally proposed by Folkman more than 30 years ago.[3] There has been interest in finding other treatments for DME, particularly central edema, in an effort to improve the ability to regain vision. Laser treatment has the potential to cause vision loss from inadvertent foveal burns or spread of laser scars over time. This survey evaluated the efficacy of intravitreal Avastin in treatment of DME.

METHODS

This was a prospective clinical trial on patients with clinically significant diabetic macular edema who referred to the ophthalmology clinic in Feiz Eye Hospital (Isfahan, Iran). Patients were excluded if they had uncontrolled hypertension, a history of myocardial infarction or stroke in the last 3 months (considering the side effects of systemic Avastin), or any types of medial opacity, e.g. cataract, or vitreous hemorrhage, due to drug injection or due to a background disease. In addition, patients who developed endophthalmitis or glaucoma during the

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study, those who needed surgery for any reason, e.g. retinal detachment or macular traction, and subjects who had or developed macular holes were also excluded.Moreover, patients were only evaluated if they were willing to.

Simple sampling method was used to select all patients with DME who referred to Feiz Eye Hospital. All eligible patients with DME were included and provided with explanations about the method and probable adverse effects and results of injection and also other methods of therapy and their results. The patients then signed an informed consent. Before injection, a full ophthalmic examination was performed by an ophthalmologist and the results as well as the individual data were recorded in special forms. Fundus photography and optical coherence tomography (OCT) were conducted for each patient and the results were recorded. Visual acuity was measured with standard Snellen charts in the distance of 6 meters. The results were then converted to LogMAR measurements for ease of calculation. Clinically significant macular edema was diagnosed using slit lamp ophthalmoscopy with a noncontact 78 D lens upon the standard definition. OCT was performed with an OTI instrument (Canada). Considering the high price of the drug, each vial was used for 25 patients. Preparing ampoules from the vials was performed under sterile conditions. Avastin was made in Gentec Company (USA).

In the operating room, the patient was prepared for intravitreal injection. Prepping and draping were done with Betadine 10%. In addition, a single drop of Betadine was instilled in the lower fornix and after 5 minutes, the fornices and the ocular surface were irrigated with balanced salt solution (BSS). A topical sterile anesthetic (tetracaine 5%) was then applied. The lids were kept open with a lid speculum. Afterwards, 0.125 ml (1.25 mg) of the Avastin solution (10 mg/ml) was injected into the vitreous body at the pars plana (the distance from limbus is 4 mm in phakic and 3 mm in aphakic or psuedophakic patients). The amount of the injected drug has been selected according to previous similar studies. After manual checking, if the intraocular pressure was high, fluid tap, with an amount less than or equal to the injected volume, was performed from the anterior chamber or the vitreous (according to surgeon's decision). A single drop of topical antibiotic was then instilled and the eyes were patched. The patients were prescribed with the antibiotics and corticosteroid drops for 10 days and discharged. The patients were visited on the next day and after 1 week. They were advised to refer quickly to the emergency room in case of symptoms of endophthalmitis such as pain, redness, and vision loss. In addition, 2 more injections were performed with a similar method (resulting in a total of 3 injections) and the examination results in the 1st, 2nd, and 3rd months were recorded. At the end of the third month, i.e. 1 month after the last injection, an OCT was performed. After the completion of the examination forms, the collected data was analyzed in SPSS15 (SPSS Inc., Chicago, IL, USA).

RESULTS

This was a prospective clinical trial on 52 eyes of 28 patients including 17 males (32 eyes) and 11 females (20 eyes). The mean age of participants was 62.60 ± 7.80 years (range: 45-80 years). Overall, 24 right eyes and 28 left eyes were treated. The mean macular thickness before injection was 259.19 ± 75.9 microns (range: 168-595 microns). It increased to 265.94 ± 109.40 microns (range: 170-700 microns) after 3 injections. Paired t-test did not show any significant differences between the two values (p = 0.48). In the case to case comparison, there was macular thickness reduction of 2-74 microns (mean = 24.60 ± 20.85 microns) in 31 cases. However, in 21 cases, macular thickness increased from 1 to 324 microns (mean = 52 ± 88.20 microns). Macular thickness before injection was 261.22 ± 77.79 microns in men and 255.95 ± 74.67 microns in women (p = 0.81). After injection, these values changed to 276.44 ± 122.79 and 249.15 ± 83.94 microns in men and women, respectively (p = 0.34). (Table 1).

DISCUSSION

DME remains the most common cause of reduced vision in diabetic patients. About one in every four diabetic patients can be expected to develop diabetic DME during their course of life[4,5] and this puts the visual acuity at risk. The treatment of DME has developed over the last 30 years. Focal or grid macular photocoagulation was established as an effective treatment in the 1980s and has remained the gold standard and the treatment of first choice.[6] Additional treatment

Table 1. Macular thickness (in microns) before and after injection stratified based on gender

	Before injection	After injection	p
Male	261.22 ± 77.79	276.44 ± 122.79	0.81
Female	255.95 ± 74.67	249.15 ± 83.94	0.34
Total	259.19 ± 75.90	265.94 ± 109.40	0.48

modalities, including intravitreal steroids and antibodies for VEGF, have emerged in recent years and have shown themselves to be effective. In this survey, we assessed the effects of Avastin on macular thickness in patients with DME. As it has been shown in the previous part, Avastin did not cause any significant changes in macular thickness 4 weeks after the last injection. This result is in contrast with some similar studies reporting the effectiveness of intravitreal Avastin in DME.[7,8] This difference may be due to our small sample size (we might have found different results if we had a larger sample size) and the time between the last injection and OCT (4 weeks). Nagasawa et al. showed a marked reduction of macular edema soon after the injection (within 1 week). However, macular edema recurred after 4 weeks.[9] A study on retinal penetration revealed the absence of bevacizumab (Avastin) 4 weeks after the injection which may suggest its limited effect on suppression of VEGF activity.[10] If this is true, it means that the injection should be repeated every 3 to 4 weeks. Seo and Park stated that intravitreal injection of bevacizumab resulted in significant improvements of best-corrected visual acuity (BCVA) and central retinal thickness as early as 1 week after injection in patients with DME. This beneficial effect persisted for up to 3 months. However, the slight reduction in this improvement at 3 months suggested that repeated bevacizumab injections might be necessary.[11] Soheilian et al. reported significant central macular thickness reduction in the eyes of patients injected with Avastin and Avastin/triamcinolone only up to 6 weeks after treatment. However, the differences between the two groups were not significant.[12] Similar to our results, one study on diffuse macular edema revealed that initial treatment results of patients with diffuse DME not responding to previous photocoagulation did not reveal any short-term safety concerns. Intravitreal bevacizumab caused a significant decrease in macular thickness and improvement in visual acuity at three months, but the effects were somewhat blunted, though still statistically significant, at the end of six months.[13] Another series of 11 eyes previously vitrectomized for DME did not show any visual acuity or macular thickness improvement after treatment with intravitreal bevacizumab.[14] The lack of improvement could be a result of permanent photoreceptor damage from the duration of disease or from extensive previous treatments. In our small, retrospective study, there were no changes in visual acuity and foveal thickness in the short after intravitreal bevacizumab for DME in previously vitrectomized eyes. This may be attributable to rapid clearance of intravitreal bevacizumab from the vitreous cavity and thus insufficient sustained therapeutic levels in vitrectomized eyes. It may also be attributable to individual systemic factors that may affect macular edema such as type and glycemic control of diabetes, age, blood pressure, serum lipid levels, and nephropathy. In addition, it is not known whether or not continued injections for six to 12 months could improve the outcomes.

Finally, it seems that Avastin may be useful for DME at least in a short period. However, its effect is temporary and needs booster doses. The authors think that the best approach to the treatment of DME is a combination of medical therapy, laser therapy, intravitreal steroid, and intravitreal Avastin and not merely a single route.

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