THE USE OF AVASTIN (BECACIZUMAB) FOR THE TREATMENT OF DIABETIC MACULAR EDEMA IN IRAQI PATIENTS

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ABSTRACT

Purpose: To evaluate the effect of intravitreal bevacizumab on visual acuity in patients with diabetic maculopathy, clinically significant macular edema (CSME).

Methods: Thirty eyes of twenty-eight patients (mean age, 57.9±13.8 years) with CSME were included in this study. Complete ophthalmic examination, including determination of best corrected visual acuity (BCVA), stereoscopic biomicroscopy with +90D lens was done at baseline and at each follow-up visit. All patients were treated with a 0.1 mL intravitreal injection containing 2.5 mg of bevacizumab (Avastin).

Results: All patients completed 3 months of follow-up with a mean follow-up period of 5.26±2.39 months. The mean BCVA at baseline was 0.73±0.36 logMAR, which significantly improved to 0.63±0.41 (p=0.02), 0.58±0.36 (p=0.003), and 0.61±0.40 logMAR (p=0.006) at 1 week, 1month, and 3 months. Final BCVA analysis demonstrated that 15 eyes (50%) remained stable and 12 (40%) improved ≥2 lines on BCVA. No ocular toxicity or significant side effects were observed.

Conclusions: Intravitreal bevacizumab injection resulted in significant improvement in BCVA as early as 1 week after injection in patients with CSME, and this beneficial effect persisted for up to 3 months. However, the slight reduction in this improvement at 3 months suggests that repeated bevacizumab injections might be necessary. To evaluate the long-term safety and efficacy, further prospective randomized controlled clinical trials will be needed.

INTRODUCTION

Diabetic maculopathy, clinically significant macular edema (CSME) is the leading cause of visual loss in patients with diabetes mellitus, and it frequently leads to irreversible changes in visual acuity.1 Macular Edema is caused by excessive vascular permeability, which leads to leakage of fluid and plasma constituents, such as lipoproteins, into the retina. This then causes retinal thickening. The Early Treatment Diabetic Retinopathy Study (ETDRS) showed that focal laser photocoagulation is beneficial in the treatment of clinically significant macular edema, reducing the rate of moderate visual loss by 50%.2 However, only 3% of patients improve by ≥3 lines of vision by the end of the study. Intravitreal triamcinolone acetonide (IVTA) injection has proven effective in improving vision and reducing macular thickness in CSME, both as an initial treatment and as a second line therapy

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after unsuccessful laser therapy.3,4 However, its effect is temporary, and a number of side effects, like transient ocular hypertension and even glaucoma have been reported.5,6 Consequently, its therapeutic value remains unclear. Vascular endothelial growth factor (VEGF) has been implicated as an important factor in the breakdown of the blood retina barrier, with increased vascular permeability resulting in retinal edema in diabetic patients through affecting endothelial tight junction proteins.7 While the normal human retina contains VEGF, hypoxia stimulates the secretion of VEGF from retinal pigment epithelial cells.8,9 VEGF levels are significantly elevated in eyes with CSME.10,11 In addition,VEGF concentrations are significantly higher in eyes with extensive macular leakage when compared to eyes with minimal leakage.11 Therefore anti-VEGF treatments have been proposed as an alternative or adjunctive treatment for triamcinolone acetonide for CSME.12 Bevacizumab (Avastin) is a complete full-length humanized antibody that binds to all subtypes of VEGF; it has been used successfully as a systemic drug in tumor therapy.13 Recent studies have demonstrated the usefulness of intravitreal injections of bevacizumab in the reduction of macular edema secondary to central retinal vein occlusion, vascular permeability , fibrovascular proliferation in retinal neovascularization secondary to proliferative diabetic retinopathy (PDR), and choroidal neovascularization secondary to age-related macular degeneration (AMD).14-17The purpose of this retrospective study was to evaluate the effect of intravitreal bevacizumab on visual acuity in patients with CSME in view of lack of studies of the effectiveness of the use of anti-VEGF in the treatment of different ocular pathologies.

Materials and Methods

The present study was designed as a retrospective, consecutive case series study of eyes with CSME treated intravitreal bevacizumab (Avastin) between February 2008 and December 2009. It included 28 patients (30 eyes) with CSME treated with intravitreal injection of 2.5 mg (0.1 ml) of bevacizumab. The inclusion criteria for the study eye included (1) decrease in best-corrected visual acuity (BCVA) ≤20/40, (2) clinically definite retinal thickening due to CSME involving the center of the macula, and (4) no history of treatment for CSME within the prior3 months.

Exclusion criteria included macular edema due to a cause other than diabetes, other ocular condition that might affect macular edema or alter visual acuity. Each patient underwent a complete eye examination,including determination of BCVA, slit-lamp examination,intraocular pressure (IOP) measurement, stereoscopic biomicroscopy of the retina using a +90-diopter lens, at baseline and at each visit. Patients were examined at 1 week and 1 month after injection, and then at 1- or 2-month intervals. Each patient's BCVA was transferred to a logarithm of the minimum angle of resolution (logMAR) scale for analysis. Topical anesthesia was induced by applying proparacaine(0.5%) eye drops before injection. The conjunctiva bulbi and the fornices were repeatedly rinsed with povidone-iodine, which was also applied to the eyelid margins and the lashes to avoid expression of the meibomian glands. After application of a sterile drape, a 30-gauge needle on a 1 mL syringe was used to inject bevacizumab intravitreally through the pars plana 3.5 to 4.0 mm posterior to the limbus, at a dose of 2.5 mg in 0.1 mL. The needle was carefully removed using non-toothed forceps to prevent reflux. After injection, antibiotic eye drops (Ciprofloxacin) were applied four times per day for 3 days. All patients provided written informed consent,

explaining its potential risks and benefits, as well as the likelihood that additional treatments might be required. The paired *t*-test was used for comparison of preoperative and postoperative BCVA. For all statistical tests, a *p* value <0.05 was considered statistically significant. The data were analyzed using statistical software (SPSS, version 12.0)

Results

Thirty eyes (28 patients) with a minimum of 3 months follow-up were included for analysis. The mean patient age was 57.9±13.8 years, and 60% were male (18 men, 12 women).

All patients completed 3 months of follow-up, with a mean follow-up period of 5.26±2.39 months (range, 3-11 months). Type 2 diabetes was present in 83.3% of patients, and type 1diabetes was present in 16.7% of patients. Eighteen eyes (60%) exhibited proliferative diabetic retinopathy (PDR), and twelve exhibited severe nonproliferative diabetic retinopathy (NPDR). Twenty-five eyes (83.3%) had received at least one alternative therapy before intravitreal bevacizumab injection. Focal laser therapy had been applied once in 4 eyes and more than twice in 4 eyes. Full scatter panretinal laser therapy had been performed on 15 eyes (50%), and 6 eyes (20%) had undergone pars plana vitrectomy. Previous intravitreal injection of triamcinolone acetonide had been performed on 4 eyes at least 3 months before undergoing intravitreal bevacizumab injection. Additional baseline characteristics by treatment group are shown in Table 1. Improvements in visual acuity were noted from 1 week after intravitreal bevacizumab injection, and these statistically significant changes continued throughout the 3-month follow up visit (Fig. 1). At baseline, the mean BCVA was 0.73±0.36logMAR. This improved significantly to 0.63±0.41 (*p*=0.02),0.58±0.36 (*p*=0.003), and 0.61±0.40 logMAR (*p*=0.006) at1 week, 1 month, and 3 months, respectively. At 3-month follow-up, the BCVA was slightly decreased, but there was no significant difference in the mean BCVA between the 1-and 3-month follow-up visits (*p*=0.536). The visual acuity results are summarized in Figure 2. Final BCVA analysis by subgroup demonstrated that 15 (50%) of 30 eyes remained stable, 12 (40%) improved ≥2 lines on BCVA, and 3 (10%) deteriorated ≥2 lines on BCVA (Table 2). Regarding the reported side effects in the enrolled cases, there were no cases of endophthalmitis, uveitis, IOP increase, or severe decrease in vision immediately after injection.Common side effects were a subconjunctival hemorrhage and ocular discomfort at injection site. At 3 months follow up, no ocular or systemic adverse events were reported, including thromboembolic events (cerebrovascular accidents, transient ischemic attacks, myocardial infarctions, or peripheral vascular disease).

Discussion

CSME is a manifestation of diabetic retinopathy that produces severe visual impairment. Although several treatment modalities are tried, the only demonstrated means to reduce the risk of vision loss from CSME are laser photocoagulation, as demonstrated by the ETDRS2; intensive glycemic control, as demonstrated by the Diabetes Control and Complications Trial and the United Kingdom Prospective Diabetes Study; and blood pressure control, as demonstrated by the United Kingdom Prospective Diabetes Study.18,19 However, there has been interest in other treatment modalities, such as pharmacologic therapy with oral protein kinase C inhibitors and the use of intravitreal corticosteroids, because most laser-treated CSME eyes do not exhibit satisfactory improvements in VA.20,21 Antibodies targeted to VEGF have also generated considerable interest and are being

investigated. VEGF is an endothelial cell-specific mitogen and angiogenic inducer in a variety of *in vitro* and *in vivo* models.22 It is upregulated by hypoxia, and it plays a role in CSME and contributes to the excessive vascular permeability that leads to macular edema in diabetic patients. Bevacizumab is a full-length humanized monoclonal antibody that binds and inhibits all biologically active isoforms of VEGF. Although preclinical experimental data from primates suggested that the full-length antibody might not penetrate the internal limiting membrane of the retina, recent studies have shown full-thickness penetration of the retina within 24 hours.23,24 It seems that all clinical and experimental studies presented thus far have not noted drug-related toxic effects in any retinal structure.14-17,25-30 Intravitreal injection of bevacizumab appears to have good efficacy in the treatment of wet AMD as a new treatment option. Injection of bevacizumab into the vitreous cavity, as is presently done mostly for patients with AMD, is based on the results of clinical reports clearly indicating an increase in visual acuity and a decrease in retinal thickness.15,16,27 Recently, Avastin was used in a prospective, noncomparative case series of patients with CSME treated with 1.25 mg bevacizumab.The mean visual acuity improved significantly at 6 weeks (p=0.02), this was not sustained at 12 weeks (Haritoglou et al.28). In the present study, however, I found that significant improvement in visual acuity was achieved soon after intravitreal bevacizumab injection, and the beneficial effects lasted for 3 months. The mean BCVA improved from0.73±0.36 logMAR at baseline to 0.63±0.41 logMAR at 1-week follow-up (p=0.02), At 1 month after the injection of bevacizumab, this beneficial effect appeared to be most prominent in the current study. Thirteen (43%) of 30 eyes showed an improvementin BCVA by 2 or more lines, and only 1 eye (3%)decreased ≥2 lines on BCVA at 1-month follow-up. Although the duration of action of intravitreal bevacizumab is unknown, recent electrophysiologicand retinal penetration studies have reported that full thickness retinal penetration is present at 24 hours.24 This may explain the earlier clinical effects of intravitreal bevacizumabobserved in the current study. In this study, the improvement of BCVA were observed at 1 week, and these results were maintained for up to 3 months. However, at 3-month follow-up, a slight decrease in visual acuity was observed as compared with the 1-month follow-up. This slight reduction in the improvement of visual acuity 3-month follow-up suggests that repeated intravitreal bevacizumab injections may be necessary within 3 months to maintain a beneficial effect. The present study demonstrates a comparable population of PDR and NPDR patients with macular edema. The results of the present study indicate that intravitreal bevacizumab injections may have a beneficial effect on visual acuity, independent of the type of diabetic retinopathy. In addition, previous treatments, such as focal laser treatment, panretinal photocoagulation, or IVTA injection, did not influence the results of the study. In conclusion, intravitreal bevacizumab injection appears to result in significant improvement in BCVA as early as 1 week after injection, and this beneficial effect was shown to persist for up to 3months. However, the slight reduction in improvement in visual acuity at 3-month follow up suggests that repeated bevacizumab injections might be necessary within 3 months to maintain its effect, as the drug is well tolerated and there are no safety concerns. To evaluate the long-term safety and efficacy of this new treatment, further prospective randomized controlled clinical trials will be needed.

Table 1. Baseline characteristics of the study eyes

Variables		
Gender, male:female		18:12
Age (years)		57.9±13.8
Diabetes type		1:2 5:25
duration (years)		15.9±7.6
Hypertension		10
Stage of retinopathy, severe NPDR* : PDR†		12:18
Preoperative treatment,	focal laser treatment	8
	panretinal photocoagulation	15
	intravitreal injection of triamcinolone	4
	pars plana vitrectomy	6
Mean follow-up period (months)		5.26±2.39
Baseline visual acuity (logMAR)		0.73±0.36

- * NPDR=noproliferative diabetic retinopathy;
- † PDR=proliferative diabetic retinopathy.

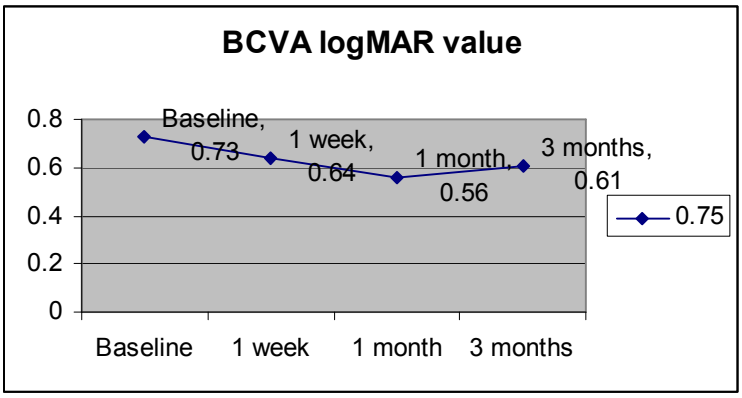

Fig. 1. Changes in best-corrected visual acuity (BCVA) after intravitreal bevacizumab injection.

Table 2. Best-corrected visual acuity (BCVA) analysis

	First Week		First Month		hird Month	
	No. of Eyes	%	No. of Eyes	%	No. of Eyes	%
Decreased ≥2 lines of BCVA	2	7%	1	3%	3	10%
Remained stable	17	57%	16	53%	15	50%
Improved ≥2 lines of BCVA	11	37%	13	43%	12	40%

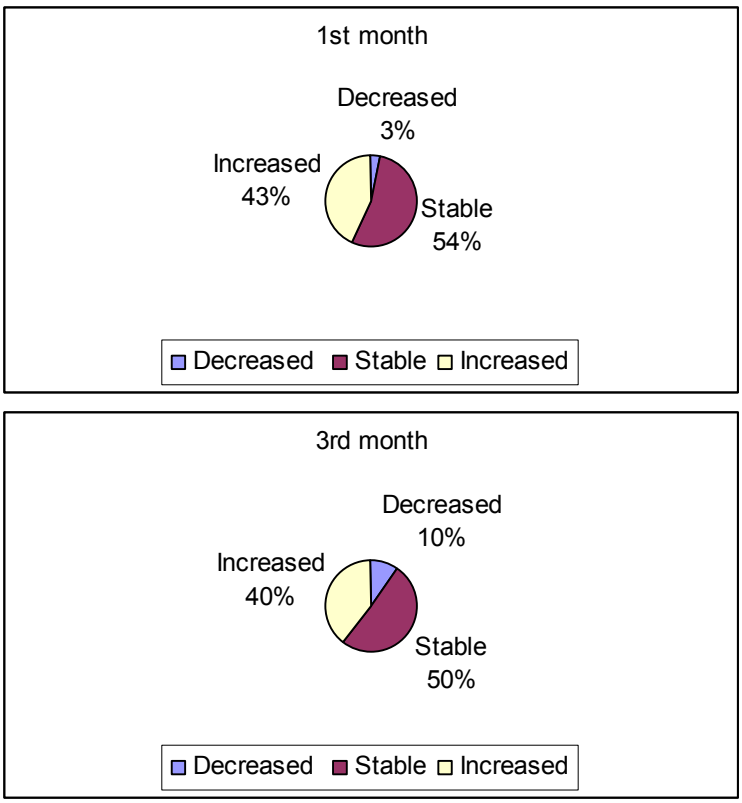

Fig. 2. Development of visual acuity (logMAR) evaluated after 1 month (A) and 3 months (B) of follow-up.

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دراسة استخدام الافاستين (بيفاسيزوماب) لعلاج وذمة الشائبة الصفراء للشبكية السكرية عند المرضى العراقيين

الباحث د. صلاح زهير الأسدي*

هدف الدراسة:
تقييم فعالية استخدام مادة الأفاستين بالزرق داخل الجسم الزجاجي على حدة الابصار لعلاج مرضى وذمة الشائبة الصفراءللشبكية
الطرق:
شملت الدراسة ثلاثين عين لثمانية و عشرون مريضا (معدل العمر ٥٧،٩ ±١٣،٨ سنة) يعانون من وذمة الشائبة الصفراء للشبكية السكرية تم الفحص العيني الكامل للمرضى ويشمل قياس حدة الأبصار و فحص الشبكية ثلاثي الأبعاد بالعدسة +٩٠ في الفحص الأولي و زيارات المتابعة اللاحقة، تم علاج المرضى بحقن ٠،١ مل تحتوي ٢،٥ ملغ من مادة الأفاستين داخل السائل الزجاجي تحت التخدير الموضعي بأستخدام قطرة (بروباراكايين ٠،٥%)
النتائج:
أكمل جميع المرضى فترة ٣ اشهر من المتابعة مع معدل فترة متابعة ٥،٢٦± ٢،٣٩ شهر. معدل حدةالأبصار كان ٠،٧٣±٠،٣٦logMAR الذي تحسن بشكل جيد الى ٠،٦٣± ٠،٤١ (p=0,02) ، ٠،٥٨± ٠،٣٦ (p=0,003) و ٠،٦١±٠،٤٠ (p=0,006) خلال الأسبوع الأول، الشهر الأول و الشهر الثالث.
التحليل النهائي لحدة الأبصار أوضح أن ٢٠ عينا (٥٠%) بقيت حدة الأبصار ثابتة و تحسنت في ١٢ (٤٠%) عين لأكثر من خط على لوحة الفحص.
لم يلاحظ مضاعفات جانبية او سمّية مهمة للعلاج اثناء الدراسة .
الأستنتاجات:
العلاج بحقن الأفاستين داخل السائل الزجاجي أدى الى تحسن حدة الأبصار مبكرا من الأسبوع الأول عند مرضى وذمة الشائبة الصفراء وهذا الأثر الأيجابي أستمر الى ٣ أشهر من المتابعة، لكن الزوال البسيط لهذا التحسن بعد ٣ أشهر قد يدلل على الحاجة الى أعادة العلاج مستقبلا والحاجة الى دراسات عشوائية سريرية لتقييم فعالية العلاج لدى المرضى العراقيين.

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