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Research Article

Evaluation of the Therapeutic Effect of Intravitreal Bevacizumab in Diabetic Macular Edema

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Abstract

Purpose: To evaluate the possible complications and effects of intravitreal bevacizumab injection (IVB) on visual acuity (VA) and central macular thickness (CMT) in eyes with diabetic macular edema (DME).

Methods: Fifty eyes of 39 patients with DME treated with 1.25 mg/0.05 ml IVB were included in this retrospective study. VA, CMT were examined in 1st, 2nd, 3rd, 6th months again after injections. Eyes with 300µ and over CMT suggested re-injection.

Results: Seventeen of cases (43.6%) were male and 22 (56.4%) were female and the mean age of men was 58.29 ± 8.8 years and the mean age of women was 61.23 ± 11.1 years. The mean VA of the patients before injection was 0.586 LogMAR and after injection 1st month 0.484 LogMAR, 2nd month 0.485 LogMAR, 3rd month 0,469 LogMAR and 0.506 LogMAR and 6th month, respectively. Mean VA before injection was increased significantly in the following exams. The mean CMT was 425µ before injection. After injection, 1st month CMT was 385µ, 2nd month 383µ, 3rd month 362µ. Decrease of CMT in 1st month, 2nd month, 3rd month and 6th month CMT was statistically significant ($p = 0.00$, $p = 0.00$, $p = 0.00$, $p = 0.00$, $p = 0.00$).

Conclusion: IVB therapy seems to be safe and effective in eyes with DME. IVB increases VA and decreases CMT in the early period.

Keywords: *Bevacizumab; Diabetic Macular Edema; Central Macular Thickness*

Abbreviations

DRP: Diabetic Retinopathy; ETDRS: The Early Treatment Diabetic Retinopathy Study; LPC: Focal Laser Photocoagulation; VA: Visual Acuity; DME: Diabetic Macular Edema; VEGF: Vascular Endothelial Growth Factor; IVB: Intravitreal Bevacizumab Injection; CMT: Central Macular Thickness

Introduction

Diabetic retinopathy (DRP) is one of the most important reason of visual loss in developed countries [1,2]. The main reason of visual loss is macular edema in diabetic patients [3]. Of these patients, 29% have developed macular edema at the end of 20 or more years. In consequence of two-year follow up patient with macular edema, visual loss of 2 or more lines was detected in more than the half of these patients. In The Early Treatment Diabetic Retinopathy Study (ETDRS), it was stated that focal laser photocoagulation (LPC) was clinically beneficial in apparent macular edema [1]. However, a visual loss of 15 letters was also determined in 12% of patients who had been

treated with LPC according to ETDRS scale as a result of three-year follow-up period; on the other hand, a visual acuity (VA) gain of 15 letters had been achieved in only 3% of the these patients. Besides, retinal thickening involving the central of macular was observed in 24% of eyes treated with laser at the end of 36-month follow-up. All these data showed that the same of the eyes with diabetic macular edema (DME) were resistant to LPC treatment.

Diffuse macular edema is characterized by common leakage in widespread retinal capillary, rarely seen hard exudates and formation of cystoid spaces [4]. It was proven by studies that LPC treatment which had been stated as beneficial in clinical cases with significant macular edema in ETDRS, had limited advantage in eyes with diffuse macular edema [2,4,5]. A study performed by Lee and Olk, the rate of recovered patients with DME was found between 68% and 94% with grid laser therapy and VA was stabilized in 61% of the patient [5]. Of the eyes in the same series, 24.6% had a decrease in visual acuity of 3 or more lines. The understanding of limited advantage of LPC treatment in most of the resistant cases directs the concern to alternative treatment methods. These methods include pars plana vitrectomy [6] as a surgical treatment and protein kinase C inhibitors as medical treatment, vascular endothelial growth factor (VEGF) inhibitors, intravitreal corticosteroid injection and time-release intravitreal corticosteroid implants.

VEGF is over expressed in diabetic eyes and plays a key role in the development of DME; therefore, anti-VEGF treatment is one of the most promising approaches for the treatment of DME [6]. A decade of clinical trials demonstrated that drugs that bind soluble VEGF restore the integrity of the blood-retinal barrier, resolve macular edema, and improve vision in most patients with DME.

Aim of the Study

The aim of this study was to observe the possible complications and effects of intravitreal bevacizumab injection (IVB) on VA and central macular thickness (CMT) in eyes with DME.

Materials and Methods

A total of 50 eyes of 39 patients with DME who had been followed-up between January 2011 and August 2012 in Sakarya University Training and Research Hospital, Retina Department of Ophthalmology Clinic, and had been taken IVB injection (Altuzan, F. Hoffman-La Roche, Switzerland) for DME treatment were included in the study. According to ETDRS classification which is a standard procedure in our clinic, patients having macular edema and edema in Fundus Fluorescein Angiography (FFA) according to Clinically Significant Macular Edema (CSME) and patients with CMT ≤300μm in optical coherence tomography (OCT) were included in the study content.

Patient having previous glaucoma history, vitreoretinal surgical history, ocular trauma history and patient having pathologies related to macular edema such as uveitis, retinal vein occlusion and age-related macular degeneration, patients who were been operated for cataract within last 6 months, patients who were treated with Nd:YAG laser capsulotomy and patients who were taken LPC therapy within last 3 months were excluded from the study. Patients who were included in the study were informed about DRP and possible course of disease. The condition of patients' eyes before the treatment, the efficiency of the treatment that had been applied until that moment and therapy options were explained to the patients. Patients were informed about the process, expected effects and possible complications of IVB injection (Altuzan, F. Hoffman-La Roche, Switzerland), and informed consents were obtained from all patients before the procedure. Complete ophthalmologic examination of patients was performed, including best-corrected visual acuity (BCVA) testing, intraocular pressure (IOP), slit-lamp biomicroscopy and dilated fundus examination. ETDRS scores of patients were evaluated by Snellen chart due to inconsistency between ETDRS chart and patients. Visual acuity scores were converted into LogMAR unit during statistical analysis. Fundus examinations of the patients were performed by using +90 dioptrics non-contact lenses after pupil dilation. FFA images and color-fundus

photography were taken of all patients. The evaluation of FFA was performed by fundus camera (Kowa VX-10İ fundus camera; Kowa Optimed Inc, JAPAN) following the administration of IV 4 ml 10% sodium fluorescein. CMT of the patients were evaluated after pupil dilation by using macular scanning protocol of OCT (Optovue Inc, Fremont, CA).

Following the clinical examinations, FFA ad OCT, patients having above-mentioned characteristics and macular edema were offered IVB injection in our clinic. In our clinic, intravitreal injections are performed in the operating room. The protocol of standard intravitreal injection is as below; eyelids are wiped with 10% povidone-iodine impregnated gauze and 0.5% proparacaine hydrochloride (Alcain, Alcon Pharmaceuticals Switzerland) is dropped for topical anesthesia. After the placement of sterile retractor cover, three drops of 5% povidone-iodine is dropped on eye surface and waited for 3 minutes. Eye surface is washed with sterile isotonic solution. The injection of 1.25 mg/0.05 ml bevacizumab is done by entering midvitreus vertically with a 30G needle behind limbus with a distance of 3.5 - 4.0 mm and 3.5 mm in phakic and pseudophakic eyes, respectively. After removing the needle, a mild and short-time pressure is applied to the injection site with cotton in order to prevent leakage of drug or vitre, and bleeding of conjunctiva. Eyes are closed following the administration of topical antibiotic and pomade. Lomefloxacin eye drop (Okacin Ophthalmic Solution Novartis Pharma AG, Basel, Switzerland) is given 5 x 1/day for a week. Patients are called for control one day after injection and biomicroscopic examinations of the patients are performed. Patients without any problem are called to their 1st week control.

Patients treated with IVB were called for check-up in order to examine their ETDRS, GİB and CMT results at 1st, 2nd, 3rd, 6th months after injection. Re-injection was suggested to the patients with CMT ≥ 300µ.

Statistical analyses were performed by using SPSS 15.0 Windows (SPSS Inc., Chicago, IL, USA). A $p < 0.05$ was accepted as statistically significant. Paired Student-t test was used for comparisons between ETDRS and CMT values before and 1st, 2nd, 3rd, 6th months after injections.

Results and Discussion

A total of 50 eyes of 39 patients were included in the study. Of these patients, 17 (43.6%) were male and 22 (56.4%) were female; the mean age of males were 58.29 ± 88 years, whereas it was 61.23 ± 11.1 in females. There was no significant difference between the genders in terms of age ($p = 0.380$, $p = 0.365$).

Of the patients, 17 (43.6%) had been taking insulin as a medical therapy and 22 (56.4%) were oral anti-diabetic (OAD) agent. The mean of duration of diabetes in patients was 11.18 and 13.23 years in males and females, respectively, the difference was not statistically significant ($p = 0.372$, $p = 0.360$). Of the 39 patients, 18 (46.2%) had diabetes mellitus (DM) whereas hypertension (HT) was present with DM in 21 (53.8%) patients.

Visual acuity scores of the patients before the injection was 0.586 LogMAR, however, the scores following the injection were 0.484 in the 1st month, 0.506 in the 2nd month, 0.469 in the 3rd month and 0.485 in the 6th month. According to pre-operative VA, an increase in VA at the first month was found as statistically significant in advanced level ($p = 0.00$), the increases were found also statistically significant at the 2nd, 3rd and 6th months ($p = 0.00$, $p = 0.017$, $p = 0.002$, $p = 0.016$, respectively) (Table 1).

	Visual Acuity BI	Visual Acuity at 1st month AI	Visual Acuity at 2nd month AI	Visual Acuity at 3rd month AI	Visual Acuity at 6th month AI
	0.586	0.484	0.506	0.469	0.485
p*		0.000	0.017	0.002	0.016

Table 1: *The comparison between before and after (1st month, 2nd month, 3rd month and 6th month) injection (Paired samples t-test) (BI: Before injection; AI: After injection).*

At the 1st month after the injection, increased VA was determined in 30 (60%) eyes that were treated with IVB; decreased VA was observed in 6 (12%) eyes and VA did not change in 14 (28%) eyes. At the 2nd month after the injection, increased VA was determined in 29 (58%) eyes that were treated with IVB; decreased VA was observed in 10 (20%) eyes and VA did not change in 11 (22%) eyes. At the 3rd month after the injection, increased VA was determined in 30 (60%) eyes that were treated with IVB; decreased VA was observed in 9 (18%) eyes and VA did not change in 11 (22%) eyes. At the 6th month after the injection, increased VA was determined in 28 (56%) eyes that were treated with IVB; decreased VA was observed in 12 (24%) eyes and VA did not change in 10 (20%) eyes.

A decrease in CMT at 1st, 2nd, 3rd and 6th month was found statistically significant in comparison with the pre-operative period (Table 2). While a decrease of CMT was detected in 42 (84%), an increase was detected in 8 (16%) eyes treated with IVB at the 1st month after the injection with respect to pre-treatment period. A decrease was detected in 39 (78%), an increase was detected in 11 (22%) eyes treated with IVB at the 2nd month after the injection with respect to pre-treatment period. A decrease was detected in 42 (84%), an increase was detected in 8 (16%) eyes treated with IVB at the 3rd month after the injection with respect to pre-treatment period. A decrease was detected in 35 (70%), an increase was detected in 15 (30%) eyes treated with IVB at the 6th month after the injection with respect to pre-treatment period; whereas, CMT did not change in 15 (30%) eyes.

	CMT BI	CMT at 1st month	CMT at 2nd month	CMT at 3rd month	CMT at 6th month
	425.00	385.42	383.14	362.76	370.68
P		0.000	0.000	0.000	0.000

Table 2: *The comparison of mean CMT values before and at the 1st, 2nd, 3rd and 6th month after the injection*

In 50 eyes treated with IVB, IVB was performed one, twice and third time in 11 (22%), 25 (50%) and 3 (28%) of them, respectively.

As post-operative complications, increased IOP was observed in 3 (6%) eyes at the first day. IOPs of the patients were brought under control with topical antiglaucoma therapy and it was regressed to normal values at the first week. In our study, subconjunctival hemorrhage was developed in 2 (4%) eyes. No intervention was performed in terms of subconjunctival hemorrhage. Moreover, anterior chamber reaction was developed in 2 (4%) patients and these patients were treated with topical steroid therapy. There were no systemic adverse events noted in our study. Also, no reports of endophthalmitis, retinal detachment, retinal breaks and cataract development were noted because of injections.

Conclusion

Macular edema is the main reason of visual loss in diabetic patients [3]. The classical treatment options for DME are strict regulation of blood sugar which has been stated by Diabetes Control and Complications Trial (DCCT) and United Kingdom Prospective Diabetes Study (UKPDS); and LPC treatment which has been stated by ETDRS and Diabetic Retinopathy Study (DRS) [1,7,8]. In some of the patients with DME, searchers have been directed to various treatment methods including intravitreal steroid, anti-VEGF, protein kinase C inhibitors, corticosteroid-release implantable intravitreal devices, pars plana vitrectomy due to insufficient LPC treatment [6].

There are many studies showing the efficiency of intravitreal triamcinolone acetonide (IVTA) injection in DME. It has been found that IVTA injection reduces neovascularization, and provides a decrease in macular thickness in patients with proliferative diabetic retinopathy (PDR) [9]. However, IVTA injection accelerates cataract development and may cause glaucoma [10,11]. Therefore, despite the fact that efficient results have been obtained from IVTA injection, alternative treatment methods have been searched due to these side-effects. Among the alternative treatment methods, anti-VEGF agents have become important since they have fewer side effects.

Different dosage regimens of IVB injection are administered in DME treatment. In a study performed by Arevalo., *et al.* the difference was found between the doses of 1.25 mg and 2.5 mg in terms of the results [12]. In a randomized-controlled study including 52 patients with DME, Lam., *et al.* were determined that IVB injected therapy which is administered at the doses of 1.25 mg or 2.5 mg had similar efficiency in BCVA and decreasing macular thickness [13]. In our study, the dosage regimen of 1.25 mg was preferred by considering the similar effects of 1.25 mg and 2.5 mg doses.

In DME, an increase in the VA is an expected result after IVB injection. In a study performed by Haritoglou., *et al.* the initial mean value of VA was 0.86 ± 0.38 LogMAR, whereas it was 0.75 ± 0.37 LogMAR ($p = 0.001$) and 0.84 ± 0.41 LogMAR at the 6th and 12th month after the treatment. An increase in visual acuity of minimum 3 lines was observed in 29% and 26% of the patients in six-week and twelve-week follow up periods, respectively [14]. In another study done by Arevalo., *et al.* the mean value of BCVA was found initially as 20/150 (0.88 LogMAR); whereas it was 20/107 (0.76 LogMAR; $p < 0.0001$) and 20/75 (0.57 LogMAR; $p < 0.0001$) in IVB 1.25 mg group, at the end of 1st and 24th months, respectively [12]. In a study conducted by Forte., *et al.* the mean value of BCVA was found as 1.07 ± 0.49 LogMAR before the injection and a significant improvement was determined in BCVA at the 1st and 3rd months after the injection in IVB 1.25 mg group. A statistically significant improvement was found in terms of VA in IVB group at the 6th and 12th months after the treatment (0.83 ± 0.21 LogMAR, $p < 0.001$ at the 6th month; 0.86 ± 0.24 LogMAR, $p < 0.001$ at the 12th month; 248 ± 18μ, $p < 0.001$ at the 6th month; 262 ± 28μ, $p = 0.001$ at the 12th month, respectively) [15]. In our study, VA of patients was determined as 0.586 LogMAR before the injection, whereas it was 0.484 LogMAR, 0.506 LogMAR, 0.469 LogMAR and 0.485 LogMAR at the 1st, 2nd, 3rd and 6th month after the injection, respectively. A statistically significant increase was found between pre-operative VA and VA at the 1st, 2nd, 3rd and 6th month after the injection ($p = 0.000$, $p = 0.017$, $p = 0.002$, $p = 0.016$, respectively).

IVB injection therapy also decreases CMT. In the present study, the mean value of CMT before the injection was 425 μm; whereas it was found as 385 μm, 383 μm, 362 μm and 370 μm at the 1st, 2nd, 3rd and 6th months after the injection, respectively. In comparison with pre-operative period, the decrease in CMT value was found as statistically significant in accordance with the variation at the1st, 2nd, 3rd and 6th months ($p = 0.000$, $p = 0.000$, $p = 0.000$, $p = 0.000$, respectively). Haritoglou., *et al.* found that the mean value of CMT was initially 501 ± 163 μm, whereas a decrease was determined at the 2nd, 6th and 12th weeks after the treatment (425 ± 180 μm ($p = 0,002$); 416 ± 180 μm ($p = 0,001$); 377 ± 117 μm ($p = 0,001$), respectively). A reduction was observed in retinal thickness after IVB injection therapy [14]. In a study performed by Arevalo., *et al.* the mean value of CMT was initially 466.5 ± 145.2 μm, whereas it was 332.2 ± 129.6 μm and 286.6 ± 815 μm at the 1st and 24th month after the injection, respectively, in IVB 1.25 mg group [12]. Similar results were obtained in another study conducted by Forte., *et al.* and a significant improvement was obtained in foveal thickness at the 1st and 3rd months [15]. In a study performed by Kook., *et al.* a total of 126 patients with chronic diffuse DME were followed up for 6 and 12 months, and the mean value of CMT was initially found as 463 μm whereas it reduced to 374 μm and 357 μm at the 6th and 12th months [16].

The number of intravitreal injections may vary in DME therapy. In a study performed by Arevalo., *et al.* patients were followed-up for 24 months and the mean value of IVB injection number per eye was found as 5.8 [12]. In the present study, of the 50 eyes treated with IVB injection, IVB was injected once in 11 (22%) and it is reinjected in 25 (50%) and 14 (28%) eyes twice and three times, respectively. The injection number per eye was found as 2,1.

In a study including patients with diffuse DME, IVB injection was performed in 43 eyes of 32 patients. The mean values of initial BCVA and fovea thickness were determined as 1.07 ± 0.49 LogMAR and 423 ± 33 μm, respectively, in IVB group. A significant improvement was found in BCVA and foveal thickness at the 1st and 3rd months after the injection. No side effects were reported in IVB group. As a result, a significant improvement was reported in VA and foveal thickness at the 6th and 12th months after the IVB injection [15].

Welch., *et al.* evaluated the short-term response of IVB injection in macular edema and they suggested that injections at 2 - 3-week intervals might provide improved clinical outcomes, compared with the currently typical 4 - 6-week interval of injections [17]. In the present study, IVB injection was performed in case of CMT values higher than 300 μm.

In a large scale study examining post-IVB injection complications performed by Wu., *et al.* a total of 1.310 eyes were included in the study and 4,303 IVB injections were performed. The complications including bacterial endophthalmitis, tractional retinal detachment, rhegmatogenous retinal detachment and intravitreal hemorrhage were reported in 7 (0.16%), 7 (0.16%), 4 (0.09%) and 1 (0.02) patients, respectively [18]. In the present study, an increase in IOP was observed in 3 (6%) eyes at the first day after the injection, and it was taken under control with topical antiglaucoma medications and normal levels were observed in the first week. Moreover, subconjunctival hemorrhage was developed in 2 (4%) eyes and no intervention was performed to these patients. Anterior chamber reaction was developed in 2 (4%) patients and these patients were treated with topical steroid therapy.

In the present study, no systemic complication was observed in the patients. The reason of this result may be related with low patient number. In a study conducted by Fung., *et al.* in 2006, the clinical data of 5,228 patients were evaluated and a total of 7,113 injections were performed. The patients were followed-up for about 3.5 months. As a result, the complications including sudden increase in blood flow, transient ischemic attack and deep vein thrombosis were observed in 0.21%, 0.07%, 0.01% and 0.03% of the patients [19].

IVB therapy seems to be safe and effective in eyes with DME. Further studies with a larger sample size and longer follow-up are required to confirm our study results as well as compare the efficacy of each and combined treatment modalities for the eyes with DME.

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Conflict of Interest

The authors report no conflicts of interest in this work.

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