

Comparison of intravitreal bevacizumab and triamcinolone acetonide therapies for diffuse diabetic macular edema

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Abstract

• **AIM:** To compare therapeutic effects of intravitreal triamcinolone acetonide (IVTA) versus intravitreal bevacizumab (IVB) injections for bilateral diffuse diabetic macular edema (DDME).

• **METHODS:** Forty eyes of 20 patients with bilateral DDME participated in this study. For each patient, 4 mg/0.1 mL IVTA was injected to one eye and 2.5 mg/0.1 mL IVB was injected to the other eye. The effects of injection for diabetic macular edema (DME) were evaluated using best-corrected visual acuity (BCVA), central macular thickness (CMT) by optical coherence tomography (OCT) and intraocular pressure (IOP) by applanation tonometer. Patients underwent eye examinations, including BCVA, CMT, and IOP at pre-injection, 1, 4, 8, 12 and 24wk after injection. During the follow-up, second injections were performed to eyes which have CMT greater than 400 µm at 12wk for salvage therapy.

• **RESULTS:** BCVA (logarithm of the minimum angle of resolution) at pre-injection, 1, 4, 8, 12 and 24wk after injection was 0.71±0.19, 0.62±0.23, 0.63±0.12, 0.63±0.13, 0.63±0.14 and 0.61±0.24 in the IVTA group and 0.68±0.25, 0.61±0.22, 0.60±0.24, 0.62±0.25, 0.65±0.26 and 0.59±0.25 in the IVB group, respectively. CMT (µm) at pre-injection, 1, 4, 8, 12 and 24wk after injection was 544±125, 383±96, 335±87, 323±87, 333±92, 335±61 in the IVTA group and 514±100, 431±86, 428±107, 442±106, 478±112, 430±88 in the IVB group respectively. Reduction ratios of mean CMT were 29% at 1wk, 38% at 4wk, 40% at 8wk, 38% at 12wk, and 38% at 24wk in the IVTA group. Second IVTA injections were performed to the 6 eyes (30%) at 12wk. Reduction ratios of mean CMT were 16% at 1wk, 17% at

4wk, 14% at 8wk, 7% at 12wk, and 16% at 24wk in the IVB group. Second IVB injections were performed to the 15 eyes (75%) at 12wk.

• **CONCLUSION:** This study showed earlier and more frequent macular edema recurrences in the eyes treated with bevacizumab compared with the ones treated with triamcinolone acetonide. Triamcinolone acetonide was found to provide more efficient and long-standing effect in terms of reducing CMT compared with the bevacizumab.

• **KEYWORDS:** bevacizumab; diabetic macular edema; triamcinolone acetonide

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INTRODUCTION

Macular edema is the main cause of visual loss in patients with diabetic retinopathy, which may occur at any stage of diabetic retinopathy and often bilaterally [1]. The Early Treatment of Diabetic Retinopathy Study (ETDRS) indicates that focal/grid laser photocoagulation for clinically significant macular edema effectively reduces the risk of moderate vision loss [2]. Later studies showed that grid laser photocoagulation has limited efficacy, and may cause decreased vision because of progressive macular scar and subretinal fibrosis [3-5]. At present, there have been several therapies for the treatment of diabetic macular edema (DME) such as intravitreal steroids and anti-vascular endothelial growth factor (VEGF) injections. Ranibizumab and bevacizumab are two main anti-VEGF agents for DME. Although ranibizumab has been approved by the United States Food and Drug Administration for the treatment of DME, bevacizumab, which costs much less than ranibizumab, is commonly used as an off-label therapeutic option in treating DME. Many studies have indicated intravitreal bevacizumab (IVB) was effective for reducing DME [6-8]. Triamcinolone acetonide (TA), one of corticosteroids, has the effect of anti-inflammatory and anti-angiogenic. Many reports have demonstrated the usefulness of intravitreal

TA (IVTA) in patients with DME^[9,10]. With the increasing use of IVB and IVTA, it is of interest to confirm which agent is more effective and safe. In the literature apart from one study, efficacy of IVTA and IVB therapies have been compared by applying them on only one eye of different patients. The purpose of this prospective, clinical controlled study to compare the efficacy of IVTA versus IVB for bilateral diffuse DME (DDME), and also their possible side effects in both eyes of the same patient.

SUBJECTS AND METHODS

Subjects Forty eyes of 20 patients with bilateral DDME were included in this study. The study was approved by the local ethic committee of Baskent University and written informed consent was taken from all patients according to the Declaration of Helsinki. Ophthalmological examination findings were included; best-corrected visual acuity (BCVA) which was measured with the Snellen chart and then converted to logMAR, intraocular pressure (IOP) by Goldmann applanation tonometry and biomicroscopic anterior-posterior segment findings. The diagnosis of diabetic retinopathy and macular edema was made with slit-lamp fundus examination and also by fundus fluorescein angiography (FFA). Retinal thickness was measured by Cirrus™ HD-OCT (Carl Zeiss Inc. MEDITEC., Dublin, CA, USA), 512×128 cube map using the macular scan pattern.

Patients were included if they had: 1) retinal thickening of two or more disk areas involving some portion of the foveal avascular zone and diffuse fluorescein leakage involving the fovea and most of the macular area on fluorescein angiography; 2) logMAR BCVA of 0.5 or worse; and 3) central macular thickness (CMT) greater than 300 μm on OCT. Exclusion criteria were: 1) previous therapies for macular edema, including grid-laser treatment, intravitreal injection of any drugs, and/or vitreous surgery; 2) macular ischemia on fluorescein angiography; 3) aphakic or 1 eye phakic and other eye pseudophakic patients; 4) glycosylated haemoglobin (HbA1c) level above 10% ; 5) history of glaucoma or ocular hypertension; 6) panretinal photocoagulation history shorter than 3mo; 7) an ocular condition other than diabetes mellitus (DM) that, the investigator thinks that might affect macular edema or alter visual acuity during the course of the study such as retinal vein occlusion, uveitis or other ocular inflammatory disease, epiretinal membrane, macular degeneration, vitreomacular traction; 8) systemic corticosteroid therapy; 9) history of thromboembolic event or current use of anticoagulative medication other than acetylsalicylic acid; 10) uncontrolled hypertension.

Intravitreal injections were performed in the outpatient clinic, under sterile conditions. The 2.5 mg/0.1 mL of bevacizumab was injected to one eye (Avastin, Genentech, Inc., San Francisco, California, USA), and 4 mg/0.1 mL of TA

(Kenacort-A, 40 mg/mL, Bristol-Myers Squibb, New Jersey, USA) was injected to the other eye for every patient with 1d interval. All patients were examined for control 1d after each injection. After the injection 0.3% ofloxacin drops were prescribed four times per day for a week.

According to the CMT values determined by OCT, TA was injected to the eye with thicker CMT and bevacizumab was injected to the other eye in first patient and subsequently in the next patient bevacizumab was injected into the eye with thicker CMT and TA was injected to the other eye. TA and bevacizumab were injected into the eye with thicker CMT of consecutive patients by turn to make possible equal conditions of macular edema between groups. Reduction ratios for CMT values were calculated by the formula; final CMT-initial CMT/initial CMT at 1, 4, 8, 12 and 24wk. Patients' visual acuity, CMT, IOP data were evaluated at 1, 4, 8, 12 and 24wk. During the follow-up, same injections were repeated to patients who have CMT greater than 400 μm at 12wk for the salvage therapy.

Statistical Analysis Statistical analysis of continuous variables with normal distribution was checked for compliance Shapiro-Wilk test. Variances were analyzed with the homogeneity of the Levene test. Parametric tests on pre-conditions are not fulfilled; in order to compare the two drug groups Mann-Whitney *U* test was used. Friedman test and then with the period between six different multiple comparison methods were compared with Bonferroni-Dunn test. Results were expressed as mean ± standard deviation. Data set SPSS program (SPSS version 15.0, SPSS Inc., Chicago, IL, USA) were analyzed using.

RESULTS

Forty eyes of 20 patients were included in this study. There were 10 (50%) female and 10 (50%) male patients, with mean age of 62 (range 53-74)y. All patients had type 2 DM, and the duration of DM from 10 to 20y. Ten (50%) patients had comorbid hypertension and were taking oral antihypertensive drugs. Thirteen (65%) patients had panretinal photocoagulation in both eyes. Patients had no ocular disease except refractive errors or cataract. There wasn't concurrent retinal or optic nerve disorder other than diabetic retinopathy. Four (20%) patients had bilateral pseudophakic, the remaining 16 (80%) patients had phakic.

BCVA was 0.71 ± 0.19 logMAR in the IVTA group and 0.68 ± 0.25 logMAR in the IVB group at baseline and there were not significant differences between these groups (*P* = 0.237). BCVA improved at one week after the injection (0.62 ± 0.23 logMAR, *P* < 0.001) in the IVTA injected eyes and remained at the same level up to 24wk (0.61 ± 0.24 logMAR, *P* < 0.001). Visual acuity in the bevacizumab injected eyes statistically significant improved at 1, 4, and 24wk (0.61 ± 0.22, 0.60 ± 0.24, 0.59 ± 0.25 *P* = 0.001). However, at 12wk, visual acuity returned to the initial level (0.65 ± 0.26). Between these

Table 1 Alteration of logMAR visual acuity after each treatment in patients with bilateral DDME

Treatment group	Basale	1wk	4wk	8wk	12wk	24wk
Triamcinolone	0.71±0.19	0.62±0.23	0.63±0.12	0.63±0.13	0.63±0.14	0.61±0.24
Bevacizumab	0.68±0.25	0.61±0.22	0.60±0.24	0.62±0.25	0.65±0.26	0.59±0.25
<i>P</i>	0.237	0.055	0.247	0.142	0.294	0.206

Table 2 Alteration of central macular thickness after each treatment in patients with bilateral DDME

Treatment group	Basale	1wk	4wk	8wk	12wk	24wk
Triamcinolone	544±125	383±96	335±87	323±87	333±92	335±61
Bevacizumab	514±100	431±86	428±107	442±106	478±112	430±88
<i>P</i>	0.715	0.045	0.007	0.001	0.001	0.001

Table 3 Alteration of intraocular pressure after each treatment in patients with bilateral DDME

Treatment group	Basale	1wk	4wk	8wk	12wk	24wk
Triamcinolone	14.6	15.5	16.2	17.6	17.5	16.4
Bevacizumab	14.8	15	14.7	15.1	14.3	14.2
<i>P</i>	0.862	0.595	0.131	0.002	0.002	0.007

two groups, visual acuity improvement was clinically significant in favor of triamcinolone acetone only at first week ($P=0.055$). Other time points of 4, 8, 12 and 24wk there were not statistically significant differences ($P=0.247$, $P=0.142$, $P=0.294$, $P=0.206$; Table 1).

Before the administration of the drugs baseline average CMT value was found $544 \pm 125 \mu\text{m}$ in the IVTA group, $514 \pm 100 \mu\text{m}$ in the IVB group, and there was no statistically significant difference between the two groups ($P=0.715$). One week after IVTA injection, CMT values were significantly decreased ($383 \pm 96 \mu\text{m}$, $P=0.001$) and these decrease continued up to 24wk. Although, triamcinolone acetone injection was administered at 12wk second time to 6 (30%) eyes in which CMT values greater than $400 \mu\text{m}$. Average CMT value was $335 \pm 61 \mu\text{m}$ at 24wk and decrease was statistically significant compared with baseline and 12wk values ($P=0.001$). After intravitreal injection of bevacizumab CMT values statistically significant decreased ($431 \pm 86 \mu\text{m}$, $P=0.001$) at 1wk and decrease continued until to 8wk. Average CMT value increased to $442 \pm 112 \mu\text{m}$ at 12wk and this change statistically insignificant compared with basale CMT. Second injection was administered at 12wk to 15 (75%) eyes in which CMT greater than $400 \mu\text{m}$. At 24wk, the decrease of the CMT values were statistically significant compared with the baseline and 12wk values ($430 \pm 88 \mu\text{m}$, $P=0.001$). Between these two groups, there was a statistically significant difference of CMT in favor for IVTA at all time points ($P=0.045$, $P=0.007$, $P=0.001$, $P=0.001$, $P=0.001$; Table 2, Figure 1).

Reduction ratios of mean CMT were 29% at 1wk, 38% at 4wk, 40% at 8wk, 38% at 12wk, and 38% at 24wk in the IVTA group. And the reduction ratios of mean CMT were 16% at 1wk, 17% at 4wk, 14% at 8wk, 7% at 12wk, and 16% at 24wk in the IVB group.

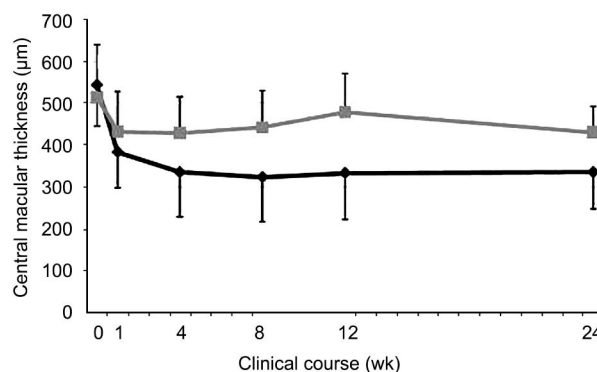


Figure 1 Comparison of the clinical course of central macular thickness between the triamcinolone acetone injected eyes (dark line) and the bevacizumab injected eyes (light line) in patients with bilateral diffuse diabetic macular edema Each square and vertical bar indicates mean central macular thickness \pm standard deviation (SD) of the mean.

Average IOP values at baseline 14.6 mm Hg in the IVTA group, and 14.8 mm Hg in the IVB group and difference were not significant between the groups ($P=0.862$). One month after the injection, IOP in the IVTA group showed a statistically significant increase and then gradually increased with time ($P=0.001$). Four (20%) patients whose IOP values were higher than 21 mm Hg, treated with topical antiglaucomatous therapy. In contrast, IOP in the bevacizumab-treated eyes did not show a statistically significant change during the clinical course. At 8, 12 and 24wk IOP in the IVTA group was significantly higher than the IVB group ($P=0.002$, $P=0.002$, $P=0.007$; Table 3).

None of the patients who received IVB or IVTA, displayed a systemic side effect or an ocular complication associated with the applied invasive procedure. The development or progression of lens opacities was occurred in 4 (25%) eyes in the IVTA group. Two of four (50%) eyes that had second

IVTA injections developed lens opacities. No cataract surgery was performed during the follow-up period. Cataract progression has not been observed in the IVB group.

DISCUSSION

Breakdown of inner blood-retinal barrier due to retinal infiltration of inflammatory cells and biochemical alterations arising from chronic hyperglycemia, plays an important part in the pathogenesis of diabetic macular edema [11-13]. Focal macular edema can be controlled by laser photocoagulation, however, eyes with diffuse macular edema generally demonstrate a resistance against therapy. Among treatment strategies towards the pathogenesis of the disease, TA and bevacizumab, alone or in combination with laser photocoagulation, have produced successful results in the treatment of DME [6,7,14,15]. In the studies by Chakrabarti *et al* [16] and Marey and Ellakwa [17], the response to therapy with bevacizumab showed superiority compared with triamcinolone for DME. However, these studies differed from that of Paccola *et al* [18], Isaac *et al* [19] and Lim *et al* [20], Song *et al* [21] who demonstrated that intravitreal triamcinolone was more efficient in reducing DME relative to bevacizumab. And in the other study by Rensch *et al* [22], IVTA and IVB did not differ markedly in term of their effects in improving VA and reducing macular thickness. Which treatment is more effective remains controversial. In these studies, efficacy of IVTA and IVB therapies have been compared by applying them on only one eye of different patients. Thus, in our study, by considering that the influence of systemic risk factors such as glycemic level, blood pressure, and nephropathy may alter the efficacy of the drugs in every individual, both eyes of the each patient received intravitreal treatment of both drugs with equal volume were compared. One of the potential limitation of this study is that, we used only the macular scan pattern of the HD-OCT. As we used just macular pattern of the HD-OCT instead of full field 3-D SD-OCT, extrafoveal vitreous tractions including vitreopapillary traction and extrafoveal traction membranes which is a common phenomenon in DDME, might not be detected, as recently re-described by Ophir [23]. Thus, the therapeutic effect of the two medications could be different if all tractional components were excluded.

The most remarkable problem encountered in cases treated with intravitreal injections is the transient nature of the therapeutic effect and frequent recurrences. Pharmacokinetic data suggest a single intravitreal injection of 1.25 mg bevacizumab is effective for 6-7wk [24]. Kreutzer *et al* [25] suggested that a single triamcinolone injection may be as effective as a 3 injections of bevacizumab for the treatment of DME. Less number of injections of triamcinolone reduces injection-related complications and improve the patient compliance. In a Meta-analysis including 6 study which

compare the efficacy of the IVTA versus IVB in the treatment of DME shows IVTA is superior in improving VA at earlier follow-up (1mo and 3mo) and in reducing CMT at later follow-up (6mo) for DME [26]. In the current study, visual acuity was observed to rise at 1 and 4wk and remain stable at 8, 12, and 24wk in the IVTA group. Reduction ratios for mean CMT values were 29% at 1wk, 38% at 4wk, 40% at 8wk, 38% at 12wk, and 38% at 24wk. Thus, CMT demonstrated a tendency to increase starting from the 12wk and therefore 6 (30%) eyes received a second IVTA injection in the IVTA group.

In multicenter trial of Pan-American Collaborative Retina Study Group (PACORES), 139 eyes of 115 DDME patients received 1.25 mg and 2.5 mg IVB injection and the patients were followed-up for a mean period of 24mo. No difference was determined between the 1.25 and 2.5 mg doses with regard to efficacy. While 95% of patients required a second injection, 84% required a third injection, 36% required 6 injections, and 11% required 9 injections [6]. In the present study, visual acuity in the IVB group increased at 1 and 4wk, restarted to decrease at 8 and 12wk, and returned to the initial levels at 24wk. The reduction ratios of mean CMT were 16.4% at 1wk, 16.8% at 4wk, 14% at 8wk, 7% at 12wk, and 16% at 24wk. Thus, CMT demonstrated a tendency to increase starting from the 8th week and 15 (75%) eyes were subjected to second bevacizumab injection at 12wk. According to the literature and our results, the reduction in CMT after intravitreal bevacizumab injection, can be maintained only for about 1mo even with 2.5 mg injection, macular thickness begins to reincrease and require a second injection after 1mo.

A crossover effect of bevacizumab in the contralateral eye on proliferative diabetic retinopathy has been reported [7]. However pharmacokinetic studies of intravitreal bevacizumab injection revealed that only a very small amounts of bevacizumab or no changes on VEGF levels were detected in the contralateral eye [27,28]. And also in a PET/CT study on small animals with I-124 radiolabeled bevacizumab and ranibizumab showed that there were no significant escape of bevacizumab and ranibizumab from the vitreous cavity after intravitreal injection [29]. Although, it may be concluded that bevacizumab may have some or little effect on the contralateral eye, we did not establish a significant effect primary eye. This study actually showed that IVB does not have a beneficial effect in DDME and such edema may be would naturally adversely affect the posterior macula over time to irreversible changes.

The most common side effect observed after IVTA injection is, raised IOP and its incidence ranges between 20%-80% in various studies [30]. Considerable IOP increases are reported even in small case series. On the other hand, clinical studies

performed with bevacizumab have shown insignificant alterations in IOP levels. In the present study, IOP levels at 4, 8, and 12wk exhibited a statistically significant elevation in the IVTA group and remained stable at 24wk. However, IOP levels in the IVB group demonstrated no significant change. At routine doses of both drugs, bevacizumab may be more advantageous than triamcinolone with regard to IOP stability. There is only one study in the literature which compares triamcinolone acetonide and bevacizumab therapies in the same patients. In that study, Shimura *et al*^[31] applied single dose of bevacizumab 1.25 mg one eye of each of 14 patients with bilateral persistent DME, while delivering single dose of triamcinolone acetonide 4 mg on the contralateral eye, after which the patients were followed-up for 24wk. Triamcinolone acetonide was found to provide more efficient and long-standing effect in terms of reducing CMT and increasing visual acuity compared with the bevacizumab. Bevacizumab the VEGF inhibitor which was used in our study as well, provided a reduction in macular edema 4wk after the injection, however, its effect was not as efficient as triamcinolone acetonide and macular edema relapsed at 12wk. While the reduction in CMT one week after the injection was 16% for the IVB group, it was 29% for the IVTA group. CMT reduction rate was 7% in the IVB group 12wk after the injection which is an evidence indicating a decrease in the effect of bevacizumab. On the other hand, CMT reduction rate among triamcinolone acetonide group was still 38% which shows the continuation of the influence of triamcinolone injection even after 12wk. At 12wk, 75% of IVB group and 30% of IVTA group received a second injection due to recurrence of macular edema.

Our results showed earlier and more frequent recurrences in the eyes treated with bevacizumab compared with the ones treated with triamcinolone. Therefore, in order to prolong the reductive effect, multiple injections of bevacizumab required. DME is not only associated with VEGF, but also with many growth factors and inflammatory cytokines. Bevacizumab reduces vascular permeability by blocking the influence of VEGF. Triamcinolone acetonide decreases VEGF expression, prevents fluid accumulation in the extracellular area, and inhibits release of edema-inducing inflammatory mediators. In this regard, triamcinolone is a multipotent drug and has more advantages when compared with bevacizumab which only reduces intraocular VEGF levels. In the current study, 6mo follow-up results of each drug regimen with the same volume and same patient were presented, however, studies with longer duration and larger sample size are required in order to further evaluate multiple dose-response relationship and safety of the drugs.

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