Intravitreal Bevacizumab for Refractory Diabetic Macular Edema*

İnatçı Diyabetik Maküla Ödeminde İntravitreal Bevacizumab

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ABSTRACT

Purpose: To evaluate the efficacy and safety of intravitreal bevacizumab (IVB) injection for refractory diabetic macular edema (DME).
Materials and Methods: This was a prospective, uncontrolled, consecutive case series of injections of 1.25 mg IVB for refractory DME. Eighty-nine eyes of 62 patients were included in this study. IVB injections were performed in all eyes according to the clinical situation.
Results: The mean visual acuity improved significantly at the posttreatment 4th (0.90±0.06 logMAR, p<0.05) and 8th (0.88±0.07 logMAR, p<0.05) weeks while there was also an increase, albeit not statistically significant, at the 12th (0.94±0.08 logMAR, p>0.05) week with respect to the baseline level (1.04±0.08 logMAR). There were significant reductions in mean central foveal thickness at the 4th (301.5±131.9 µm, p<0.01), 8th (302.6±113.4 µm, p<0.01) and 12th (326.3±171.7 µm, p<0.05) weeks of treatment when compared to the baseline value (352.8±154.7 µm). During the follow-up period, no significant change was observed in the mean intraocular pressure. Vision-threatening complications including endophthalmitis in one and temporary anterior chamber reaction in six eyes were observed while no serious systemic adverse events were detected.
Conclusion: Intravitreal bevacizumab injection at doses of 1.25 mg seems to be an effective and safe treatment agent for refractory DME.
Key Words: Diabetic macular edema, intravitreal bevacizumab, vascular endothelial growth factor.

ÖZ

Amaç: İnatçı diyabetik maküla ödeminde (DMÖ) intravitreal bevacizumab (İVB) enjeksiyonunun etkinlik ve güvenilirliğini değerlendirmek.
Gereç ve Yöntem: Bu çalışma inatçı DMÖ için 1.25 mg IVB enjeksiyonu yapılan ileriye dönük, kontrolsüz, ardışık olgu serileridir. Altmış iki hastaya ait 89 göz çalışmaya alındı. Tüm gözlere klinik takiplerine göre intravitreal bevacizumab enjeksiyonu uygulandı.
Bulgular: Ortalama görme keskinliği tedavi öncesi seviyeye göre (1.04±0.08 logMAR) tedavi sonrası dördüncü (0.90±0.06 logMAR, p<0.05), sekizinci haftada (0.88±0.07 logMAR, p<0.05) anlamlı ve onikinci haftada ise istatistiksel olarak anlamlı olmasa da (0.94±0.08 logMAR, p>0.05) arttı. Ortalama fovea merkez kalınlığında (FMK) tedavi öncesi değerle karşılaştırıldığında (352.8±154.7 µm), tedavi sonrası dördüncü (301.5±131.9 µm, p<0.01), sekizinci (302.6±113.4 µm, p<0.01) ve on ikinci haftada (326.3±171.7 µm, p<0.05) anlamlı azalma mevcuttu. Takip süresince ortalama göz içi basıncında başlangıca göre anlamlı değişiklik gözlenmedi, görmeyi tehdit edici komplikasyon olarak bir gözde endoftalmi ve altı gözde geçici ön kamara reaksiyonu gözlendi. Ancak hiçbir ciddi sistemik yan etki saptanmadı.
Sonuç: İnatçı DMÖ'de 1.25 mg dozunda intravitreal bevacizumab enjeksiyonu etkili ve güvenilir bir tedavi ajanı gibi görünmektedir.
Anahtar Kelimeler: Diyabetik maküla ödemi, intravitreal bevacizumab, vasküler endotelyal büyüme faktörü.

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INTRODUCTION

Diabetic retinopathy (DR) remains the major threat to sight in the working-age population worldwide.[1] Diabetic macular edema (DME) is a manifestation of DR that causes loss of central vision.[2] Visual loss is more commonly due to proliferative changes and macular edema in patients with type 1 and type 2 diabetes, respectively.[3] Diabetic macular edema has been characterized by inflammation, including intravitreous induction of proinflammatory cytokine, intraretinal expression of proinflammatory caspases and mediators.[4] It occurs because of excessive vascular permeability due to the leakage of plasma contents and liquid within the intraretinal layers of the macula, leading to thickening of macula.[5]

Vascular endothelial growth factor (VEGF) has been demonstrated to be an endothelial cell-specific mitogen and an angiogenic inducer in a variety of in vitro and in vivo models.[6] Besides, VEGF release into the vitreous cavity as a response to ischemia causes increased retinal vessel permeability by increasing the phosphorylation of tight junction proteins, and the growth of new vessels from the retina or optic nerve, and form microvascular occlusions and microaneurysms, all hallmarks of DR.[6,7] For these reasons, anti-VEGF treatments including pegaptanib (Macugen; Eyetech Pharmaceuticals, New York, NY, USA), ranibizumab (Lucentis; Novartis Pharmaceuticals, East Hanover, NJ, USA) and bevacizumab (Avastin; Genentech, Inc., South San Francisco, CA, USA) which seem to have shown favorable short-term results as an alternative adjunctive treatment for DME were suggested.[8-11]

Bevacizumab is a recombinant humanized antibody directed at all subtypes of VEGF-A. An intravitreal injection of bevacizumab seems to be beneficial in a wide variety of ocular disease including macular edema secondary to central retinal vein occlusion, proliferative diabetic retinopathy (PDR), retinopathy of prematurity, neovascular glaucoma, and choroidal neovascularization (CNV) secondary to age related macular degeneration (AMD).[12,13]

The aim of this study was to evaluate the efficacy and the safety of intravitreal bevacizumab (IVB) injection in patients with refractory DME, which did not respond other treatments including laser photocoagulation and intravitreal triamcinolone acetonide injections, by examining visual acuity (VA), macular thickness and macular volume in a short time.

MATERIALS AND METHODS

This was a prospective, uncontrolled, consecutive case series of IVB injections of 1.25 mg bevacizumab for refractory DME.

Eighty-nine eyes of 62 patients with refractory DME treated with at least one intravitreal injection of 1.25 mg of bevacizumab from June 2007 to December 2007 were evaluated at the Retina Unit of Eye Clinic I, Ulucanlar Eye Education and Research Hospital, Ankara, Turkey prospectively. The off-label use of the drug and its potential risks and benefits were discussed extensively with all patients. All participants gave written informed consent before the intravitreal injection was performed. The study protocol adhered to the tenets of the Declaration of Helsinki and was approved by the local Institutional Review Board.

Patient Eligibility and Baseline Evaluation

Patient conditions included refractory DME [defined as the presence of "clinically significant macular edema" (as per ETDRS criteria)[14] by biomicroscopic evaluation] that had not responded to alternative treatments including macular photocoagulation (MPC), panretinal photocoagulation (PRP) or intravitreal triamcinolone injection (IVTA) in the last six months, and diffuse fluorescein leakage involving the foveal centre and most of the macular area on fluorescein angiography. Throughout the study, measurement of VA assessment by Snellen chart as well as the central foveal thickness (CFT) measured using OCT were evaluated.

Exclusion criteria were:

1- Uncontrolled hypertension;

2- The presence of a comorbid ocular condition arising from reasons other than diabetes that might affect macular edema or alter the VA;

3- Media opacity including cataract or vitreous hemorrhage;

4- Systemic corticosteroid therapy;

5- History of thromboembolic event (including myocardial infarction or cerebral vascular accident);

6- Major surgery within the prior 6 months or planned within one month;

7- Chronic renal failure maintained with renal dialysis;

8- Known coagulation abnormalities or current use of anticoagulant medication other than aspirin.

Each patient received a detailed ophthalmologic examination including measurement of VA assessment by Snellen chart, as well as noncontact tonometry, undilated and dilated slit-lamp biomicroscopic examination, indirect fundus examination, and colour fundus photography. OCT analysis was performed in several patients with a third generation OCT evaluation (Stratus Tomographer, Model 3000, Carl Zeiss Ophthalmic Systems Inc., Humphrey Division, Dublin, CA, USA) using the macular thickness protocol.

Table 1: *Baseline Characteristics.*

Characteristics (n = Participants/Eyes)	Value
Gender, n (%)	
Female	31 (50.0)
Male	31 (50.0)
Age (year)*	57.2±8.1
Eye, n (%)	
Right	41 (46.1)
Left	48 (53.9)
Diabetes Type, n (%)	
Type 2	62 (100.0)
Duration of diabetes (year)*	14.2±5.4
Treatment of diabetes, n (%)	
Oral hypoglycemic medication	31 (50.0)
Insulin	31 (50.0)
Systolic blood pressure (mm Hg)*	139.0±21.4
Diastolic blood pressure (mm Hg)*	75.7±11.5
Hypercholesterolemia, n (%)	25 (40.3)
Hypertension, n (%)	35 (56.5)
Coroner artery disease, n (%)	11 (17.7)
DR type, n (%)	
NPDR	55 (61.8)
PDR	34 (38.2)
NVE, n (%)	34 (38.2)
NVD, n (%)	16 (18.0)
Intraocular pressure (mm Hg)*	13.1±3.6
Duration of ME (months)*	9.9±9.8
Treatment within last 6 months, n (%)	40 (44.9)
Macular photocoagulation, n (%)	35 (39.3)
PRP, n (%)	15 (16.9)
IVTA injection, n (%)	11 (12.4)
Intravitreal bevacizumab injection†	1.3±0.5
Lens status, n (%)	
Phakic	75 (84.3)
Pseudophakic	14 (15.7)
Baseline central macular thickness (µm)*	352.8±154.7
Macular volume (mm^3)	8.8±2.0
Baseline logMAR visual acuity scores (Snellen)*	1.0±0.8

DR;Diabetic Retinopathy, NPDR;Nonproliferative Diabetic Retinopathy, PDR;Proliferative Diabetic Retinopathy, NVE;Neovascularization Elsewhere, NVD;Neovascularization of the Disc, ME;Macular Edema, PRP;Panretinal Photocoagulation, IVTA;Intravitreal Triamsinolon Asetonid.

**Mean±SD.*

†Injection number per eye (Mean±SD).

Injection Technique

Bevacizumab (25 mg/mL) was prepared for all patients and put into the tuberculin injector with aseptic technique. The prepared drug was stored under refrigeration. After using a topical anesthetic (a drop of 0.5% proparacaine), the intravitreal bevacizumab injections were performed in the usual sterile fashion with a sterile lid speculum and 5% topical povidone-iodine.

Table 2: *After intravitreal bevacizumab injection changes in visual acuity, central foveal thickness, macular volume, intraocular pressure, and systolic and diastolic blood pressure.*

Findings*	Baseline	4th week	P	8th week	P	12th week	P
VA (logMAR)	1.04±0.08	0.90±0.06		0.88±0.07		0.94±0.08	
VA change (logMAR)†		-0.14±0.07	0.038‡	-0.16±0.06	0.015‡	-0.10±0.07	0.197‡
CFT (µm)	352.8 ±154.7	301.5 ±131.9		302.6±113.4		326.3±171.7	
CFT change (µm)†		-102.6±39.4	0.001§	-91.8±27.5	0.001§	-40.0±33.5	0.041§
MV (mm^3)	8.8±2.0	8.6±1.7		8.4±2.1		14.8±8.2	
MV change (mm^3)†		-0.7±1.1	0.002§	-1.0 ±1.0	0.003§	-0.8 ±1.5	0.091§
IOP (mm Hg)	13.12±3.56	12.89±3.22		13.30±3.47		13.67±4.80	
IOP change (mm Hg)†		-0.24±0.34	0.484‡	0.18± 0.36	0.615‡	0.55±0.51	0.283‡
Systolic BP (mm Hg)	138.96±21.37	131.85±17.16		132.59±21.02		131.11±14.49	
Systolic BP change (mm Hg)†		-6.48±2.75	0.022‡	-5.74±3.16	0.075‡	-7.22±2.97	0.019‡
Diastolic BP (mm Hg)	75.71±11.52	75.19±9.47		75.37±7.70		75.37±6.05	
Diastolic BP change (mm Hg)†		-0.56±1.70	0.745‡	-0.37±1.50	0.805‡	-0.37±1.79	0.837‡

VA;Visual Acuity, CFT;Central Foveal Thickness, MV;Macular Volume, IOP;Intraocular Pressure, BP;Blood Pressure.
**Values are presented in terms of mean±SD.*
†Negative indicates an increase in findings.
‡Repeated-measures analysis of variance (ANOVA) and LSD corrected double compare test
§Wilcoxon signed ranks test.

Bevacizumab at a dose of 1.25 mg in 0.05 mL was injected into the vitreous. The injector was drawn back gently to prevent reflux and a sterile cotton applicator was applied.

The intraocular pressure (IOP) and retinal artery perfusion were then checked and the patients were told to use topical antibiotics for 7 days.

Follow-up Examinations and Outcome Measures

Patients were examined at the first day, and 4, 8 and 12 weeks after the injection. During each visit, the patients' VA was determined and they underwent complete ophthalmic examination using the same procedures as at the baseline. OCT or FA was performed in several patients and the injections were repeated according to the investigator's decision and preference. In addition, the blood pressure (BP) was measured and local and systemic adverse events were recorded throughout the study.

Reinjection criteria were:

1- Continuation of DME, increase of CFT, or impaired VA; and

2- No detected serious adverse effect after the first injection.

Primary outcome measures were:

1- Anatomical effects (that is, changes in CFT between baseline and the 4th, 8th, and 12th weeks) on OCT; and

2- Changes in VA between baseline and the 4th, 8th, and 12th weeks.

Secondary outcomes were:

1- Changes in IOP;

2- Changes in BP; and

3- The presence of local and systemic adverse events, which were monitored throughout the study. Patients' VAs detected using Snellen testing were transferred from their records and converted to a "logarithm of the minimum angle of resolution" (logMAR) scale for analysis.[15]

Statistical Analysis

The statistical analysis was performed by SPSS (version 15; SPSS, Chicago, IL, USA). For descriptive purposes, qualitative variables were stated using percentages and quantitative data were reported by mean±SD.

Statistical differences between pre- and post-drug application clinical data were assessed using the Wilcoxon signed-rank test for the mean value of CFT, and repeated-measures analysis of variance (ANOVA) and LSD-corrected double compare test for mean IOP, BP and logMAR VA. A p value<0.05 was considered to be significant.

RESULTS

All the eyes included underwent more than 1 (range, 1-3) IVB injections. Twenty-one eyes (23.6%) received 2, three eyes (3.4%) received 3 injections. After the injection, the minimum follow-up was 12 weeks. All patients had type II diabetes.

Table 3: *Change in visual acuity assessment by Snellen chart.*

Change in visual acuity	4th week	8th week	12th week
≥2 lines decrease, n (%)	17 (19.1)	17 (19.1)	17 (19.1)
Not change, n (%)	51 (57.3)	46 (51.7)	44 (49.4)
≥2 lines increase, n (%)	21 (23.6)	26 (29.2)	28 (31.5)

At the last 6 months, 40 eyes (44.9%) were treated for macular edema. Macular photocoagulation had been applied once in 29 eyes (32.6%), twice in 6 eyes (6.7%). Panretinal photocoagulation had been performed on 15 eyes (16.9%), and previous IVTA had been performed once on 11 eyes (12.4%). The baseline characteristics are shown table 1. Changes in VA, CFT, MV, IOP, systolic and diastolic BP are summarized in table 2.

Visual Acuity

Mean VA was improved significantly at posttreatment 4th (0.90±0.06 logMAR with a 95% confidence interval of 0.01 to 0.27, p<0.05) and 8th (0.88±0.07 logMAR with a 95% confidence interval of 0.03 to 0.29, p<0.05) weeks and without statistical significance at the 12th (0.94±0.08 logMAR, p>0.05) week with respect to the baseline level (1.04±0.08 logMAR), (Table 2). Visual loss of ≥2 lines on the Snellen chart was detected in 17 eyes (19.1%) at the 4th, 8th, and 12th weeks (Table 3).

Central Foveal Thickness

There were significant reductions in mean CFT at the 4th (301.5±131.9 µm, .p<0.01), 8th (302.6±113.4 µm, p<0.01) and 12th (326.3±171.7 µm, p<0.05) weeks of treatment when compared to the baseline value (352.8±154.7 µm) (Table 2). A ≥20% decrease in CFT was detected in twelve eyes (44.4%) at the 4th week, eleven eyes (73.3%) at the 8th week, and six eyes (50%) at the 12th week. Figure 1 represents an exemplary course.

Factors Affecting the Success of Treatment

A multiple stepwise regression model for VA at 4th week was found to be significant (total model R^2=0.472; p=0.023). In the model equation, only baseline VA contributed significantly to the model (standardized β-0.432; p=0.014), while other variables including age, sex, duration of diabetes, or not being treated within the last 6 months, number of intravitreal injections, type of DR, and baseline CFT did not contribute to the model (p>0.05). However, the multiple stepwise regression model for VA at the 8th and 12th weeks was not found to be significant (respectively total model R^2=0.350; p=0.152 and total model R^2=0.398; p=0.079). In spite of this, in model equation for VA at the 8th week with baseline VA as the only factor contributed to the model (standardize β-0.381; p=0.045), while no variable contributed to the model for VA at the 12th week (p>0.05).

Intraocular Pressure

Changes in IOP are summarized in table 2. Mean baseline IOP was 13.12±3.56 mm Hg. During the follow-up, a statistically significant change in IOP was not found in eyes treated with Bevacizumab.

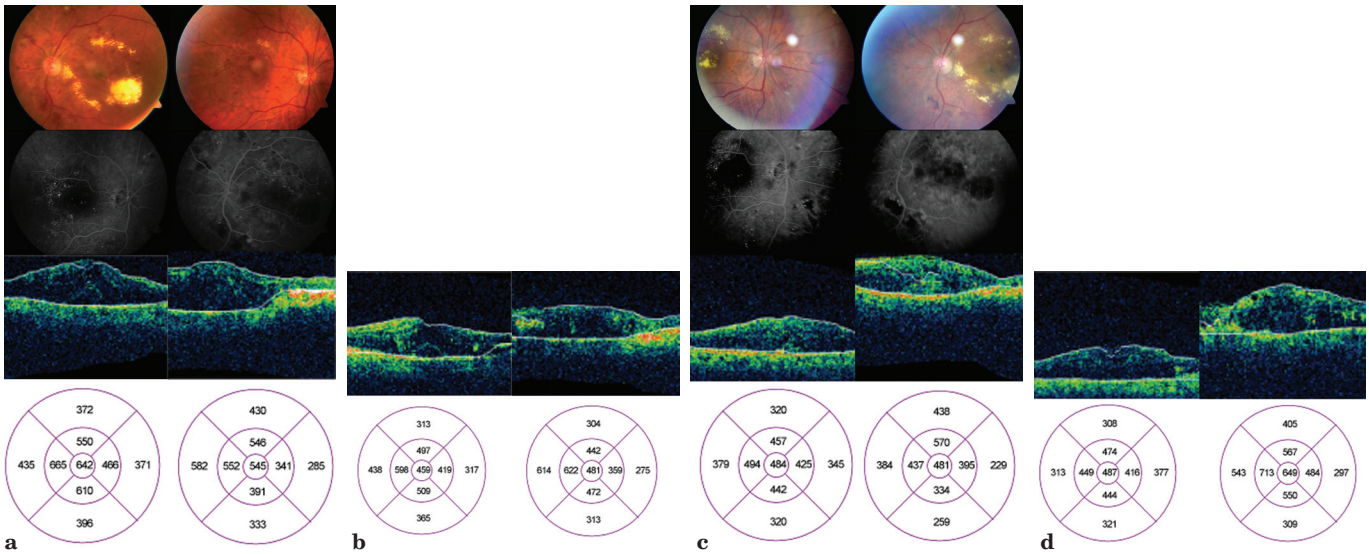

Figure 1a-d: *The patient with bilateral diabetic macular edema underwent an intravitreal injection of bevacizumab at a dose of 2.5 mg in bilateral eyes. Colour fundus photography and fluorescein angiography were taken. Retinal thickness measured by optical coherence tomography at* ***a****, baseline;* ***b****, four weeks;* ***c****, eight weeks;* ***d****, twelve weeks after the injections. There were reductions in CFT at 4th, 8th in either eyes, and 12th weeks of treatment only in the right eye when compared to baseline value. OD, right eye; OS, left eye.*

IOP rise over 21 mmHg was observed in 5 eyes (5.5%) [in one eye (%1.1) at the 4th week, in two eyes (%2.2) at the 8th week, and in two eyes (2.2%) at the 12th week]. The elevated IOP was temporary and controlled with an anti-glaucoma drop.

Blood Pressure

Changes in BP are demonstrated in table 2. Mean baseline systolic and diastolic BP was 139.0±21.4 mm Hg (100-180) and 75.7±11.5 mm Hg (60-110), respectively. Thirty-five patients (56.5%) were hypertensive and their BP was regulated with medical therapy. Although the difference between baseline and the 4th and 12th week systolic BP was statistically significant, no considerable clinical change was observed in the patients. Change in diastolic BP was not found to be statistically significant during the follow-up.

Other Adverse Effects

After the IVB, potential procedure-related adverse effects were observed in three eyes (3.3%) [corneal epithelial abrasion in one eye (1.1%), subconjunctival hemorrhage in one eye (1.1%), and endophthalmitis in one eye (1.1%)]. Corneal abrasion and subconjunctival hemorrhage were temporary and improved on the 2nd day and first week respectively. In only one case with endophthalmitis, pars plana vitrectomy and phacoemulsification were performed after intravitreal vancomycin-ceftazidime injection. A bevacizumab-related adverse effect was temporary anterior chamber reaction seen in six eyes (6.6%) which were treated with medical treatment. No systemic adverse effect was seen in the patients during follow-up.

DISCUSSION

Anti-VEGF agents have led to an advancement in the treatment of various vascular diseases. Considering the role of VEGF in influencing structural and functional changes in DR, VEGF blockade is an attractive therapeutic approach.[1] After IVB injection, Paccola et al.[16] and Haritoglu et al.[17] reported significant improvement in VA from baseline at weeks 4 (logMAR 0.14) and 6 (logMAR 0.11) respectively. Sohelilian et al.[18] observed a 0.2-logMAR improvement in VA (≈ 2 Snellen lines), persisting for at least 12 weeks. Moreover, Arevalo et al. showed continued improvement in best-corrected VA throughout the 1-, 3-, 6-, 12-, and 24-month follow up.[19] We found a significant improvement in VA at weeks 4 (logMAR 0.14) and 8 (log MAR 0.16). Although it was not statistically significant, improvement in VA from baseline at week 12 (logMAR 0.10) was also determined. We also evaluated factors potentially correlated with VA at the 4th, 8th, and 12th week and detected that only baseline VA was significantly associated with VA at the 4th and 8th week. Patients with worse baseline VA, which may be a sign of more severe and/or more prolonged disease, were more prone to loss of vision.

Haritoglu et al.,[17] determined significant reduction in CMT values from baseline at weeks 2 (15%), 6 (17%) and 12 (25%) after repeated IVB (1.25 mg) injections. Similarly, Paccola et al.[16] detected significant CMT reduction at weeks 4 (23%) and 8 (21%) after only one IVB (1.5 mg) injection. Shimura et al.[4] found significant CMT reduction at week 1 (24%), 4 (18%) and 12 (6%) after one IVB injection, and this effect decreased in the course of time.

The Pan-American Collaborative Retina Study Group (PACORES)[9] demonstrated a dramatic decrease (26%) of DME one month after multiple IVB injections, and those decreased levels were maintained for up to six months. Arevalo et al.,[19] detected that the decrease in CMT continued throughout the 24-month follow up. In our study, we found significant CMT reductions at week 4 (44%), 8 (73%) and 12 (50%). The crucial difference between the studies is the initial foveal thickness, representing severe macular edema (525.0 µm) in the Shimura et al. study,[4] moderate macular edema (387.0 µm) in the PACORES study[9], and moderate macular edema (352.8 µm) in our group. In this respect, IVB injection may be thought to be more effective in reducing CFT in minor or moderate DME rather than severe edema. At the same time, VA changes would not be always parallel to CMT changes in DME because of structural damage to the photoreceptors, RPE atrophy, lipid exudates and macular ischemia.[20] Although our study is non-comparative, some studies were designed to compare bevacizumab therapy with other treatment strategies including MPC and IVTA for DME.[21-23]

The DRCR Network group and the Bevacizumab or Laser Therapy in the management of diabetic macular edema study (BOLT) demonstrated the use of bevacizumab to be more effective than MPC in patients with center-involving DME without advanced macular ischemia at the 12-month follow up.[21,22] Also Soheilian et al.[23] detected that the slight superiority of IVB over combined IVB/IVTA and MPC at month 6 did not continue to 24 months in the treatment of primary DME.

In the RESTORE study on Ranibizumab, another inhibitor of VEGF approved for the treatment of visual impairment associated with DME, 1-year treatment with ranibizumab was reported to be more effective than sham or focal/grid laser therapy and 1 year of treatment with ranibizumab as an adjunct to laser therapy was also demonstrated to be more effective than laser monotherapy in improving VA and CMT in patients with visual impairment associated with DME.[24]

In addition, improvements in best corrected VA with ranibizumab alone or as an adjunct to laser therapy were associated with gains in vision-related quality of life, as assessed using the National Eye Institute Visual Functioning Questionnaire-25.[24]

Systemic VEGF blockage can give rise to complications including systemic hypertension, thromboembolic disease, gastrointestinal perforation, hemorrhage, hypertensive crisis, nephrotic syndrome or even death.[1,25] Rosenfeld et al.,[26,27] suggested the administration of IVB as an alternative to minimize the systemic risks associated with systemic anti-VEGF treatment. Fewer adverse effects may be expected as the intravitreal dose (1.25 mg) is 300-400 times less than intravenous dose.

In the internet-based voluntary survey of Fung et al.[28] on IVB treatment of neovascular and exudative ocular disease (7.113 injections on 5.228 patients), 2 deaths, 5 cerebrovascular accidents and 15 BP elevations were reported. In the series of PACORES[25] on IVB treatment of proliferative diabetic retinopathy, DME, retinal vein occlusions and choroidal neovasculazation (4.303 injections on 1.173 patients), systemic adverse events including 7 acute systemic BP elevations, 6 cerebrovascular accidents, 5 myocardial infarctions, 2 iliac artery aneurysms, 2 toe amputations and 5 death were detected.

Kernt et al.,[29] detected that the 1-hour and 6-hour diastolic BP values were significantly lower than before surgery, but was not significant at future weeks. They interpreted this alteration as physiological diurnal change or a response to the easing of survey-related stress. On the other hand, most clinical and experimental studies confirmed a lack of serious systemic and ocular complications following an IVB injection and intravitreal bevacizumab has been thought to be safe to use at least in the short term.[30]

We did not detect acute systemic BP elevations and cerebrovascular accidents after IVB injection, and the 4-week and 12-week systolic BP was statistically significant lower than the baseline. We did not observe any statistically significant change in diastolic BP. No serious clinical change was detected so we interpreted any alterations as physiological diurnal changes similar to Kernt et al.[29]

Ocular complications following IVB including seven (0.16%) endophthalmitis, seven (0.16%) tractional retinal detachment, four (0.09%) uveitis, one (0.02%) rhegmatogenous retinal detachment and one (0.02%) vitreous hemorrhage cases were detected in the series of PACORES[25] (4.303 injections on 1,173 patients). Adverse events such as glaucoma and cataract progression may be expected after intravitreal injection of triamcinolone.[16]

We did not find any relation between the incidence of elevation of IOP, cataract developing or progression, and endophthalmitis and the use of IVB, similar to other studies[10,29,31-33]. No significant change in the mean IOP was observed during the follow-up period, and only one serious vision-threatening complication associated with IVB infectious endophthalmitis was encountered. Bacterial endophthalmitis is an expected and fearful complication of any intravitreal injection. The rate of bacterial endophthalmitis following intravitreal injections is 0.1% to 1.6%.[25,34] Our rate of bacterial endophthalmitis of 0.86% (1/116 injections) is similar to that reported in the literature.[34]

Anterior chamber reaction within 1 week of IVB injection was not detected by Kiss et al.,[35] On the other hand, Soheilian et al.,[18] and Ahmadieh et al.,[36] observed a rate of mild anterior chamber reaction of 18.9% and 19.5% respectively. Ahmadieh et al.,[36] detected that this finding disappeared spontaneously in all eyes within 1 week. Similarly, we found a 2.2% rate of mild anterior chamber reaction and it was easily managed with topical corticosteroids.

The first restrictive property of bevacizumab is the necessity for repeat doses due to recurrence of macular edema;[37] moreover, the terminal half-life ($T_{1/2}$) of intravitreal injection of 1.25 mg of IVB has been shown to be 9.8 days.[38] During the application of repeated IVB injections, one should pay attention not to impair VEGF-mediated normal physiological functions, causing regression of normal vasculature as well as reduction of VEGF-mediated neuroprotection.[18] The other restrictive property of bevacizumab is its off-label use.

A major drawback of this study is the lack of a control group. The other limitations include its short time interval, lack of patients with homogeneous eye conditions such as macular morphology, lens status, previous treatment history, and different intervals between the sequential injections and lack of subgroup analysis according to the initial characteristics of DME such as mild versus moderate visual loss or focal versus diffuse macular edema. In addition, our study included an insufficient number of cases to determine the IVB safety and this was another weak aspect. On the other hand, the positive characteristic of this study is its prospective design.

In summary, an intravitreal injection of 1.25 mg bevacizumab causes visual improvement and CMT decrease, leading to hope for its use in patients with refractory DME as a new treatment agent. Moreover, it appears to be safe and well tolerated during a 12-week period.

Further randomized controlled studies with larger numbers and longer follow-up periods are needed.

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