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Research Article

Effect of bevacizumab, which remain after withdrawal of the first dose/s from a single-use vial on diabetic macular edema

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ABSTRACT

Background: The objective of this study was to investigate the effect of bevacizumab remaining after withdrawal of the first dose/s from a single-use vial in diabetic macular edema (DME) secondary to diabetic retinopathy.
Methods: Patients were divided into four groups according to duration of storage of the single-use vial of bevacizumab in the refrigerator: Group 1 received IVB when the vial was first opened, and Groups 2, 3, and 4 received IVB after 3, 7, and 15 days, respectively, after the first dose or doses had been withdrawn with an insulin (27-gauge) needle from the single-use vial. The Wilcoxon test was used to compare the results in four groups. $p<0.05$ was considered as statistically significant.
Results: Mean age, mean glycosylated hemoglobin, severe of retinapathy and status of the lens were similar in all groups ($p>0.05$). Preinjection mean best corrected visual acuity (BCVA) was 0.41±0.2; 0.39±0.2; 0.39±0.2 and 0.34±0.2 logMAR Group 1, 2, 3 and 4, respectively. Preinjection mean central macular thickness (CMT) was 503±88; 502±99; 565±63 and 491±107 µm in Group 1, 2, 3 and 4, respectively. After injection mean BCVA was 0.30±0.16; 0.28±0.20; 0.29±0.19 and 0.25±0.20 logMAR and mean CMT was 321±75; 315±97; 360±83 and 279±82 in Group 1, 2, 3 and 4, respectively. The mean BCVA increased significantly, and CMT decreased significantly after injection in all groups. No observed serious ophthalmologic or systemic side effects.
Conclusion: Bevacizumab which remain in the single use vial after first dose/s is safe and effective for treatment of DME. These results are useful for poor countries.

Keywords: Diabetic macular edema, Bevacizumab, Central macular thickness

INTRODUCTION

Diabetic retinopathy (DR) is a major cause of visual loss and blindness.[1] Diabetic macular edema (DME), a common complication of DR, is caused by accumulation of excess extracellular fluid in the macula, disruption of the blood-retina barrier, and abnormal permeability and is associated with increased levels of vascular endothelial growth factor (VEGF).[2] Visual impairment caused by DME may be reversible in the early stages, but prolonged edema causes irreversible damage.[3]

VEGF-A, a strong pro-angiogenic factor, is produced by retinal tissue as well as hypoxic cells and probably contributes to the pathogenesis of DME.[4,5] Intravitreal bevacizumab (a humanized monoclonal antibody to VEGF-A) inhibits all isoforms of VEGF and has been used to treat numerous ophthalmologic disorders. Many studies demonstrate a decrease of macular edema (ME) in diabetic patients with DME and improvement of best corrected visual acuity (BCVA) after intravitreal bevacizumab treatment.[6-12] Anti-VEGF agents are proven therapeutic agents in ophthalmology for the treatment of age-related macular degeneration, DME, and neovascular glaucoma and intravitreal injections of anti-VEGF drugs are effective in decreasing systemic VEGF values.[13-18] Its use for retinal vein occlusion (RVO) was first reported by Rosenfeld in 2005.[19] Currently available vial of bevacizumab contains 100 mg/4 mL and 400 mg/16 mL.

The aim of this study was to evaluate the effect of bevacizumab, which remain and stored in the vial after first dose/s withdrawal from single use vial, on DME.

METHODS

Patients were divided into four groups, and their records were retrospectively evaluated. Group 1 patients received the first dose of bevacizumab from a single-use vial with a 27-gauge needle, and Groups 2, 3, and 4 received bevacizumab, which

remain 3 days, 7 days and 15 days, after the first dose had been withdrawal from the single-use vial, respectively.

All patients were treated in the operating room and received 1.25 mg bevacizumab intravitreally. The injections were performed under topical anesthesia (proparacaine 0.5%) after topical 5% povidone-iodine irrigation at a distance of 3.5 mm from the limbus in the inferior quadrant.

Inclusion criteria were DME (central macular thickness [CMT] >320 μm), no history of intraocular surgery in the last 6 months, and intravitreal injection treatment. Exclusion criteria were the ischemic maculopathy, retinal branch or central RVO, vitreomacular traction syndrome, active proliferative DR, refractive errors (spheric equivalent) <±3.00, epiretinal membrane, glaucoma, trauma, and optic atrophy.

Clinical evaluation of the injected patients was performed at 1, 7, and 30 days after intravitreal bevacizumab injection, and included assessments of BCVA (logMAR) and intraocular pressure (IOP; mmHg) and fundus evaluation using slit lamp biomicroscopy with a +78D (Ocular Osher MaxField® 78D; Ocular Instrument, Concord, CA). CMT was measured using optical coherence tomography (RTVue-100; Optovue Inc., Fremont, CA) before and 1 month after injection. Before injection, all patients underwent fundus fluorescein angiography (Kowa VX-10i; Kowa Company, Ltd., Tokyo, Japan) after pupillary dilatation ([tropicamide 1%; Alcon, Texas, USA], three drops with 5 mins intervals) to exclude ischemic maculopathy. The values of BCVA, IOP, and CMT were compared before and 1 month after intravitreal injection of bevacizumab. All patients provided informed written consent, and all procedures were performed in accordance with the Declaration of Helsinki. Approval of the Local Ethics Committee was obtained.

Data analysis was performed using SPSS 18.00. Descriptive statistics were determined for overall patients and patients by groups. Numeric variables are presented as mean and standard deviation. The Kruskal–Wallis test was used to compare age and BCVA variables among the groups, and the Wilcoxon signed-rank test was used to compare CMT scores before and after treatment.

RESULTS

This study included 56 eyes of 56 (female: 32, male: 24), (Table 1), patients with DME secondary to DR. BCVA, IOP, and CMT for baseline and after injection were summarized in Table 2. All patients received one injection of bevacizumab (1.25 mg/0.05 mL). The vial of bevacizumab (Avastin®; Genentech Inc., South San Francisco, CA) was stored in the refrigerator at 4°C in the operating room.

Subconjunctival hemorrhage (SCH) was recorded in 10 (17.8%) patients and was the most frequent side-effect observed as a result of intravitreal bevacizumab injection. Retinal detachment (RD), endopthalmitis, elevated IOP, and intraocular hemorrhage were not observed, and no systemic side effects occurred in any of the patients (Table 3).

Table 1: Demographic and clinical data of patients.

Parameters	Group 1 (n=14)	Group 2 (n=12)	Group 3 (n=16)	Group 4 (n=14)	p
Mean age	58.43±6.6	59.34±6.2	64.88±10.3	59±10.4	p>0.05
F/M	8/6	7/5	9/7	8/6	p>0.05
Hypertension	10	9	11	10	p>0.05
DR (mild/moderate NPDR/inactive PDR)	6/7/1	6/5/1	7/8/1	7/6/1	p>0.05
Phakic/pseudophakic	12/2	11/1	14/2	13/1	p>0.05
HbA1c	7.2±2.1	6.9±2.3	7.0±2.0	7.1±1.9	p>0.05

F/M: Female/male, DR: Diabetic retinopathy, NPDR: Nonproliferative diabetic retinopathy, PDR: Proliferative diabetic retinopathy, HbA1c: Glycosylated hemoglobin

Table 2: Data of four group for preinjection and after injection.

Parameters	Group 1 (n=14)	Group 2 (n=12)	Group 3 (n=16)	Group 4 (n=14)	p
BCVA (pre injection)	0.41±0.2	0.39±0.2	0.39±0.2	0.34±0.2	>0.05
BCVA (after injection)	0.30±0.16	0.28±0.20	0.29±0.19	0.25±0.20	>0.05
IOP (pre injection)	17.3±3.2	16.4±2.8	17.8±2.7	16.2±3.1	>0.05
IOP (after injection)	16.8±2.9	16.2±3.2	17.8±2.7	15.8±4.2	>0.05
CMT (pre injection)	503±88	502±99	565±63	491±107	>0.05
CMT (after injection)	321±75	315±97	360±83	279±82	>0.05
z	−2.366	−1.363	−2.240	−2.366	
p	0.018	0.173	0.025	0.018	

BCVA: Best corrected visual acuity, IOP: Intraocular pressure, CMT: Central macular thickness

Table 3: Complications of intravitreal bevacizumab injection.

Parameters	n
Endopthalmitis	0
VH	0
Glaucoma	0
RD	0
SCH	10
Systemic side events	0

VH: Vitreous hemorrhage, RD: Retinal detachment, SCH: Subconjunctival hemorrhage

There were significantly improved BCVA and significantly decreased CMT, and there was no diminished effect of injection of bevacizumab that had been refrigerated after the first dose had been withdrawn from the single-use vial.

DISCUSSION

Diabetic maculopathy is the main cause, apart from proliferative DR, of visual loss in patients with DR.[20-22] If left untreated, 25-30% of patients affected by DME experience a 15-letter decrease in BCVA score within 3 years, and approximately 50% of DME patients will exhibit a loss of more than two lines of BCVA after 1 year of follow-up.[23-25] Available alternative therapies for DME are laser photocoagulation, intravitreal corticosteroids, and anti-VEGF.[26] Macular laser photocoagulation has been the standard of care since the early treatment of DR study demonstrated in 1985 that it reduced the risk of moderate visual loss in patients with clinically significant DME by nearly 50% at 3 years. However, improved BCVA was found in <3% of cases at 3 years, even though 40% of patients with entry BCVA of ≥20/40 showed an improvement of one or more lines.[27] As a result, it should be considered that a notable number of patients are unresponsive to photocoagulation. The anti-inflammatory activity of corticosteroids is related to several paths of action. Corticosteroids interfere with regulatory components of gene expression and inhibit the expression of proinflammatory genes such as tumor necrosis factor α and other cytokines, and corticosteroids inhibit the expressions of VEGF and VEGF gene.[28-30] However, elevation of IOP and the need for cataract surgery were higher in patients that received triamcinolone acetonide.[31,32]

VEGF has been linked to leakage of retinal vessels and hence to the formation of retinal edema, and anti-VEGF therapy for DME has been extensively studied.[33-36] Ranibizumab is effective on DME also its have single dose/s for ophthalmologic indications but it is very costly.

Commercially available vial of bevacizumab contains 100 mg/4 mL or 400 mg/16 mL. The optimal treatment is a vial for each patient, but this is expensive and not suitable for developing or poor countries. Using one vial for each patient or throw the vial after first dose/s withdrawn would be very costly. Currently, there is no small preparation dose of bevacizumab for ophthalmic indication.

Two studies reported that use of refrigerated bevacizumab after first use from vial is safe and effective in patients with DME.[37,38] In practice, many ophthalmologists use a single vial of bevacizumab for more than one patient during 1 day or treatment situation. This involves collecting patients with DME over a period of time, which may result in irreversible loss of photoreceptors of the retina with a poor vision outcome for patients and a long treatment session for the ophthalmologist and patient.

Visual impairment caused by DME may be reversible in the early stages, but prolonged edema causes irreversible damage, waiting for an adequate number of patients is hazardous for long-term BCVA.

Performed multiple intravitreal injection for multiple patients in one session or in 1 day can be associated with side effects. There is an increased risk of endopthalmitis - A serious risk for vision loss - with injections performed on multiple patients at the same time.[39] Subconjunctival hemorrhage (SCH) was recorded in 10 (17.9%) patients, but marked inflammation, lens injuries, vitreous hemorrhage, RD, and endophthalmitis were not recorded.

In a 2-year retrospective study of bevacizumab treatment for DME, the rate of cardiovascular events was found to be only 1.2%.[40] Although cardiovascular events do not appear to be increased with intravitreal anti-VEGF drugs, large-scale safety studies are still needed. It should also be noted that most trials exclude patients with recent cardiovascular events. Endophthalmitis secondary to anti-VEGF treatment is rare. Systemic side effects were not recorded in this study.

This study had the following limitations: small sample size, grade of DR was not determined, VEGF levels in the vitreous before and after injection were not measured, only DME secondary to DR was included, and DME secondary to RVO was excluded.

Effectiveness of remaining bevacizumab after withdrawal of the first dose or doses from a single-use vial was not lost over 15 days if the vial was stored in suitable conditions. This approach appears to be safe and effective. Current results were supported by literature.

The use of remaining drug will help lower costs in treatment of DME. Studies with larger sample size are warranted to substantiate this finding, which has tremendous socioeconomic implications for resource-poor countries.

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Ethics Committee

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