

Short term effect of intravitreal bevacizumab for diabetic macular edema associated with epiretinal membrane

Maryam Ashraf Khorasani, Tafgeh Mohammadi, Mahmoud Motallebi, Pasha Anvari, Ahad Sedaghat, Khalil Ghasemi Falavarjani
Eye Research Center, Rassoul Akram Hospital, Iran University of Medical Sciences, Tehran, Iran

Correspondence to: Khalil Ghasemi Falavarjani, MD,
Eye Research Center, Rassoul Akram Hospital, Sattarkhan-Niaiesh St., Tehran, Iran,
PO Box: 1445613131, Tehran, Iran,
Phone: +9812 172 5850, +9821 665 091 62, Fax: +9821 665 091 62,
E-mail: drghasemi@yahoo.com

Accepted: August 19th, 2018

Abstract

Purpose: To evaluate the effect of intravitreal bevacizumab (IVB) injection on central macular thickness (CMT) in patients with diabetic macular edema (DME) associated with epiretinal membrane (ERM) and compare the results to those with DME without ERM.

Methods: 54 eyes of 54 patients with DME were included in this prospective comparative case series. Twenty-eight patients had ERM. All patients received 2.5 mg/0.1 ml IVB. The primary outcome measure was the change in central macular thickness (CMT) and the secondary outcome measure was the change in best corrected visual acuity (BCVA), one month after the IVB injection.

Results: All the patients completed 1-month follow-up. One month after the IVB injection, there was no statistically significant reduction in terms of CMT for the ERM group ($22.64 \pm 70.1 \mu\text{m}$; $P = 0.099$), unlike eyes with DME alone ($60.34 \pm 88.5 \mu\text{m}$; $P = 0.002$). Patients with ERM had a -0.09 ± 0.14 log MAR improvement in their BCVA ($P = 0.001$) vs. 0.03 ± 0.14 log MAR change in the patients who did not have ERM ($P = 0.37$).

Conclusion: In this study, intravitreal bevacizumab resulted in improvement in BCVA in patients who had DME associated with ERM. However, in patients who only had DME, despite a reduction in CMT, no improvement in BCVA occurred. Future randomized clinical trials are warranted to precisely assess the effect of bevacizumab on the ERM.

Keywords: diabetic macular edema, epiretinal membrane, Bevacizumab

Introduction

Diabetic macular edema (DME) is the most common cause of visual impairment in diabetic patients [1]. The estimated prevalence of DME ranged from 3.15% to 19.96% in patients with diabetes, but the prevalence of this disorder was notably variable according to the population and method of the study [2].

According to the ETDR study, macular laser photocoagulation was considered the standard treatment for eyes with clinically significant DME for many years [3]. After the introduction of anti-vascular endothelial growth factor (anti-VEGFs) drugs, many studies have shown superiority of these agents to macular photocoagulation in DME. Currently, the anti-VEGF medications are standard treatment for center-involving DME [4,5].

Epiretinal membrane (ERM) is a fibrocellular membranous structure over the retinal surface that presents as a hyperreflective membrane over the innermost layer of the retina in optical coherence tomography (OCT) [6]. Diabetic retinopathy is one of the most important risk factors for ERM formation. ERM has been reported in 14-30% of the eyes with center involving diabetic macular edema [7,8]. In addition, eyes with DME who received intravitreal injection of anti-VEGFs may be at risk of ERM formation [9].

The simultaneous presence of ERM and diabetic macular edema may affect the therapeutic role of anti-VEGF agents on DME. To date, only very few studies have focused on the effect of epiretinal membrane on outcomes of intravitreal anti-VEGFs for treating DME and results of these studies are not consistent [10,11]. Also, none of them has been specifically studied the effect of Bevacizumab. The aim of this study was to evaluate the effect of ERM on anatomical and visual outcomes of intravitreal Bevacizumab injection (IVB) in eyes with center involving DME.

Methods

Consecutive patients with DME with and without ERM were included in this prospective comparative case series, from October 2014 to October 2017. The study protocol was approved by the Institutional Review Board/ Ethics Committee of the Eye Research Center of Rasoul Akram Hospital and carried out in accordance with the Helsinki Declaration. The patients included had to have DME with a central macular thickness more than 300 microns and best corrected visual acuity (BCVA) between 20/400 and 20/40. Patients with proliferative diabetic retinopathy, any ocular disease other than diabetic retinopathy (including glaucoma, cataract, and uveitis), any intravitreal injection (anti-VEGF, steroid) within the past three months, previous vitreoretinal surgery, any ocular surgery (except for uncomplicated phacoemulsification within the past six months), and history of macular photocoagulation in past three months were excluded. Informed consents were obtained.

Complete ophthalmic examination (BCVA measurement with E chart, slit lamp biomicroscopy, fundus examination, and

Goldmann applanation tonometry) and retinal imaging using spectral domain OCT (Spectralis; Heidelberg Engineering, Heidelberg, Germany) was performed for all patients before and one month after IVB.

OCT scans were obtained for all patients, using either Spectralis HRA-OCT (Heidelberg Engineering, Heidelberg, Germany) or Topcon OCT (1000-type 2, Tokyo, Japan) instruments. The OCT device was the same for each patient before and after injections. The OCT volume scan size was 20°×20° area for Spectralis, and 6 × 6 mm² 3D scan pattern for Topcon device. Average thickness of points within the 1-mm circle of the center of fovea in each OCT device was recorded as CMT. Epiretinal membrane was defined as a hyper-reflective layer over the retinal surface. Eyes with vitreomacular traction were excluded.

Intravitreal bevacizumab (Avastin; Genentech Inc, South San Francisco, CA) was performed for all patients under sterile condition in operating room. After applying topical tetracaine 1%, periocular skin and eyelid and eyelashes were scrubbed with povidone-iodine 10%, then eyelid speculum was inserted and ocular surface and fornices were rinsed with 1-2 drops of povidone-iodine 5% for 2 minutes. Intravitreal injection of 2.5 mg (0.1 ml) bevacizumab was administered using a 30-gauge needle.

The main outcome measure was changes in central macular thickness (CMT), one month after injection. The secondary outcome measure was the change in BCVA.

For statistical analysis, Snellen visual acuity was converted to logarithm of the minimum angle of resolution (log MAR). Changes in BCVA and CMT were compared between the two groups. Data were analyzed using SPSS software version 16 (SPSS Inc., Chicago, IL, USA). Variables were checked for normal distribution with the Kolmogorov-Smirnov test. Mann-Whitney U test was used to make a comparison between the groups and the Wilcoxon test was used to analyze changes in the variables before and after injection. A P value less than 0.05 was considered statistically significant.

Results

Twenty-eight eyes of 28 patients (12 males and 16 females) with ERM and twenty-six eyes of 26 patients (12 males and 1 female) without

ERM were enrolled into the study. Baseline characteristics are presented in **Table 1**. The age, sex, lens status, duration of DM and the

presence of hypertension were statistically similar between the groups.

Table 1. Baseline characteristics of patients included in the study

	DME without ERM	DME with ERM	P value
No. of eyes (patients)	26(26)	28(28)	
Eye (right/ left)	18/ 8	14/ 14	0.151
Average age (\pm SD), years	59.9 \pm 9.7	60.7 \pm 8.0	0.518
Sex (male/ female)	12/14	12/16	0.651
Duration of DM (years \pm SD)	15.2 \pm 4.4	13.5 \pm 4.7	0.806
Hypertension (yes/ no)	9/ 17	11/ 17	0.723
Lens status (phakic/ pseudophakic)	23/ 3	19/ 9	0.069
Average BCVA at baseline (log MAR \pm SD)	0.57 \pm 0.26	0.88 \pm 0.29	0.000
Average CMT at baseline (micron \pm SD)	446.96 \pm 125.48	479.28 \pm 110.43	0.319
Average BCVA at one month (log MAR \pm SD)	0.60 \pm 0.33	0.78 \pm 0.26	0.035
Average CMT at one month (micron \pm SD)	386.61 \pm 114.73	456.64 \pm 123.54	0.036

ERM = Epiretinal membrane, BCVA = Best corrected visual acuity, CMT = Central macular thickness, DME = Diabetic macular edema, Log MAR = Logarithm of minimal angle of resolution.

Baseline central macular thickness was statistically similar between the two groups; however, baseline BCVA in DME associated with ERM was statistically significantly worse than in the no-ERM group (0.88 ± 0.29 versus 0.57 ± 0.26 , $P < 0.001$).

One month after the injections, the mean CMT was $456.6 \pm 123.5 \mu\text{m}$ in the ERM group and $386.6 \pm 114.7 \mu\text{m}$ in the no-ERM group ($P=0.036$). The statistically significant decrease in CMT ($P=0.002$) was detected in the no-ERM group, but not in the ERM group ($P=0.09$).

One month after the injection, the mean BCVA in the ERM group was 0.78 ± 0.26 logMAR, and in the no-ERM group was 0.60 ± 0.33 logMAR ($P=0.35$). The BCVA change was statistically significant in the ERM group, but not in the no-ERM group ($P=0.002$ and $P=0.324$, respectively). The mean change in BCVA was -0.09 ± 0.14 logMAR in the ERM group and 0.03 ± 0.16 logMAR in the no-ERM group ($P=0.004$).

Discussion

DME is one of the most common causes of blindness in diabetic patients [1]. Currently,

intravitreal injection of anti-VEGFs drugs is the most effective and safe treatment for DME causing decreased vision [12,13]. Approximately 30% of the eyes with DME may have ERMs [14]. Few studies have investigated the effect of ERM on the therapeutic effects of anti-VEGFs agents on DME [10,11] and there is no study reported the impact of ERM specifically on bevacizumab effects for treating DME. Therefore, this is the first report specifically describing the effects of IVB on DME associated with ERM.

Several studies have reported the effect of ERM on response to anti-VEGF agents in retinchoroidal diseases other than diabetic retinopathy [15-19]. In a retrospective chart review of 63 eyes of 63 patients, Alkin et al. did not find any significant differences in terms of BCVA improvement, central retinal thickness (CRT) change and mean number of bevacizumab injections in eyes with naive treatment newly diagnosed neovascular AMD alone, and those associated with ERM in an over 24-months follow-up [15]. Chatziralli et al. stated that in a one-year follow-up, patients with wet AMD and ERM needed more injections than patients with

wet AMD alone. Both groups had significant BCVA improvement and CRT reduction, although there was no significant difference in BCVA and CRT between the two groups at the end of the follow-up [16]. Cho et al. concluded that the presence of ERM in eyes with neovascular AMD decreases the effect of anti VEGFs intravitreal injection in reducing central foveal thickness but does not have an effect on visual improvement by using this drug [17].

In this study, we found significant improvement in BCVA despite the insignificant reduction in CMT. In the no-ERM group, the BCVA remained unchanged despite significant reduction in CMT. Baseline BCVA was different between the two groups; however, the main outcome measure was CMT, which was similar at baseline. Yoon et al. noted that the presence of vitreomacular interface abnormalities reduced the effect of anti-VEGFs (ranibizumab and bevacizumab) on DME. Their study included ERM associated with DME as a vitreomacular interface abnormality. In contrast with our findings, baseline BCVA did not differ between groups, and after three injections both groups showing significant improvement compared to baseline BCVA but BCVA increase was statistically significant higher in the DME group. This finding can be related to the inclusion criteria that in their study any abnormalities in vitreomacular interface were included [10]. Ercalik and his associates found that intravitreal ranibizumab in patients with DME and ERM reduced CMT significantly but the change in BCVA after injection was not significant, both of BCVA and CMT reduced significantly in patients with DME alone. Significantly worse baseline BCVA in their study was consistent with our study. They hypothesized that insignificant improvement in BCVA was associated with the worse baseline BCVA in DME/ ERM group and this difference was attributable to the older age of this group [11].

Several studies have reported the absence of a linear correlation between the improvement in BCVA and the reduction of CMT [20-22]. The contradiction between the various studies that examined the effect of ERM on the response to treatment with anti-VEGFs, intravitreal triamcinolone, or macular photocoagulation may be due to the fact that there are other parameters in the OCT that can predict the BCVA

in DME more strongly than the retinal thickness [23-27]. Disruption of the photoreceptor IS/ OS junction and the integrity of the external limiting membrane are other important parameters for BCVA prediction in patients with DME [23,25-27].

Our study had several limitations. The sample size was small, the follow up was short, and the groups were not matched for BCVA. Also, the pattern of diabetic macular edema, and the integrity of inner and outer retinal layers were not analyzed. The response to treatment may be different based on the pattern of DME [11,28].

In conclusion, this study demonstrated that after the single injection of intravitreal Bevacizumab, BCVA improved significantly in eyes with DME associated with ERM and resulted in significant CMT reduction in eyes with DME alone. Future larger studies are needed to determine the effect of ERM on the response to anti-VEGF agents.

Financial interest

None of the authors has any financial interest in the subject matter of this paper.

Acknowledgement

Authors would like to thank Dr. S. Bakhti for her contribution in gathering the data of some patients.

References

1. Varma R, Bressler NM, Doan QV, Gleeson M, Danese M, Bower JK, Selvin E, Dolan C, Fine J, Colman S. Prevalence of and risk factors for diabetic macular edema in the United States. *JAMA Ophthalmol.* 2014; 132(11):1334-40.
2. Yau JW, Rogers SL, Kawasaki R, Lamoureux EL, Kowalski JW, Bek T, Chen S-J, Dekker JM, Fletcher A, Grauslund J. Global prevalence and major risk factors of diabetic retinopathy. *Diabetes Care.* 2012; 35(3):556-64.
3. Group ETDRSR. Photocoagulation for diabetic macular edema: Early Treatment Diabetic Retinopathy Study report number 1. *Arch Ophthalmol.* 1985; 103:1796-806.
4. Tan GS, Cheung N, Simó R, Cheung GC, Wong TY. Diabetic macular oedema. *Lancet Diabetes Endocrinol.* 2017; 5(2):143-55.
5. Jampol LM, Bressler NM, Glassman AR. Revolution to a new standard treatment of diabetic macular edema. *JAMA.* 2014; 311(22):2269-70.
6. Stevenson W, Ponce CMP, Agarwal DR, Gelman R, Christoforidis JB. Epiretinal membrane: optical

- coherence tomography-based diagnosis and classification. *Clinical Ophthalmology*. 2016; 10:527.
7. Khan IA, Mohamed M, Mann S, Hysi P, Laidlaw D. Prevalence of vitreomacular interface abnormalities on spectral domain optical coherence tomography of patients undergoing macular photocoagulation for centre involving diabetic macular oedema. *Br J Ophthalmol*. 2015; 99(8):1078-81.
 8. Cheung N, Tan S-P, Lee SY, Cheung GCM, Tan G, Kumar N, Cheng C-Y, Wong TY. Prevalence and risk factors for epiretinal membrane: the Singapore Epidemiology of Eye Disease study. *Br J Ophthalmol*. 2017; 101(3):371-6.
 9. Chang C, Cheng C, Peng C. The incidence and risk factors for the development of vitreomacular interface abnormality in diabetic macular edema treated with intravitreal injection of anti-VEGF. *Eye*. 2017; 31(5):762.
 10. Yoon D, Rusu I, Barbazetto I. Reduced effect of anti-vascular endothelial growth factor agents on diabetics with vitreomacular interface abnormalities. *International Ophthalmology*. 2014; 34(4):817-23.
 11. Ercalik NY, Imamoglu S, Kumral ET, Yenerel NM, Bardak H, Bardak Y. Influence of the epiretinal membrane on ranibizumab therapy outcomes in patients with diabetic macular edema. *Arquivos Brasileiros de Oftalmologia*. 2016; 79(6):373-5.
 12. Virgili G, Parravano M, Menchini F, Evans JR. Antiangiogenic therapy with anti-vascular endothelial growth factor modalities for diabetic macular oedema. *Cochrane Database Syst Rev*. 2012; 12:CD007419.
 13. Wells JA, Glassman AR, Ayala AR, Jampol LM, Bressler NM, Bressler SB, Brucker AJ, Ferris FL, Hampton GR, Jhaveri C. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema: two-year results from a comparative effectiveness randomized clinical trial. *Ophthalmology*. 2016; 123(6):1351-9.
 14. Ophir A, Martinez M, Mosqueda P, Trevino A. Vitreous traction and epiretinal membranes in diabetic macular oedema using spectral-domain optical coherence tomography. *Eye*. 2010; 24(10):1545.
 15. Alkin Z, Ozkaya A, Osmanbasoglu OA, Agca A, Karakucuk Y, Yazici AT, Demirok A. The role of epiretinal membrane on treatment of neovascular age-related macular degeneration with intravitreal bevacizumab. *ScientificWorld Journal*. 2013; 24:2013:958724.
 16. Chatziralli I, Stavrakas P, Theodossiadis G, Ananikas K, Dimitriou E, Theodossiadis P. The Impact of Epiretinal Membrane in Neovascular Age-Related Macular Degeneration Treatment: A Spectral-Domain Optical Coherence Tomography Study. *Semin Ophthalmol*. 2017; 8:1-6. doi: 10.1080/08820538.2017.1395892.
 17. Cho HJ, Kim JM, Kim HS, Lee DW, Kim CG, Kim JW. Effect of epiretinal membranes on anti-vascular endothelial growth factor treatment for neovascular age-related macular degeneration. *J Ocul Pharmacol Ther*. 2017; 33(6):452-8.
 18. Munk MR, Ram R, Rademaker A, Liu D, Setlur V, Chau F, Schmidt-Erfurth U, Goldstein DA. Influence of the vitreomacular interface on the efficacy of intravitreal therapy for uveitis-associated cystoid macular oedema. *Acta Ophthalmologica*. 2015; 93(7):e561-7.
 19. Terao R, Yuda K, Kure K, Inoue T, Ohtsu H, Yanagi Y. Effect of vitreomacular adhesion on anti-vascular endothelial growth factor therapy for macular edema secondary to branch retinal vein occlusion. *Jpn J Ophthalmol*. 2014; 58(2):139-45.
 20. Mori Y, Suzuma K, Uji A, Ishihara K, Yoshitake S, Fujimoto M, Dodo Y, Yoshitake T, Miwa Y, Murakami T. Restoration of foveal photoreceptors after intravitreal ranibizumab injections for diabetic macular edema. *Sci Rep*. 2016; 6:39161.
 21. Channa R, Sophie R, Khwaja A, Do D, Hafiz G, Nguyen Q, Campochiaro P, Abraham P, Green B, Livermont K. Factors affecting visual outcomes in patients with diabetic macular edema treated with ranibizumab. *Eye*. 2014; 28(3):269.
 22. Mitchell P, Chong V. Baseline predictors of 3-year responses to ranibizumab and laser photocoagulation therapy in patients with visual impairment due to diabetic macular edema (DME): the RESTORE study. *Invest Ophthalmol Vis Sci*. 2013; 54(15):2373.
 23. Maheshwary AS, Oster SF, Yuson RM, Cheng L, Mojana F, Freeman WR. The association between percent disruption of the photoreceptor inner segment-outer segment junction and visual acuity in diabetic macular edema. *Am J Ophthalmol*. 2010; 150(1):63-7.
 24. DRCR Network. Relationship between optical coherence tomography-measured central retinal thickness and visual acuity in diabetic macular edema. *Ophthalmology*. 2007; 114(3):525-36.
 25. Otani T, Yamaguchi Y, Kishi S. Correlation between visual acuity and foveal microstructural changes in diabetic macular edema. *Retina*. 2010; 30(5):774-80.
 26. Shin HJ, Lee SH, Chung H, Kim HC. Association between photoreceptor integrity and visual outcome in diabetic macular edema. *Graefes Arch Clin Exp Ophthalmol*. 2012; 250(1):61-70.
 27. Uji A, Murakami T, Nishijima K, Akagi T, Horii T, Arakawa N, Muraoka Y, Ellabban AA, Yoshimura N. Association between hyperreflective foci in the outer retina, status of photoreceptor layer, and visual acuity in diabetic macular edema. *Am J Ophthalmol*. 2012; 153(4):710-7.
 28. Alkuraya H, Kangave D, El-Asrar AMA. The correlation between optical coherence tomographic features and severity of retinopathy, macular thickness and visual acuity in diabetic macular edema. *International ophthalmology* 2005;26(3):93-9.