The Effect of Epiretinal Membrane on Intravitreal Anti-Vegf Treatment in Diabetic Macula Edema

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ABSTRACT

Purpose: In the study we aimed to investigate effect of concomitant epiretinal membrane on results of anti-VEGF treatment in diabetic macular edema.

Materials and Methods: In the study we included patients with epiretinal membrane and diabetic macular edema who were followed in the retina unit. Patients received initial loading doses of three injections; followed by 0.5 mg/month ranibizumab injections as needed. In all patients, central macular thickness, optical coherence tomography findings and best-corrected visual acuity were evaluated.

RESULTS: The study included 31 eyes of 37 patients (4 patients received bilateral treatment). The mean age of the patients was 62.4±7.4 years. The patients received an average of 3.9 doses of ranibizumab injection. In the study, 12 (38%) of 31 eyes underwent cataract surgery. The mean central macular thickness (CMT) was 429.25±127.41µm at baseline and 324.42±69.74 at the end of treatment ($p< 0.01$). The mean BCVA (logMAR) was determined as 0.64±0.34 at baseline and 0.50±0.27 after the treatment ($p< 0.01$). No significant differences were found in the CMT and BCVA between genders ($p> 0.05$).

Conclusion: It was found that anti-VEGF (ranibizumab) treatment provided significant improvement on CMT and BCVA (logMAR) values in cases with diabetic macular edema and epiretinal membrane.

Keywords: Epiretinal membrane, macular edema, anti-VEGF.

INTRODUCTION

Epiretinal membrane develops through deposition of fibrocellular tissue at inner layer of retina. This fibrocellular tissue is semi-translucent.[1] Many cell types play important role in the pathogenesis, including retina pigment epithelial (RPE) cells, fibrocytes, fibrous astrocytes, glial cells, endothelial cells and macrophages.[2] Idiopathic form is the most common type while secondary causes include intraocular inflammation, trauma, retinal vascular diseases and tumors.[3-5] It is generally seen in patients aged >50 years; however, there is no difference between gender.[6,7] The primary symptoms are metamorphopsia, decreased visual acuity and loss of central vision.[8] Optical coherence tomography (OCT) imaging is gold standard for follow-up and monitoring progression.[9]

Diabetic macular edema (DME) occurs as a result of retinal microvascular injury. Loss of pericytes, glial cell changes and endothelial cell damage develop through several mechanisms. The VGEF is released from damaged retinal structures with impaired oxygenation, which plays role in the progression of macular edema.[10, 11] Although diabetes mellitus appears as most common cause of macular edema, it may be seen as result of macular degeneration-CNVM or in some retinal vascular or hereditary disorders and due to intraocular inflammation. Currently, macular edema can be treated using intravitreal anti-VEGF administration.[12, 13]

In the present study, it was aimed to investigate the likelihood of decreased efficacy by epiretinal membrane, that may occur concurrently with macular edema and form a mechanical barrier for intravitreal anti-VEGF administration.

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Received: 11.04.2021
Accepted: 25.07.2021
Ret-Vit 2021; 375-378
DOİ: 10.37845/ret.vit.2021.30.64

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MATERIAL AND METHOD

This retrospective study was approved by Ethics Committee of Manisa Celal Bayar University (approval date: 25.03.2015/20478486). The study was conducted in accordance to tenets of Helsinki Declaration.

The study included 31 eyes of 27 DME patients (4 patients received bilateral treatment) with had concomitant epiretinal membrane, which could be defined as cellophane maculopathy based on OCT findings, who were followed at Retina Unit of Ophthalmology Department. The inclusion criteria were presence of clinically meaningful macular edema on fundus examination, macular edema confirmed by fluorescein angiography and CMT>300 µm as measured by OCT. The exclusion criteria were decreased vision due to reasons other than macular edema or ERM, previous history of vitreoretinal surgery or previous treatment with intravitreal bevacizumab and corticosteroid.

The patients received loading dose of three consecutive monthly injection, followed by PRN regimen. Mean number of ranibizumab injections was 3.9 over 6 months. In control visits, best-corrected visual acuity was assessed while optical coherence tomography (OCT, Carl Zeisss Cirrus HD*OCT-5000) findings and central macular thickness were assessed. In addition, macular edema was confirmed using fluorescein angiography (FFA, Visucam 500, Carl Zeiss Meditec, Jena, Germany) (Figure 1A, 1B, 1C and 2). In all patients, the injections were performed in a committed injection room. Topical anesthesia was achieved using 0.5% proparacaine hydrochloride in both eyes before procedure; in addition, 5% povidone iodine was used for prophylaxis against endophthalmitis. After topical anesthesia and preparation of eye, 0.5 mg intravitreal ranibizumab was injected using 30 G injector tip at a point 4 mm from limbus in phakic eyes and at a point 3.5 mm from limbus in pseudophakic eyes. After intravitreal injection, 0.3% topical ofloxacin (4x1 for a week) was prescribed to patients. Control visits were scheduled on month 1, 2, 3 and 6.

All statistical analyses were performed using SPSS version 21. Paired samples t test was used to analyze groups. A p value<0.05 was considered as statistically significant.

RESULTS

Macular edema and epiretinal membrane were present in 31 eyes of 27 patients including 14 men and 13 women. Mean age was 62.4±7.4 years in the study population. Twelve (38%) of 31 patients had previous cataract surgery. Mean CMT was 429.25±127.41µm at baseline and 324.42±69.74 µm at the end of study (mean number of ranibizumab dose: 3.9) (p<0.01). Mean BCVA (logMAR) was 0.64±0.34 at baseline and 0.50±0.27 at the end of treatment (p<0.01). No significant difference was detected in CMT and BCVA between genders (p>0.05).

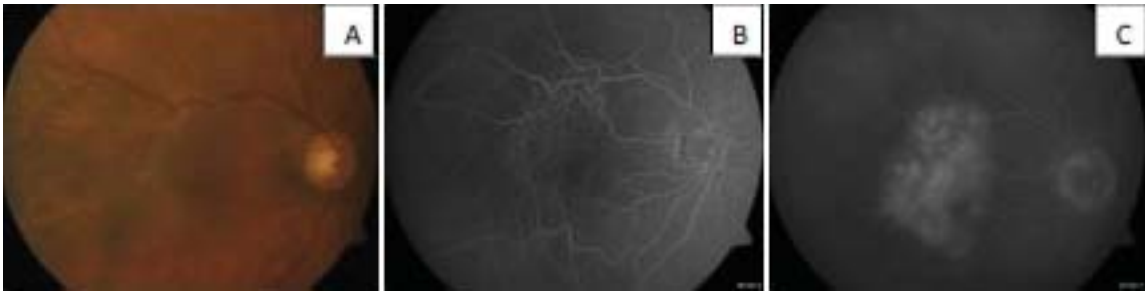

Figure 1: *A, color fundus image; B, distortion of vessels due to ERM; c, increased macular edema at late phase on FFA.*

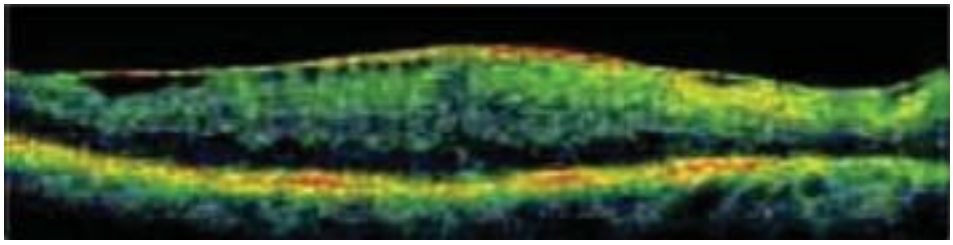

Figure 2: *Epiretinal membrane appearing as a hyper-reflective band at inner retinal layer.*

Table 1: *Ocular findings before and after intravitreal anti-VEGF administration in cases with cellophan maculopathy and macular edema.*

Parameters	CMT (µm)	BCVA (logMAR)
Before anti-VEGF treatment	429.25± 127.41	0,64± 0.34
After anti-VEGF treatment	324.42±69.74	0.50± 0.27
P valuee	P< 0.01	P< 0.01

DISCUSSION

In the literature, there are studies showing that VEGF plays role in immunological process in the development of epiretinal membrane.[14, 15] In a study by Harada et al., it was shown that several mediators such as bFGF, HGF, NF-kB, AP-1 and receptors are increased not only in vitreous and aqueous humor but also in ERM in proliferative diabetic retinopathy and proliferative vitreoretinopathy.[16]

Although vitreoretinal surgery is the mainstay in the treatment of ERM in patients describing symptomatic decrease in vision or distortion, success of surgical treatment is higher in patients with preoperative visual acuity between 20/50 ad 20/60.[17] The threshold visual acuity for consideration of surgery is generally 20/40. It was reported that visual acuity was decreased within 3 years in 10-37% of patients left untreated.[18, 19]

Ranibizumab is a biological anti-VEGF agent shown to be effective and safe in a phase 3 trial. It is particularly effective on VEGF-A isoform and it has been introduced in the treatment of diabetic macular edema and age-related macular degeneration.[20, 21]

Based on immunopathological studies, VEGF is known to play role in ERM.[14] In addition, some studies showed evidence supporting its tendency to change effect of anti-VEGF treatment via forming a mechanical barrier. Lee et al. emphasized that the number of ranibizumab doses in PRN regimen should be increased in patients with ERM as shown by OCT.[22]

In our study, a significant improvement was observed in BCVA (logMAR) by assessments before and after injection (p=0.00). In 31 eyes of 27 patients, mean CMT was decreased by 99.5 µm following 3.9 injections (in average) administered forh diabetic macular edema and epiretinal membrane in our study.

In a study by Luttrull and Spink, it was shown that surgical removal of ERM after anti-VEGF injection may further improve visual acuity in eyes with age-related subfoveal neovascularization and ERM.[23]

In our study, it can be predicted that ERM excision together with vitreoretinal surgery will improve likelihood of treatment success given that vitreoretinal surgery may be needed after anti-VEGF injections. However, ERM severity was low to plan surgery in our population.

In another study, Kuiper et al. suggested that anti-VEGF treatment alters angiogenic signal to pro-fibrotic signal in diabetic retina by changing balance between TGF (tissue growth factor) and VEGF.[24] Again, in some studies, it was found that ERM did not decrease effects of ranibizumab on CMT but failed to provide marked improvement in visual acuity in patients with ERM and macular edema, supporting our results.[7]

There are studies comparing surgical treatment (PPV) and anti-VEGF administration in the treatment of ERM and macular edema. Although Christoforidis JB et al. reported that PPV might be choice of treatment, they emphasized that this reduces half-life of anti-VEGF agents, leading frequent anti-VEGF injections at higher doses.[25] In our study, ranibizumab was preferentially used in the treatment of ERM and macular edema.

Namba et al. showed that presence of ERM in DME eyes decreased efficacy of anti-VEGF treatment.[26]

In a study on macular contraction and changes in vitreoretinal interface in diabetic macular edema treated with intravitreal anti-VEGF injections, it was shown that macular capillaries were displaced; however, it was associated with changes in central macular thickness rather than macular contraction.[27]

In cases with ERM, it was found that anti-VEGF treatment (ranibizumab) provided significant improvement in CMT and BCVA (logMAR); however, the improvement in BCVA was not correlated with resolution of macular edema, concluding that epiretinal membrane is not a mechanical barrier against effectiveness of anti-VEGF.

This study has some limitation including incompliance to monthly injections, small sample size and lack of long-term anti-VEGF treatment.

It was shown that anti-VEGF agent (ranibizumab) can be used in the presence of ERM in agreement with literature. Ranibizumab has the smallest molecular size among anti-VEGF agents; thus, it may pass membranes more than other agents.[28]

It will helpful to assess these results in different anti-VEGF molecules.

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