Aflibercept Versus Ranibizumab in Diabetic Macular Edema Associated with Epiretinal Membrane

Yalcin Karakucuk[1], Bulent Arazay[2], Serhat Eker[3], Gizem Semerci[3], Ugur Acar[4], Suleyman Okudan[4]

ABSTRACT

Purpose: To compare the efficacy of ranibizumab and aflibercept in the treatment of diabetic macular edema (DME) associated with epiretinal membrane (ERM).

Materials and Methods: This is a retrospective, comparative study. The treatment-naïve diabetic macular edema patients who had diabetic macular edema associated with epiretinal membrane and underwent intravitreal aflibercept or intravitreal ranibizumab treatment were included. The patients were treated on a loading dose of 3-monthly injections. The primary outcome measures of this study were the changes in best corrected visual acuity (BCVA) (LogMAR), central macular thickness (CMT) (µm) and intraocular pressure (IOP) (mmHg).

Results: A total of 98 patients with ERM and DME were included in the study. Ranibizumab group included fourty five patients who received intravitreal ranibizumab 3 times with a 1-month interval and Aflibercept group included 53 patients who received intravitreal aflibercept 3 times with a 1-month interval. After the 3 months follow-up period, there was no statisticaly difference in terms of CMT, BCVA and IOP (p=0.507, p=0.269, p=0.897, respectively).

Conclusion: It seems that three monthly injections of aflibercept and ranibizumab ensured statistically significant improvement in visual acuity and decrease in CMT in DME patients associated with ERM. There were no difference in intravitreal aflibercept and ranibizumab response in DME patients associated with ERM.

Keywords: Aflibercept, anti-VEGF, diabetic macular edema, epiretinal membrane, ranibizumab.

INTRODUCTION

Diabetic retinopathy (DR) is one of the leading causes of blindness in the working-age population.[1,2] It is also well-known that the most common cause of low vision in patients with DR is diabetic macular edema (DME). Nowadays, the treatment of DME is to provide the inhibition of the vascular endothelial growth factor (VEGF) and/or inflamatuar mediators by the application of intravitreal anti-VEGF and steroids respectively.[1]

Epiretinal membrane (ERM) which may influence the response to treatment of DME is a diverse group of proliferations at the vitreoretinal interface involving varying amounts of cells, extracellular stroma, and neovascular tissue.[3-9] It should be kept in mind that there is a higher prevalence of ERM in diabetic patients and the pathological structure of ERM in diabetic patients differs.[3,6,10-12]

Thanks to the development of optical coherence tomography (OCT) technology, all of the vitreomacular interface abnormalities can be detected very easily.[9-15] The treatment strategy of ERM which is characterized by symptoms of decreased visual acuity and metamorphopsia is to ensure the retina to remodel by removing the membranes from the surface of the retina, surgically.

Currently, intravitreal anti-VEGF drug application is the first choice and standard treatment modality in diabetic patients with center-involving DME. Ranibizumab (Lucentis®; Novartis International AG, Basel, Switzerland), and aflibercept (Eylea®; Bayer, Berlin, Germany) are two anti-VEGF drugs currently licensed. The aim of this study is to compare the effects of these two anti-VEGF drugs in patients who have DME and ERM. To the best of our knowledge, there is no study comparing the effects of two drugs head-to-head on this issue in the literature.

1- MD, Assoc. Prof., Selcuk University Faculty of Medicine, Department of Ophthalmology, Konya, Turkey

2- MD, Mardin Nusaybin State Hospital, Mardin, Turkey

3- MD, Selcuk University Faculty of Medicine, Department of Ophthalmology, Konya, Turkey

4- MD, Prof., Selcuk University Faculty of Medicine, Department of Ophthalmology, Konya, Turkey

Received: 07.04.2021
Accepted: 20.02.2022

Ret-Vit 2022; 31: 166-171

DOİ:10.37845/ret.vit.2022.31.28

Correspondence Adress:
Yalcin Karakucuk
Selcuk University Faculty of Medicine, Department of Ophthalmology, Konya, Turkey

Phone: +90 536 065 2075
E-mail: drkarakucuk83@gmail.com

SUBJECTS AND METHODS

This study was conducted at a tertiary university hospital. All procedures were conducted in accordance with the Declaration of Helsinki. After receiving approval from the ethics committee of the local institutional review board (*Protocol no: 2019/5*), a retrospective chart review was performed.

Participants

A total of 98 naive patients with DME and ERM were included in the study. Exclusion criteria for the study were as follows: (1) history of ocular surgery except for cataract surgery; (2) history of intravitreal drug injection; (3) history of ocular trauma; (4) deficiencies in the follow-up and treatment of patients; (5) patients whose intravitreal anti-VEGF drugs were not applied or were interrupted or were switched; (6) presence of macular edema due to other ocular pathologies such as retinal vein occlusion, uveitis, hypertensive retinopathy, or age-related macular degeneration. We administer an initial series of 3 monthly loading injections of ranibizumab or aflibercept to patients with DME in our clinic.

Ophthalmic examination

A detailed chart review including the best-corrected visual acuity (BCVA) with the Snellen chart, intraocular pressure (IOP; measured by Goldmann applanation tonometry), fundus examination and central macular thickness measurement. BCVA levels were converted from decimal values to the logarithm of the minimum angle of resolution (logMAR) values. The CMT and CT measurements were done by the same experienced technician at the intervals of baseline, 4, 8, and 12 weeks after the injections with a spectral-domain OCT (SD-OCT; Spectralis, Heidelberg Engineering, Heidelberg, Germany). The CT measurement was done manually from the outer portion of the hyperreflective line corresponding to the retinal pigment epithelium to the inner surface of the sclera at the subfoveal point as previously described.[16]

Surgical Procedure

Intravitreal injections of ranibizumab and aflibercept were performed under sterile conditions in the operating room. Topical povidone-iodine 10% was applied to periorbital skin and 5% was applied into ocular surface. The eyes were completely draped and the wire lid speculum was placed. The povidone-iodine 5% was applied to the ocular surface for 3 minutes again. After washing the ocular surface with saline intravitreal injections of commercially available ranibizumab 0.5 mg/0.05 mL and aflibercept 2 mg/0.05 mL were performed by the same ophthalmologist using a 27-gauge needle through the superotemporal quadrant at 3.5 or 4.0 mm posterior to the limbus in pseudophakic and phakic eyes, respectively. The needle was carefully removed using a sterile cotton applicator to prevent reflux. After the injections, at least hand motion vision was checked to confirm retinal perfusion. Lastly, moxifloxacin 0.5% ophthalmic solution (Vigamox, Alcon) was applied and the eye was closed with a sterile patch.

Statistical Analysis

Mean, standard deviation, median, minimum, maximum value frequency and percentage were used for descriptive statistics. The distribution of variables was checked with the Kolmogorov-Smirnov test. Independent Samples t-test and Mann-Whitney U test were used for the comparison of quantitative data. Wilcoxon test was used for the repeated measurement analysis. Chi-Square test was used for the comparison of qualitative data. SPSS 26.0 was used for statistical analysis and and the statistical significance level was set 0.05.

RESULTS

A total of 98 patients with ERM and DME were included in the study. The mean age of participants was 64.8 ± 8.3 years (47-81 years). Demographic data of 45 patients who received intravitreal ranibizumab 3 times with a 1-month interval and 53 patients who received intravitreal aflibercept 3 times with a 1-month interval are specified in **Table 1**. There was no statistical difference in terms of age, gender, duration and stage of diabetes, presence of cataract and history of cataract surgery, baseline values of CMT, intraocular pressure and BCVA between the groups (**Table 2**). No statistically significant difference was found between the two groups in terms of CMT, IOP and BCVA in any time in 3 months follow up period (**Table 2**) (**Figure 1**).

DISCUSSION

DME is the most common cause of visual impairment in diabetic patients and nowadays intravitreal anti-VEGF application is first-choice and gold standard treatment modality. In this study, we compared the effect of two labelled anti-VEGF drugs in naive patients with ERM and DME. We determined a statistically significant decrease in CMT and a statistically significant improvement in BCVA levels with both anti-VEGF drugs, whereas there was no significant difference between the drugs in terms of the alterations (**Figure 2a-d**).

The fact that ERM is more common in diabetic patients and the presence of ERM potentially affects the response to intravitreal anti-VEGF treatment in DME patients are increased the importance of the topic of this study.

Table 1: *Demographic and characteristic data of Ranibizumab group and Aflibercept group.*

		Ranibizumab					Aflibercept				P	
		Mean±sd/n-%			Median		Mean±sd/n-%			Median		
Age (year)		66,3	±	7,8	67,0		63,5	±	8,5	64,0	0,089	t
Gender	Female	26		57,8%			23		43,4%		0,156	X^2
	Male	19		42,2%			30		56,6%			
Duration of DM (year)		18,2	±	6,5	18,0		15,5	±	5,9	15,0	0,067	m
Non Proliferative	Proliferative	18		40,0%			28		52,8%		0,205	X^2
	Diabetic RP	27		60,0%			25		47,2%			
Phakic		33		73,3%			33		62,3%		0,244	X^2
Pseudophakic		12		26,7%			20		37,7%			
Presence of Cataract	(-)	30		90,9%			24		82,8%		0,339	X^2
	(+)	3		9,1%			5		17,2%			
Presence of ERM	(+)	45		100,0%			53		100,0%		1,000	X^2

[t] t test / [m] Mann-whitney u test / [X^2] Chi-square test, sd: Standart deviation, DM: Diabetes mellitus, ERM: Epiretinal membrane

Although there are some studies [4-9] investigating the effect of intravitreal anti-VEGF drugs in diabetic patients with ERM, there is no study comparing aflibercept and ranibizumab head-to-head on this issue.

Maryam et al.[4] compared the effect of single-dose 2.5 mg/0.1 ml intravitreal bevacizumab injection in diabetic patients with and without ERM. They determined that the patients with ERM had a statistically significant improvement in visual acuity, whereas a statistically insignificant decrease in CMT. Interestingly; the improvement in visual acuity was statistically insignificant, the decrease in CMT was statistically significant in diabetic patients without ERM.[4] The authors did not explain why they administered a 2-fold dose of bevacizumab intravitreally. The important limitations of their study are that the study has a short duration (only 1-month) and the patients' baseline BCVA levels are different.

Lai et al.[5] investigated the prognostic factors of three consecutive monthly intravitreal ranibizumab for DME in 51 eyes of 35 patients. They found that the presence of ERM was associated with a smaller reduction in CMT although it does not affect the visual outcomes. It may have been because they applied the anti-VEGF drugs 3 times with a 1-month interval strictly as in our study.

Wong et al.[6] evaluated the effects of intravitreal ranibizumab injection over a 1-year period in a total of 104 eyes of 77 diabetic patients with and without vitreoretinal interface abnormalities. They determined that ERM was associated with a worsened visual and anatomic outcome.

Yoon et al.[7] investigated the effects of the presence of vitreomacular interface abnormalities in 15 eyes of 11 patients with DME after three intravitreal anti-VEGF injections (either 0.3 mg/0.05mL ranibizumab or 1.25 mg/0.05mL bevacizumab). They found that the reduction in CMT levels was not statistically different between the groups. They also determined the highest increase in BCVA in diabetic patients with a normal vitreomacular interface. This outcome showed that the presence of ERM has a negative effect on visual prognosis even though ERM does not prevent the penetration of anti-VEGFs. The fact that the number of patients was so limited was a big limitation of their study.

Namba et al.[8] investigated the effect of ERM on the effectiveness of ranibizumab by both clinical and in vitro studies. They found that the presence of ERM in DME eyes lowered the efficacy of intravitreal ranibizumab by 12 months of follow-up clinical data. They also demonstrated that the ERM caused an increase in resistance to antibody permeabilization by creating an in vitro ERM model using MIO-M1, ARPE-19, and NTI-4 cells on Transwell membranes.[8]

Kulikov et al.[9] compared the effects of 0.3 mg/0.05mL intravitreal ranibizumab in a total of 105 eyes of 89 diabetic patients with a normal and abnormal vitreoretinal interface. They found that CMT decreased statistically insignificant in all abnormal vitreoretinal interface subgroups, whereas CMT decreased statistically significantly in patients with the normal vitreoretinal interface.

Cho et al.[17] evaluated the effect of ERM on the outcome of intravitreal aflibercept or ranibizumab treatment

Table 2: *Comparison of the parameter changes in Ranibizumab group and Aflibercept group.*

	Ranibizumab					Aflibercept					P	
	Mean±sd/n-%			Median		Mean±sd/n-%			Median			
Central Macular Thickness (CMT) (µm)												
Baseline	454,7	±	105,6	445,0		487,5	±	112,2	465,0		0,112	m
1 Month	367,0	±	103,1	342,0		404,6	±	87,4	391,0		***0,009***	m
2 Month	318,3	±	79,6	298,0		358,6	±	77,0	356,0		***0,006***	m
3 Month	305,0	±	78,0	285,0		337,7	±	79,6	328,0		***0,029***	m
Baseline/1 Month Difference	87,6	±	82,1	80,0		82,9	±	78,8	72,0		0,420	m
Intra Group Difference p			***0,000***	w				***0,000***	w			
Baseline/2 Month Difference	136,4	±	96,2	127,0		128,9	±	114,6	100,0		0,310	m
Intra Group Difference p			***0,000***	w				***0,000***	w			
Baseline/3 Month Difference	149,6	±	90,7	141,0		149,8	±	127,6	128,0		0,507	m
Intra Group Difference p			***0,000***	w				***0,000***	w			
Best Corrected Visual Acuity (BCVA) (logMAR)												
Baseline	0,65	±	0,37	0,52		0,66	±	0,36	0,52		0,754	m
1 Month	0,62	±	0,37	0,40		0,62	±	0,31	0,52		0,642	m
2 Month	0,55	±	0,31	0,40		0,55	±	0,27	0,52		0,641	m
3 Month	0,56	±	0,38	0,40		0,54	±	0,27	0,52		0,599	m
Baseline/1 Month Difference	0,02	±	0,12	0,00		0,04	±	0,17	0,00		0,804	m
Intra Group Difference p			0,146	w				0,052	w			
Baseline/2 Month Difference	0,09	±	0,18	0,10		0,10	±	0,22	0,05		0,766	m
Intra Group Difference p			***0,002***	w				***0,000***	w			
Baseline/3 Month Difference	0,08	±	0,18	0,05		0,12	±	0,23	0,10		0,269	m
Intra Group Difference p			***0,004***	w				***0,000***	w			
Intraocular Pressure (IOP) (mmHg)												
Baseline	16,1	±	3,4	16,0		15,6	±	3,4	16,0		0,654	m
1 Month	15,8	±	2,8	16,0		15,0	±	3,0	15,0		0,129	m
2 Month	15,7	±	3,2	16,0		15,5	±	3,0	15,0		0,564	m
3 Month	15,9	±	3,6	17,0		15,6	±	3,6	15,0		0,363	m
Baseline/1 Month Difference	0,22	±	2,67	0,00		0,62	±	3,45	1,00		0,475	m
Intra Group Difference p			0,528	w				0,198	w			
Baseline/2 Month Difference	0,40	±	3,41	0,00		0,15	±	3,30	0,00		0,685	m
Intra Group Difference p			0,432	w				0,710	w			
Baseline/3 Month Difference	0,16	±	3,59	0,00		0,00	±	3,54	0,00		0,897	m
Intra Group Difference p			0,774	w				0,885	w			

[m] Mann-whitney u test / [w] Wilcoxon test, sd: Standart deviation

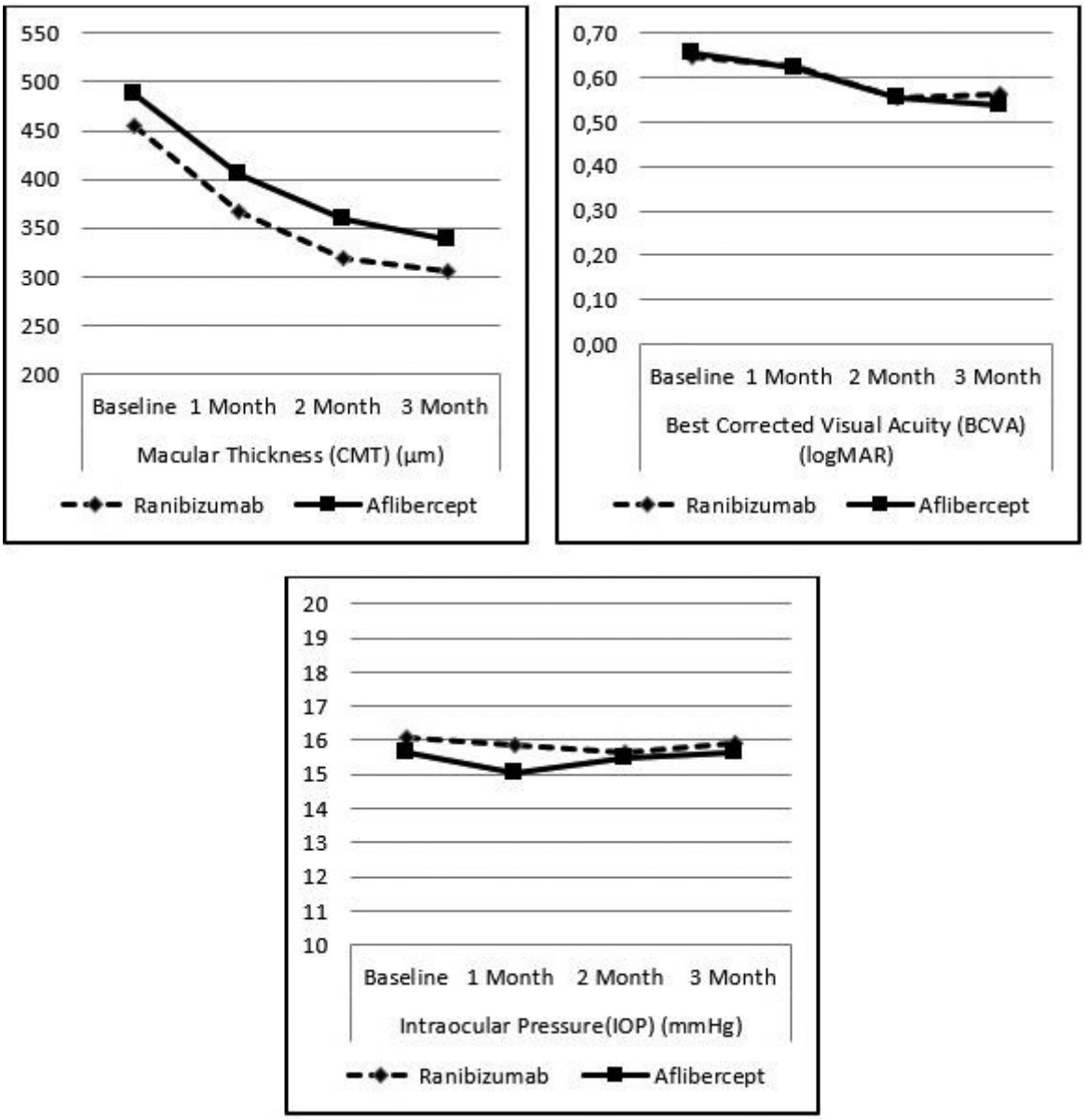

Figure 1: *Graphs showing the changes in CMT (µm), IOP (mmHg) and BCVA (LogMAR) during the 3-month follow up in patients with DME associated with ERM.* (DME: diabetic macular edema, ERM: epiretinal memb.)

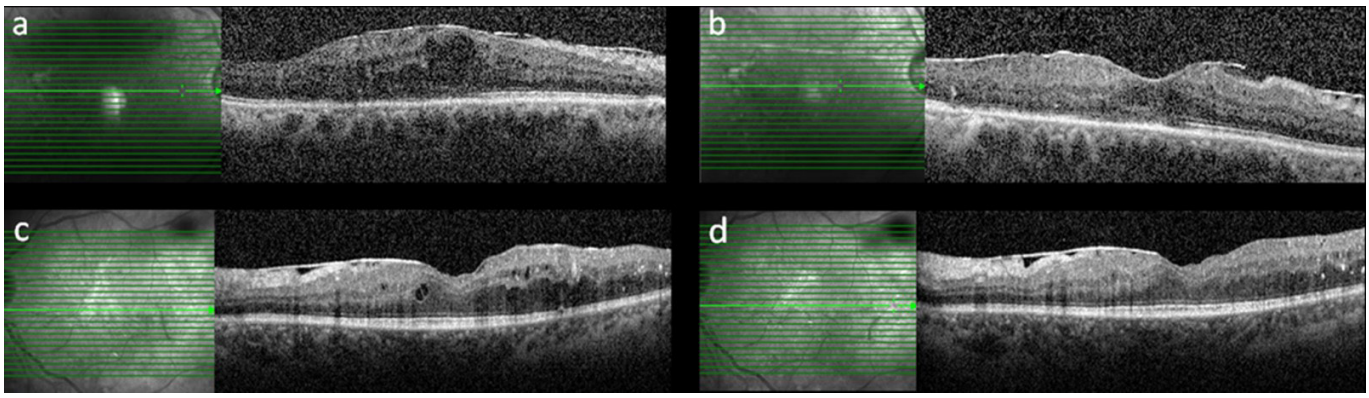

Figure 2: *OCT macula analysis of 3-month aflibercept (a,b) or ranibizumab (c,d) loading injections administered to patients with DME before and after.*

for neovascular age-related macular degeneration by comparing the visual and anatomical outcomes between the eyes with ERMs and those without. They observed significantly thicker central foveal thickness without affecting visual acuity in eyes with neovascular age-related macular degeneration and ERM. Actually, there is no study investigating aflibercept as an intravitreal anti-VEGF drug in patients with DME and ERM.

The outcome of most studies in the literature is that ERM affects the outcome of intravitreal anti-VEGF treatment. In light of these studies, there may be several reasons why the anti-VEGF response is poor in diabetic patients with ERM. The first hypothesis; additional structural damage to photoreceptors caused by ERM may be limiting the visual acuity improvements. The second one; ERM may decrease the effects of anti-VEGFs by preventing the penetration of them. Lastly; the reason for the increase in retinal thickening in diabetic patients with ERM related to not only by rising of VEGF level but also anteroposterior or tangential tractions. In support of this hypothesis, visual acuity significantly improves after vitrectomy surgery in diabetic patients with ERM.[18]

The strengths of the current study are that it has a sufficient number of naive patients with DME and compares two anti-VEGF drugs head-to-head. The most important limitations of this study are that it has a retrospective design and short follow-up time. Besides, 3 months results in Anti-VEGF treatment is a short time for comparison of treatment results.

In conclusion, we determined that three monthly injections of aflibercept and ranibizumab ensured statistically significant improvement in visual acuity and decrease in CMT. We could not detect any difference in intravitreal aflibercept and ranibizumab response in patients with DME and ERM. We also found the effectiveness of the two anti-VEGF drugs similar. Further studies that are randomized, multicenter, controlled and prospective with a larger sample size are needed in order to confirm the outcomes of present study.

REFERENCES

1- Haritoglou C, Maier M, Neubauer AS, et al. Current concepts of pharmacotherapy of diabetic macular edema. Expert Opin Pharmacother. 2020; 21:467-75.

2- Gangwani RA, Lian JX, McGhee SM, et al. Diabetic retinopathy screening: global and local perspective. Hong Kong Med J. 2016; 22:486-95.

3- Snead DR, James S, Snead MP. Pathological changes in the vitreoretinal junction 1: epiretinal membrane formation. Eye. 2008; 22:1310-7.

4- Maryam AK, Tafgeh M, Mahmoud M, et al. Short term effect of intravitreal bevacizumab for diabetic macular edema associated with epiretinal membrane. Rom J Ophthalmol. 2018; 62:212-6.

5- Lai IA, Hsu WC, Yang CM, et al. Prognostic factors of short-term outcomes of intravitreal ranibizumab in diabetic macular edema. Int J Ophthalmol. 2017; 10:765-71.

6- Wong Y, Steel DHW, Habib MS, et al. Vitreoretinal interface abnormalities in patients treated with ranibizumab for diabetic macular oedema. Graefes Arch Clin Exp Ophthalmol. 2017; 255:733-42.

7- Yoon D, Rusu I, Barbazetto I. Reduced effect of anti-vascular endothelial growth factor agents on diabetics with vitreomacular interface abnormalities. Int Ophthalmol. 2014; 34:817-23.

8- Namba R, Kaneko H, Suzumura A, et al. In Vitro Epiretinal Membrane Model and Antibody Permeability: Relationship With Anti-VEGF Resistance in Diabetic Macular Edema. Invest Ophthalmol Vis Sci. 2019; 60:2942-9.

9- Kulikov AN, Sosnovskii SV, Berezin RD, et al. Vitreoretinal interface abnormalities in diabetic macular edema and effectiveness of anti-VEGF therapy: an optical coherence tomography study. Clin Ophthalmol. 2017; 11:1995-2002.

10- Cheung N, Tan SP, Lee SY, et al. Prevalence and risk factors for epiretinal membrane: the Singapore Epidemiology of Eye Disease study. Br J Ophthalmol. 2017; 101:371-6.

11- Akbar Khan I, Mohamed MD, Mann SS, et al. 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; 99:1078-81.

12- Kawasaki R, Wang JJ, Sato H, et al. Prevalence and associations of epiretinal membranes in an adult Japanese population: the Funagata study. Eye. 2009; 23:1045-51.

13- Ophir A, Martinez MR, Mosqueda P, et al. Vitreous traction and epiretinal membranes in diabetic macular oedema using spectral-domain optical coherence tomography. Eye. 2010; 24:1545-53.

14- Ghazi NG, Ciralsky JB, Shah SM, et al. Optical coherence tomography findings in persistent diabetic macular edema: the vitreomacular interface. Am J Ophthalmol. 2007; 144:747-54.

15- Miguel AI, Legris A. Prognostic factors of epiretinal membranes: A systematic review. J Fr Ophtalmol. 2017; 40:61-79.

16- Vural E, Acar U, Sevinc MK, et al. Choroidal Thickness in Patients wıth Stargardt Disease. Retina. 2018; 38:614-9.

17- Cho HJ, Kim JM, Kim HS, et al. Effect of Epiretinal Membranes on Antivascular Endothelial Growth Factor Treatment for Neovascular Age-Related Macular Degeneration. J Ocul Pharmacol Ther. 2017; 33:452-8.

18- Kim JY, Kim DY, Kim KT, et al. Visual Prognostic Factors of Epiretinal Membrane Surgery in Patients with Pseudophakia. Ophthalmologica. 2020; 243:43-50.