Factors Affecting the Visual Acuity and Anatomic Recovery in the Treatment of Diabetic Macular Edema

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ABSTRACT

Purpose: To evaluate the parameters which affect the anatomic and functional results of diabetic macular edema (DME) patients who are treated with intravitreal ranibizumab.

Methods: Patients who have been diagnosed with DME are included in this research. Patients who have been treated with Pro Re Nata (PRN) regime before three months of ranibizumab injection are included in this research. Stage of diabetic retinopathy, type of edema in OCT, epiretinal membrane (ERM) ellipsoid zone damage, and presence of exudate in subretinal fluid and fovea of the patients are determined. The effect of these parameters on final central fovea thickness and best-corrected visual acuity is investigated.

Results: 110 eyes of 65 patients are included in this research. In the multivariate regression analysis, it is found that the poor visual acuity is highly correlated with severe non-proliferative diabetic retinopathy and proliferative diabetic retinopathy, while shows an interrelation with the presence of subretinal fluid in OCT, exudate in fovea, and ellipsoid zone damage ($p=0.004$, $p=0.009$, $p<0.0001$, respectively). A greater decrease in thickness of central fovea is found among the patients with diffuse macular edema, greater central fovea thickness, and without ERM ($p=0.018$, $p=0.001$, $p=0.003$, respectively).

Conclusion: Poor visual acuity in patients who are treated for DME is correlated with advanced stage diabetic retinopathy and especially, ellipsoid zone damage in OCT. While it is found that ERM affects anatomic recovery adversely, there is no significant correlation found between ERM and visual acuity.

Keywords: Diabetes mellitus; Macular edema; Optical coherence tomography; Prognostic factors; ranibizumab.

INTRODUCTION

Macular edema is the most frequent reason of visual impairment in diabetic retinopathy.[1] Impairment of blood-retina barrier in the pathogenesis of diabetic macular edema ends up with inflammation and choroidopathy.[2] Focal or grid laser photocoagulation was the main treatment of DME.3 However, recently it has been proved that Vascular Endothelial Growth Factor (VEGF) plays a great role in the pathogenesis of DME and anti-VEGF medication has started to be used in the treatment.[4-7] These medications are Ranibizumab (Lucentis® Novartis), Bevacizumab (Avastin®, Genentech), Aflibercept (Eylea® Bayer Healthcare Pharmaceuticals) and novel anti-VEGF Brolucizumab (Beovu® Novartis).[4-7] Response of patients with diabetic macular edema to treatment with anti-VEGF is varied.[8] Some of the prior work investigates the factors that affect the response of treatment with anti-VEGF agents.[9-11] In this work it is aimed to obtain the parameters that would help to predict the prognosis by means of comparing the pre and after-treatment data of the patients who are treated with IV ranibizumab.

MATERIALS AND METHODS

Between January 2015 and May 2018, files of the patients who have been treated for DME in the retina clinic of our hospital are evaluated retrospectively. Patients with a retinal thickness increase greater or equal to 300 microns in the macula which is measured with Optical Coherence Tomography (OCT, RTVue-XR 100 Avanti software v.6.1, Optovue, Inc., Fremont, CA, USA) and focal or diffuse leakage in macula wich is detected with fluorescein angiography are included in this research.

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Patients who have experienced intravitreal (IV) injection and/or argon laser photocoagulation within the last three months, vitreoretinal surgery, vitreomacular traction, and/or tractional retina decollement before are excluded in this research. DME patients are offered options of grid laser or intravitreal anti-VEGF as a treatment. Legal approval is taken from patients who are approved to be treated with an anti-VEGF injection. All the patients are given intravitreal ranibizumab injection (Lucentis® Novartis). Intravitreal injections are applied in the operating room in aseptic conditions. After maintaining topical anesthesia with 0.5% of proparacaine, 5% povidone-iodine is applied to the ocular surface. 0.5 mg/0.05 mL ranibizumab is applied to the vitreous cavity to posterior of 3.5 mm in pseudophakic patients and 4 mm in phakic patients of limbus with 30 gauge needle. The eye is closed with an eye patch, and 0.3% of ofloxacin topical drop is advised 4 times for 5 days. During the first three months, injections are applied for each month, and after, the PRN regime is applied. Patients are called to appointments for each month. In each examination, the best-corrected visual acuity of the patients is evaluated with the Snellen scale and converted to logMAR. Besides, a complete ophthalmologic examination including but not limited to SD-OCT and fundus photography is completed. Whenever a patient's visual acuity is determined to decrease equal or more than one row on the Snellen scale or 50 micron of thickness increase in SD-OCT, the patient is given IV ranibizumab injection. Visual acuity and thickness of central fovea are recorded at the beginning and the end of the 1st, 6th,9th, and 12th month. The number of injections is recorded. As the Global Retinopathy Project Group Suggested, patients, are grouped according to their stage of diabetic retinopathy as for primary phase non-proliferative diabetic retinopathy (NPDR), moderate NPDR, severe NPDR, and proliferative diabetic retinopathy (PDR). ERM, ellipsoid zone damage, subretinal fluid, and exudate in the fovea are determined within the 1500-micron diameter about the fovea center's horizontal and vertical axes in SD-OCT. Macular edema is classified as diffuse or cystoid macular edema. Formal approval is taken from the research ethics committee of our hospital.

All data were analyzed using the SPSS version 20 (SPSS Inc., Chicago, IL, USA). The independent sample *t*-test and paired *t*-test were employed to analyze changes in BCVA and CFT. Pearson chi-square test was used for comparative analyses of categorical variables. To evaluate the prognostic factors for changes in BCVA and CST at month 12, multivariate logistic regression models were used with the patient as a random effect. For all statistical tests, $p < 0.05$ was considered significant.

RESULSTS

110 eyes of 65 patients are included in this research. Demographic findings of patients are given in Table 1. Initial visual acuity (BCVA) of the patients is 0.81 ± 0.47 logMAR and after treatment, a significant increase is observed ($p<0.0001$). When the increase is analyzed month-wise, the greatest increase in visual acuity is in the first 3 months and this increasing trend continues throughout the 3rd,6th, 9th, and 12th months (Figure 1) ($p<0.0001$, $p=0.029$, $p<0.001$, $p=0.051$, respectively). At the end of the 12th month, average visual acuity is 0.29±0.31 logMAR and 58 (52.7%) patients are determined to show 3 or more rows of increase in terms of vision.

Table 1: *Demographic and clinical properties of the patients*

Age (year)	63,5± 6,1
Female / Male	36 (55%) / 29 (45%)
Time of diabetes mellitus (year)	15,3± 5,3
Hypertension (n)	31 (56,4%)
Panretinal laser photocoagulation (n)	38 (34,5%)
Stage of diabetic retinopathy	Moderate NPDR 32 (%29,1) Severe NPDR 40 (%36,4) PDR 38 (%34,5)
Epiretinal membrane (n)	34 (30.9%)
Subretinal fluid (n)	40 (36,4%)
Ellipsoid zone distruption (n)	22 (20%)
Foveal exuda (n)	12 (10,9%)
Type of macular edema (n)	Cystoid 22 (26%) Diffuse 84 (76,4%)
Baseline visual acuity (logMAR)	0,81±0,47
Baseline central foveal thickness (micron)	407± 88

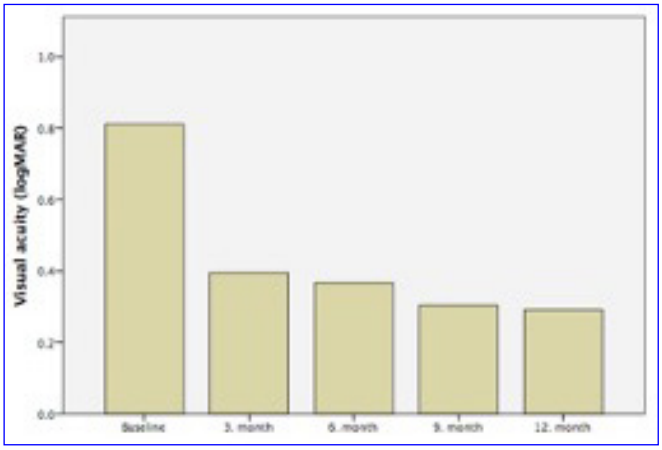

Figure 1: *Visual acuity of the patients.*

In the multivariate multinomial logistic regression model, a model with the following parameters is constructed: subretinal fluid, exude in the fovea, type of macular edema, stage of diabetic retinopathy, ellipsoid zone damage, initial central foveal thickness, age, and the epiretinal membrane (Table 2). According to these parameters for the increase in visual acuity, bad prognostic factors were found as ellipsoid zone damage, exude in the fovea, terminal stage diabetic retinopathy, low initial visual acuity ($p<0.0001$, $p=0.01$, $p=0.025$, $p=0.014$, $p=0.021$, respectively).

Initial central fovea thickness (CFT) is 407 ±88 micron and during examinations that are three months apart, a decrease in the thickness is found ($p<0.001$). At the end of the 12th month, the average CFT is found to be 284± 68 micron. The greatest decrease in the thickness of fovea is detected within the first 3 months and this trend is sustained throughout the regular examinations (Figure 2) ($p<0.0001$, $p=0.001$, $p=0.003$,

$p<0.0001$, respectively.).

In the multivariate multinomial logistic regression model, a model with the following parameters is constructed: subretinal fluid, exude in the fovea, type of macular edema, stage of diabetic retinopathy, ellipsoid zone damage, initial central foveal thickness, age, and the epiretinal membrane (Table 2). The presence of initial macular diffuse, thick initial central fovea, and absence of ERM are found to be correlated with a decrease in thickness of fovea ($p=0.018$, $p=0.001$, $p=0.003$, respectively).

DISCUSSION

In the treatment of diabetic macular edema, laser and anti-VEGF treatments are used. In the literature it is mentioned that, before the irrevocable structural damage has been made, early stage treatment of DME patients with recursive intravitreal anti-VEGF application would not only result in better visual outcome but also when it compared with laser, it would result a swifter recovery of macular edema.[5] However, it has been observed that patients with DME responded differently to anti-VEGF treatment. There are not many literatures based on this difference. For this group of patients, determination of factors that are prognostically important is helpful when it comes to treatment and tracing of these patients.[9-11]

There is some research that investigate the stage of the diabetic retinopathy and response to the treatment in the literature.[9] Lai et al. detected a better recovery in the vision

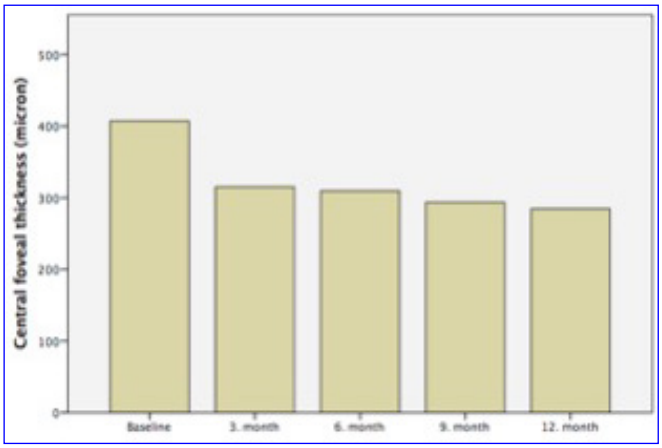

Figure 2: *Central foveal thickness of the patients.*

Table 2: *Multivariate multinomial logistic regression analysis of baseline OCT features with Influence on BCVA treatment outcome and central foveal thickness*

	Influence on BCVA			Influence on central foveal thickness		
	p	95% confidence interval		p	95 % confidence interval	
		Lower bound	Upper bound		Lower bound	Upper bound
Constant	.464	-.704	1.535	.971	-1.241	1.288
Epiretinal membrane	.475	-.246	.115	.001	-.560	-.152
Subretinal fluid	***.010***	-.387	-.053	.346	-.278	.098
Stage of diabetic retinopathy	***.014***	.031	.265	.379	-.191	.074
Ellipsoid zone disruption	***.000***	-.839	-.407	.451	-.338	.151
Foveal exuda	***.025***	.037	.546	.751	-.333	.241
Type of macular edema	.241	-.299	.076	.010	.069	.493
Baseline Visual acuity	***.021***	.039	.468	.930	-.231	.253
Baseline central foveal thickness	.842	-.001	.001	.006	.001	.003
Age	.848	-.012	.015	.594	-.020	.011

Table 3: *Multivariate multinomial logistic regression analysis of baseline OCT features with influence on central foveal thickness*

	Unstandardize coefficients		Standardize coefficients			%95confidence interval	
Model	**B**	**SE**	**BETA**	**t**	**p**	**Lower bound**	**Upper bound**
Constant	.023	.637		.037	.971	-1.241	1.288
Epiretinal membrane	-.356	.103	-.356	-3.461	.001	-.560	-.152
Subretinal fluid	-.090	.095	-.090	-.947	.346	-.278	.098
Type of diabetic retinopathy	-.059	.067	-.098	-.883	.379	-.191	.074
Ellipsoid zone disruption	-.093	.123	-.078	-.757	.451	-.338	.151
Foveal exuda	-.046	.145	-.030	-.319	.751	-.333	.241
Type of macular eudema	.281	.107	.250	2.636	.010	.069	.493
Baseline Visual acuity	.011	.122	.011	.088	.930	-.231	.253
Baseline central foveal thickness	.002	.001	.335	2.783	.006	.001	.003
Age	-.004	.008	-.053	-.534	.594	-.020	.011

acuity after IV ranibizumab provocation in the patients with PDR than patients with mild NPDR.[9] Along with that, there are no difference between PDR patients treated with pan retinal laser photocoagulation (PLF) and patients with mild NPDR in terms of visual acuity recovery. However, PDR patients who are not treated with LF obtains a better visual acuity recovery than the patients who are treated with LF.[10] These findings explained with provocation of VEGF. They also claim that since vitreous VEGF levels are higher in PDR and severe NPDR, these group of patients are more responsive to anti-VEGF treatment.[9] According to the RISE and RIDE research on monthly ranibizumab or sham injection for DME treatment, PDR patients who are applied LF have lower visual acuity while they have no significant difference in terms of letter gain. Reason of such outcome is not explicitly explained but they doubt that since laser photocoagulation is applied to patients who have more severe disease, the reason is ischemia and fibrosis which may cause poor vision acuity.[10] According to the DRCR-net research that investigates the 5-year difference between eyes that are treated for DME with ranibizumab according to their level of severeness in diabetic retinopathy, patients with NPDR show a better recovery than the PDR patients who are treated with LF.[11] They conclude that patients with more severe retinopathy show more frequent ischemia and permanent damage.[11] In this work, similar to previous, patients with severe PDR show a lower increase in visual acuity than other stages. Besides, it has been concluded that ischemia and damage is more frequent in severe stage diabetic retinopathy since there is no difference in terms of decrease in central fovea thickness while PDR patients show a worse recovery in visual acuity.

Kaya et al. classified DME patients after an average of 1 year of IV ranibizumab treatment as a diffuse retinal thickening, cystoid macular edema, and subretinal fluid.[12] In these 3 groups, while there is no significant difference in terms of anatomic recovery, the group with subretinal fluid shows a less increase in terms of visual acuity.[12] Besides, in this group, they concluded that visual acuity decreases because of damage in the external limiting membrane (ELM) and ellipsoid zone.[12] In BRDME research, when the presence of subretinal fluid and disorganization in internal retina layers (DRIL) are compared after 6 months of IV bevacizumab and ranibizumab injection, patients with subretinal fluid shows a better recovery in terms of visual acuity.[13] In this research, while pathogenesis of the subretinal fluid is not emphasized very well, it has been detected that inhibition of VEGF is effective in DME with subretinal fluid. In this work, despite it is found that the presence of subretinal fluid harms the recovery of visual acuity, it does not affect the decrease in CFT. However, there is no clear explanation of the effect presence of subretinal fluid on visual prognosis.[12,13] Different results between the existing literature might stem from the choice of patients, number of injections, and duration of the presence of subretinal fluid. Moreover, while patients with subretinal fluid respond favorably to IV anti-VEGF at the beginning, the presence of fluid for too long results in both damage in ELM and in the ellipsoid zone on top of harming recovery of vision.

It has been found that while the presence of hard exude affects the recovery of vision adversely, it does not affect the change of thickness of the central fovea. The presence of exude in diameter of 1500 microns centered around

the fovea center throughout the horizontal and vertical axes is considered to be the presence of exude. It is also concluded that the location and size of the exude might affect the vision. Differences between the presence of exude in the existing literature might stem from these size and location variety. In this work, while the reason why the presence of exude harms vision is not explicitly explained, the reason might be the exudes of the patients included are subfoveal located and greater in size. In DRCR.net research, the presence of exude within 6 mm proximity of fovea center is considered to be a good prognostic factor.[11] This is also explained by the presence of a partially stable internal blood-retina barrier. That is why in this research, it is concluded that edema in the eyes with exude responded better to ranibizumab treatment. It is also decided that the reason for retinal thickening in the eyes without exude is mostly ischemia, traction, or cystoid degeneration.[11] Domalpally et al. found that the presence of exude does not affect visual and anatomic recovery.[14] They also interpreted this result as the tracing of the patients is not significantly longer and it is also found that among the patients treated with ranibizumab, dissolution in exude can be observed starting from 6th month.[9] In ETDRS research, there is a correlation found between the application of grid laser and adverse consequences of the presence of hard exude on poor vision.[15] However, it is decided that it would not be appropriate to compare results in this work since the type of treatment is different. In our work, while patients with ellipsoid zone damage show a lower rate of visual recovery, there is no correlation for anatomic recovery. The ellipsoid zone is an OCT finding that indicates a link between internal and external photoreceptors of the ellipsoid zone.[16] In this type of damage, recovery cannot be observed after IV ranibizumab treatment and this may be the reason for the absence of a significant increase in vision. The finding of the researches of Chartres[17] and Maheshwart et al.[18] are similar to our findings.

We detected more decrease in CFT in patients with diffuse ME compared to those who have CME in our study. Kim et al. found in a study that in 6 month monitoring after IV anti-VEGF injections, diffuse ME patients responded better in terms of both visual and anatomical improvement compared to CME patients.[19] In this study, they linked the high level of VEGF in diffuse DME pathogenesis to the fact that prostaglandins are also effective in addition to VEGF.[19,20] These findings support our study. In another study, it has been shown that as intraretinal cyst size increases functional and anatomic recovery decreases after IV ranibizumab treatment.[21] We did not measure the cyst size in our study. Pelosini et al. concluded in a study that the structure that binds retinal photoreceptor and ganglion cells contains Mueller fibrils and relocation of Mueller fibrils in the presence of an intraretinal cyst harms bipolar cells and may lead to permanent sight impairment.[22]

Kuikov et al. found that the decrease in central fovea thickness in patients without a vitreoretinal interphase (VRI) problem is less than those with VRI problems. They also stated in this study that the response to anti-VEGF changes in accordance with sub-types of VRI problems. It has been emphasized that interface pathologies that affect the macula center negatively affects the response to the treatment. In our study, we did not detect any effects on visual recovery when determining the effect of ERM presence on decrease in CFT. Lai et al. also found similar results in their study. However, ERM has been found to be a malicious prognostic factor in the DRCR.net study.[11] This difference can arise from the ERM phase and the differences in ERM's localization. In our study, we divided the patients into two groups according to the presence of ERM in SD-OCT. However, in the DRCR.net study patients might have been chosen among those who had surface ripples in fundus photographs and therefore who were in advanced stages. This difference might be due to patient selection. A study based on ERM classification might give more precise results. Kulikov et al. examined the change in central fovea thickness in DME treatment after IV anti-VEGF [23] Patients with ERM that does not perform fine traction responded better to anti-VEGF treatment visually, however they responded poorly anatomically. However, they found that patients that have ERM that performed advanced stage traction responded poorly to both visual and anatomic recovery.

In our study, we first found that patients with high CFT responded better to the treatment. Other studies in the literature support this finding.[9-11] In the DRCR.net study they detected better response to the treatment in patients who had worse initial sight levels and defined it as ceiling effect. We also attributed this effect to the ceiling effect. So, patients who have thicker initial central fovea have more change ratio for thickness change.

Our study has some restrictions because it is retrospective. Patients' systemic findings, blood sugar regulations, whether nephropathy exists or not are unknown. These findings may alter the response to the treatment. Also the subretinal fluid, exudate, ellipsoid zone damage, presence of ERM that we examined SD-OCT needs to be examined in detail. A more detailed examination where the location and size of these parameters are detected is needed.

In conclusion; initial advanced staged diabetic retinopathy presence, ellipsoid zone damage in OCT, subretinal fluid and presence of exudate in fovea has been found to be associated with low sight sharpness in patients who are being treated with IV ranibizumab because of DME.

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Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participants included in the study.

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