Comparison of Ranibizumab Efficacy in Treatment-Naive and Previously Treated Patients with Diabetic Macular Edema and Evaluation of Prognostic Parameters

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ABSTRACT

Purpose: To evaluate the efficacy of intravitreal ranibizumab in the treatment of diabetic macular edema (DME) and parameters believed to affect prognosis.

Materials and Methods: Patients who were given ranibizumab injections due to DME in the Department of Ophthalmology, at Cukurova University Medical Faculty Hospital, were included in the study. Treatment-naive patients comprised Group 1; those who had prior treatment other than ranibizumab comprised Group 2. The two groups were compared in terms of best corrected visual acuity (BCVA) and central macular thickness (CMT) in post-treatment examinations.

Results: BCVA did not differ significantly between group 1 and 2 before (p=0.746) or after (p=0.468) treatment. Also, there was no significant difference between the two groups in terms of the change in BCVA after treatment (p=0.068). There was no significant difference between the two groups in terms of CMT before the treatment (p=0.167), whereas post-treatment CMT was significantly greater in Group 2 than in Group 1 (p=0.000). Group 1 showed a significantly larger decrease in CMT than Group 2 (p=0.041). Glycemic control method was significantly associated with change in BCVA and CMT in all eyes and in Group 1. Post-treatment decrease in CMT was significantly greater in patients who used oral antidiabetics compared to those who used insulin (p=0.010).

Conclusion: We observed a relationship between glycemic control method and change in CMT in treatment-naive patients. The reduction in CMT was significantly more in patients using OADs compared to those using insulin. Awareness of the ocular and systemic factors that may affect prognosis is important when developing treatment regimens for DME.

Keywords: Central macular thickness, diabetic macular edema, ranibizumab.

INTRODUCTION

Diabetic maculopathy is the most important cause of vision loss in patients with diabetes. It is responsible for 80% of visual losses in the nonproliferative stage[1].This pathology can emerge in nearly every stage of diabetic retinopathy (DR) and manifests as diabetic macular edema (DME) or macular ischemia.

The term 'clinically significant macular edema' (CSME) was first described in 1987 by the Early Treatment Diabetic Retinopathy Study (ETDRS) in an effort to determine the severity of focal edema in clinical practice and facilitate the development of treatment criteria. Focal DME is considered CSME in the presence of one of the following:

I. Retinal thickening at or within 500 microns of the foveal avascular zone (FAZ).

II. Hard exudates at or within 500 microns of the center of the FAZ with adjacent retinal thickening.

III. Retinal thickening at least 1 disc diameter in size, any part of which is located within 1 disc diameter of the center of the FAZ[2].

Pericyte loss, microaneurysm formation, basement membrane thickening, focal occlusions in the capillary bed, increased vascular permeability, and deterioration of the blood-retina barrier play a role in the development of DME. Of the vasoactive agents believed to be involved in

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Received: 30.10.2020
Accepted: 27.11.2020

Ret-Vit 2021; 30:238-244

DOİ: 10.37845/ret.vit.2021.30.42

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DME pathogenesis, the best known is vascular endothelial growth factor A (VEGF-A). Anti-VEGF agents such as pegaptanib sodium, bevacizumab, ranibizumab, and aflibercept have recently gained importance in the treatment of DME. Of these, ranibizumab was developed specifically for ophthalmic use, and is a human monoclonal antibody that inhibits all isoforms of VEGF-A. It consists of the antigen-binding fragment (Fab) of humanized anti-VEGF antibodies. The anatomical and functional efficacy of ranibizumab in DME was reported first in pilot studies and then in multicenter, prospective trials involving large patient series[3-4].

In this study, we aimed to compare treatment-naive patients and patients who had prior treatment other than ranibizumab in terms of the efficacy of intravitreal ranibizumab treatment and evaluate the ocular and systemic factors believed to affect prognosis.

MATERIALS AND METHODS

A total of 163 eyes of 109 patients treated for DME with intravitreal ranibizumab treatment in the Department of Ophthalmology, at Cukurova University Medical Faculty Hospital, between April 2012 and June 2014 were retrospectively evaluated. This study was conducted in accordance with the rules of the Declaration of Helsinki, and the approval of the Local Ethics Commitee was obtained. All patients were informed about the study procedure and risks of the treatments and informed consent forms were obtained. Patients diagnosed with type 2 diabetes mellitus, reduced best corrected visual acuity (BCVA) due to DME, and central macular thickness (CMT) of 250 microns or greater on optical coherence tomography (OCT) scans (Spectralis; Heidelberg Engineering, Heidelberg, Germany) were screened and recorded. Macular cube examination (6 mm, 49 lines, horizontal, cross sectional) scans were performed. Treatment-naive patients comprised Group 1 and; those who had prior treatment other than ranibizumab comprised Group 2. In Group 2 eyes had underdone one of the following treatment regimens: Intravitreal bevacizumab, intravitreal triamcinolone (IVTA), IVTA and intravitreal bevacizumab, grid laser photocoagulation, grid laser photocoagulation and intravitreal bevacizumab or grid laser photocoagulation and IVTA. Patients with incomplete medical data, low quality images and irregular follow-up visits were excluded.

All patients underwent detailed ophthalmologic examinations prior to treatment and at all follow-up visits, as well as OCT scanning. BCVA was evaluated using Snellen chart and converted to logMAR for statistical analysis. Intraocular pressure (IOP) was measured with Goldmann applanation tonometer. Anterior segment examinations were done with slit-lamp biomicroscope and posterior segment examinations were done with a 90D lens. Fundus fluorescein angiography (FFA) was performed in all patients before treatment and DR stage was identified as proliferative (PDR) or nonproliferative (NPDR). CMT was measured with OCT before and after treatment. All patients were assessed by the Internal Medicine Endocrinology outpatient clinic in terms of metabolic control, and their blood sugar and HbA_{1c} levels were measured.

The patients' age and sex, diabetes duration, glycemic control method, HbA_{1c} level, DR stage, history of laser photocoagulation or prior treatment for DME, lens status (phakic/pseudophakic), number of injections and follow-up period, and initial and post-treatment BCVA and CMT values were recorded from their medical records.

Intravitreal ranibizumab treatments were performed under sterile conditions in the operating room. After instilling topical anesthetic (proparacaine HCl 0.5%), the eyelids were cleaned with 10% povidone iodine. The patient was covered with a sterile drape such that the eyelashes were not exposed. A lid speculum was placed and 5% povidone iodine was instilled on the ocular surface and left for 3 min. Ranibizumab 0.5 mg/0.05 ml was injected intravitreally 4 mm from the limbus in phakic patients and 3.5 mm from the limbus in pseudophakic and aphakic patients. Pressure was applied to the injection site to prevent drug reflux. The eyes were covered with a sterile pad for a few hours. Lomefloxacin drops were recommended 4 times daily for 1 week after the injection. Patients were followed for possible treatment-related ocular and systemic complications.

Our patients were followed with a pro re nata (PRN: as needed) treatment protocol in the monthly follow-ups after the first dose. The re-treatment decision was made based on changes in BCVA and CMT. Treatments were repeated for patients who showed one line or more reduction in BCVA and/or CMT of greater than 250 microns in follow-up examinations. Patients with PDR and severe NPDR in addition to macular edema underwent panretinal laser photocoagulation (PRP). Treatment efficacy was evaluated by comparing BCVA and OCT findings prior to treatment (pre-treatment) with those at final examination (post-treatment). The two groups were compared in terms of BCVA and CMT at follow-up visits.

SPSS version 22.0 software package was used for statistical analyses of the data. Categorical measurements were expressed as numbers and percentages; numerical

measurements were expressed as mean and standard deviation or median and minimum-maximum. Chi-square test was used to compare categorical measurements between groups. For between-group comparisons of numerical data, independent samples t-test was used when the assumptions were met, and the Mann-Whitney U test was used when these assumptions were not met. Repeated measures analysis was used to compare changes in BCVA and CMT over time. Spearman correlation coefficient was used for correlation analysis. The level of significance was accepted as 0.05 for all analyses.

RESULTS

One hundred sixty-three eyes of 109 patients (42 female, 67 male) were included in the study. Group 1 included 105 eyes (64.41%), and group 2 comprised 58 eyes (35.59%).

All patients had type 2 DM and the mean follow-up time was 8.25 ± 5.17 (2-27) months. There were no significant differences between the two groups in terms of age, sex, DM duration, Hemoglobin A_{1c} (HbA_{1c}) levels, glycemic control methods, DR stage, PRP, lens status, or number of injections (Table 1).

Table 1: *Comparison of age, gender, duration of DM, HbA1c levels, glycemic control method, diabetic retinopathy stage, rate of panretinal photocoagulation, lens status, and number of injections in treatment-naive (group 1) and treatment-experienced eyes (group 2).*

		Group 1					Group 2 2					p
		Mean ± SD			%	Median (Min-Max)	Mean ± SD			%	Median (Min-Max)	
Age (years)		60.0	±	9.0		60 (33-81)	58.8	±	6.6		58 (45-72)	0.375
Sex	Female	40			38.1		28			48.3		0.207
	Male	65			61.9		30			51.7		
Duration of DM (months)		12.7	±	7.0		12 (1-30)	14.1	±	5.1		15 (4-26)	0.107
HbA_{1c}		7.8	±	1.8		7 (4-14)	7.8	±	1.5		8 (5-11)	0.302
Glycemic Control Method	Insulin	57			54.3		30			51.7		0.754
	OAD	48			45.7		28			48.3		
DR stage	NPDR	27			25.7		18			31		0.59
	PDR	78			74.3		40			69		
PRP	(-)	13			12.4		3			5.2		0.139
	(+)	92			87.6		55			94.8		
Lens status	Phakic	77			73.3		40			69.0		0.553
	Pseudophakic	28			26.7		18			31.0		
Number of Injections		3.2	±	1.3		3 (1-7)	3.5	±	1.4		3 (1-7)	0.142

DM: Diabetes Mellitus, **HbA1c:** Hemoglobin A1c, **OAD:** Oral antidiabetic drug, **DR:** Diabetic retinopathy, **NPDR:** Nonproliferative diabetic retinopathy, **PDR:** Proliferative diabetic retinopathy, **PRP:** Panretinal photocoagulation.

Table 2: *Distribution of eyes (all eyes and by subgroup) according to number of intravitreal ranibizumab injections received for diabetic macular edema.*

	All eyes (n=163)		Group 1 (n=105)		Group 2 (n=58)	
Injections	Eyes	(%)	Eyes	(%)	Eyes	(%)
1	53	32.5	37	35.2	16	27.6
2	62	38	41	39.0	21	36.2
3	20	12.3	13	12.4	7	12.1
4	17	10.4	7	6.7	10	17.2
5	5	3.1	4	3.8	1	1.7
6	3	1.8	1	0.9	2	3.4
7	3	1.8	2	1.9	1	1.7

The distributions of all eyes, group 1 eyes, and group 2 eyes according to number of intravitreal ranibizumab treatments are shown in Table 2.

During the post-treatment follow-up period, BCVA increased significantly in both groups. There was a mean increase of 0.14 ± 0.23 logMAR (p=0.000) in group 1 and 0.08 ± 0.26 logMAR (p=0.025) in group 2. There was no significant difference between the groups in amount of BCVA change (p=0.068).

In group 1, mean CMT was 385.9 ± 93.6 (253-750) microns before intravitreal ranibizumab treatment and 325.2 ± 108.9 (123-778) microns after treatment. In group 2, mean CMT was 407.5 ± 101.7 (259-850) microns before intravitreal ranibizumab treatment and 394.9 ± 140.5 (150-890) microns after treatment. Although there was no significant difference between the groups in terms of pre-treatment CMT (p=0.167), post-treatment CMT was significantly greater in group 2 than in group 1 (p=0.000). The reduction in CMT was significantly greater in group 1 compared to group 2 (p=0.041).

When the entire patient group was analyzed, change in BCVA with treatment was not associated with age, sex, duration of DM, glycemic control method, HbA_{1c} levels, DR stage, PRP, or lens status (Table 3).

In group 1, post-treatment change in BCVA was not associated with age (p=0.614), sex (p=0.373), duration of DM (p=0.084), glycemic control method (p=0.598), HbA_{1c} level (p=0.653), DR stage (p=0.499), PRP (p=0.529), or lens status (p=0.174).

In group 2, there was also no significant association between post-treatment change in BCVA and age (p=0.845), sex (p=0.817), duration of DM (p=0.711), glycemic control method (p=0.571), HbA_{1c} level (p=0.457), DR stage (p=0.316), PRP (p=0.705), or lens status (p=0.334).

When all patients were evaluated together, change in CMT after treatment was not significantly associated with age, sex, duration of DM, HbA_{1c}, DR stage, PRP, or lens status. However, in terms of glycemic control method, CMT values decreased significantly more in patients who used OADs compared to those who used insulin (p=0.010) (Table 4).

Comparison of the eyes in group 1 revealed no significant differences in post-treatment CMT based on age (p=0.746), sex (p=0.728), DM duration (p=0.712), HbA_{1c} level (p=0.838), DR stage (p=0.283), PRP (p=0.265) or lens status (p=0.938), while there was a significantly greater reduction in CMT was observed in patients using an OAD for glycemic control compared to those using insulin (p=0.010).

In group 2, there was no significant relationship between post-treatment CMT and age (p=0.061), sex (p=0.652), DM duration (p=0.566), glycemic control method (p=0.327),

Table 3: *Association between post-injection BCVA and sex, glycemic control method, DR stage, PRP, lens status, age, duration of DM and HbA_{1c}*

		Post-treatment change in BCVA							
		Mean ± SD			Median (Min-Max)				P
Sex	Female	-0.09	±	0.22	0.00	-0.80	-	0.40	0.371
	Male	-0.14	±	0.26	-0.05	-0.70	-	0.70	
Glycemic Control Method	Insulin	-0.11	±	0.27	0.00	-0.80	-	0.70	0.479
	OAD	-0.13	±	0.22	-0.10	-0.70	-	0.40	
DR stage	NPDR	-0.11	±	0.29	-0.02	-0.80	-	0.70	0.74
	PDR	-0.12	±	0.22	-0.01	-0.70	-	0.40	
PRP	(-)	-0.15	±	0.23	-0.10	-0.50	-	0.30	0.342
	(+)	-0.11	±	0.25	0.00	-0.80	-	0.70	
Lens status	Phakic	-0.12	±	0.24	-0.10	-0.70	-	0.70	0.848
	Pseudophakic	-0.12	±	0.26	0.00	-0.80	-	0.40	
Age									0,663
Duration of DM									0,535
HbA_{1c}									0,421

BCVA: Best corrected visual acuity, **DM:** Diabetes mellitus, **OAD:** Oral antidiabetic drug, **DR:** Diabetic retinopathy, **NPDR:** Nonproliferative diabetic retinopathy, **PDR:** Proliferative diabetic retinopathy, **PRP:** Panretinal photocoagulation.

Table 4: *Association between post-treatment CMT and sex, glycemic control method, DR stage, PRP, lens status, age, duration of DM and HbA_{1c}*

		Post-treatment Change in CMT							
		Mean ± SD			Median (min-max)				p
Sex	Female	-51.4	±	126.5	-36.0	-397.0	-	331.0	0.665
	Male	-38.0	±	130.2	-47.0	-298.0	-	480.0	
Glycemic Control Method	Insulin	-24.9	±	117.9	-21.0	-257.0	-	480.0	0.010*
	OAD	-65.1	±	137.1	-72.5	-397.0	-	376.0	
DR stage	NPDR	-39.24	±	140.4	-36.0	-325.0	-	331.0	0.885
	PDR	-42.6	±	129.1	-49.5	-397.0	-	480.0	
PRP	(-)	-78.8	±	77.1	-70.0	-214.0	-	49.0	0.252
	(+)	-39.8	±	132.4	-43.0	-397.0	-	480.0	
Lens status	Phakic	-46.7	±	130.4	-55.0	-397.0	-	480.0	0.538
	Pseudophakic	-36.0	±	124.2	-23.0	-247.0	-	309.0	
Age									0.302
Duration of DM									0.746
HbA_{1c}									0.286

CMT: Central macular thickness, **DM:** Diabetes mellitus, **OAD:** Oral antidiabetic drug, **DR:** Diabetic retinopathy, **NPDR:** Nonproliferative diabetic retinopathy, **PDR:** Proliferative diabetic retinopathy, **PRP:** Panretinal photocoagulation.

HbA_{1c} level (p=0.119), DR stage (p=0.07), PRP (p=0.930), or lens status (p=0.993).

DISCUSSION

Intraocular treatment of ranibizumab significantly reduced foveal thickness and improved visual acuity in patients with DME, which demonstrated that VEGF is an important therapeutic target for DME[5]. Intravitreal anti-VEGF treatment is on its way to becoming a powerful alternative to laser photocoagulation, which is accepted as standard treatment for DME[6]. Most cases of focal ME can be controlled with laser photocoagulation; however, eyes with diffuse ME usually proven resistant to this treatment[7-9].

In initial studies by Chun et al. evaluating the use of ranibizumab to treat DME, 10 eyes of 10 patients with DME received 3 monthly injections of 0.3 or 0.5 mg ranibizumab and the patients were followed for 2 years. In the 3-month follow-ups, 40% had a visual increase of more than 15 letters, 50% had a visual increase of more than 10 letters, and 80% had a visual increase of at least 1 letter. In addition, CMT had decreased by 45.3 microns in the 0.3 mg group and by 197.8 microns in the 0.5 mg group[9].

In three different phase II/III trials (RESOLVE, RIDE, RISE), ranibizumab was found to be superior to the sham group in preventing visual loss due to DME and decreasing macular thickness[10]. Ranibizumab was also shown to be more effective than focal/grid laser in the READ-2 and RESTORE studies.[3]

In phase I and II trials, ranibizumab doses up to 2 mg/month for 6 months were found to be safe and effective[11].

Injections were administered monthly in the RISE and RIDE studies, while in the RESOLVE trial, injections were given monthly for the first 3 months and pro re nata (PRN) thereafter[10,12]. In the READ trial, injections were administered at month 0, 1, 3, and 5, followed by a PRN schedule[13].

Our patients were followed with a pro re nata (PRN: as needed) treatment protocol in the monthly follow-ups after the first dose. Fifty-three of the eyes in the study received 1 injection, 62 received 2 injections, and 48 received 3 or more injections.

BCVA improved significantly after treatment in both groups, but there was no significant difference between the groups in the magnitude of this change (p=0.068) or final BCVA (p=0.468). Previous studies have shown that initial visual acuity is one of the factors that affect visual outcomes after intravitreal ranibizumab treatment[14].The Luminous Study results have shown that ranibizumab treatment in treatment-naïve patients with DME led to better mean BCVA gains in patients who had a lower baseline BCVA.[15] Our findings may be attributable to the lack of significant difference between initial BCVA levels of the two groups.

We observed a significantly greater decrease in CMT in eyes treated with ranibizumab as primary DME treatment compared to the eyes that had received prior treatment for DME (p=0.041). The fact that post-treatment CMT reduction was less in previously treated eyes despite there being no significant difference between the groups in terms of DR severity prior to treatment may be associated with vitreoretinal surface disorder, which was not among the parameters evaluated in this study. Previous studies have shown that vitreoretinal interface abnormalities significantly reduce the effectiveness of intravitreal anti-VEGF therapy in eyes with DME[16-17].Nevertheless, the previously treated eyes showed a significant increase in BCVA after treatment, which may be related to individual variations in the functional and anatomic improvement achieved with treatment. Another explanation for the greater CMT reduction in eyes given ranibizumab injections as primary treatment may be shorter duration of edema and therefore fewer adverse effects of persistent macular edema in these eyes. Importance of early recognition of disease and prompt treatment to achieve best visual outcomeis discussed in the previous studies. Several studies suggest that chronicity of edema results in poor final visual acuity despite anatomic resolution that might result after institution of a new therapy[18]. Chronic DME and laser-related structural damage could also cause irreversible vision loss from retinal atrophy, neural cell loss, and other permanent structural changes[19]. Bressler et al. retrospectively screened the patients of the Diabetic Retinopathy Clinical Research Network (DRCR Network) study group and reported factors affecting visual acuity after ranibizumab therapy[7]. According to this study, young age (<60 years), earlier DR stage, lack of macular wrinkling, and good visual acuity at start of treatment were regarded as factors for favorable prognosis in terms of final visual acuity in DME patients treated with intravitreal ranibizumab. Expected improvements in visual acuity did not occur in cases of severe DR, due to excessive ischemia or permanent damage. In addition, the presence of a vitreoretinal surface disorder involving the macula also negatively affected anatomical and functional improvement after treatment. It was also noted that in eyes with higher initial CMT values, CMT decreased to a greater extent but was less likely to reach normal range.

The results of our study showed an association between glycemic control method and post-treatment change in CMT in all patients and in the group of eyes treated primarily with ranibizumab. The post-treatment reduction of CMT was significantly greater in patients using OADs compared to those using insulin (p=0.010). Previous studies have reported that better glycemic control is associated with a greater reduction in CMT after the anti-VEGF theraphy in DME[20]. Insulin users have higher final visual acuity and attributed this to better control of blood sugar levels[21]. However, in the study conducted by Matsuda et al., the effectiveness of anti-VEGF therapy was compared in OAD and insulin users and it was shown that the glycemic control method did not change the anatomical and functional efficiency in DME treatment[22]. Our findings may be explained by the fact that the blood sugar of patients using OADs may be regulated well enough that they do not require insulin, and therefore DR is better controlled. In our study there is no significant relationship between HbA_{1c} level and both final BCVA and final CMT . In accordance with our study, Shalchi et al have shown that HbA_{1c} is not related to functional or anatomical outcomes at 1 year in DME treated with ranibizumab[23].

Nevertheless Öztürk et al have showen that there is an inverse correlation between the decrease in MMK and HbA_{1c}, and the increase in BCVA is better for those who have not received treatment for DME before[24]. Our study confirmed the beneficial effect of ranibizumab on functional and anatomical outcomes in DME patients with or without previous treatment. These results are consistent with other studies in the literature[25-27].

We observed no ocular or systemic complications related to ranibizumab treatment in the present study.

All systemic and ocular findings of patients should be taken into consideration when evaluating the outcomes of intravitreal ranibizumab injection for the treatment of DME. Ocular results are highly dependent on the type and duration of DM, the presence of systemic comorbidities, and the metabolic control of DM.

In conclusion, we found that there was an association between the glycemic control method and change in CMT in treatment-naive patients. The reduction in CMT was significantly more in patients using OADs compared to those using insulin. Similarly, in Group 2, we found significant changes in CMT and BCVA as a result of ranibizumab treatment, but we did not find a relationship between the glycemic control method and change in CMT. Intravitreal ranibizumab treatment is effective in the treatment of DME. Being aware of the ocular and systemic factors that may impact prognosis is important when developing treatment regimens. In light of these findings, informing patients before the intravitreal treatment about visual prognosis and to be aware of systemic findings of patients will be beneficial for both the patient and the physician.

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