Comparison of the Efficacy of Intravitreal Aflibercept and Ranibizumab in the Treatment of Diabetic Macular Edema

Latif Tuncer[1], Utku Limon[1], Betul Ilkay Akcay[2]

ABSTRACT

Purpose: To compare the functional and anatomical efficacy of intravitreal injection of Ranibizumab and Aflibercept in the treatment of diabetic macular edema.

Material and Method: The medical records of patients who received intravitreal ranibizumab or aflibercept injection due to diabetic macular edema (DME) in our clinic were reviewed retrospectively. We included patients who received intravitreal ranibizumab injections in Group 1 and patients who received intravitreal aflibercept injections in Group 2. Best-corrected visual acuity (BCVA), central macular thickness (CMT), intraocular pressures (IOP), and the total number of injections at baseline, 1st, 3rd, 6th, and 12th-month controls were compared between the two groups.

Results: We included 31 eyes in Group-1 and 35 eyes in Group-2. The baseline mean BCVA in Group-1 was 0.64±0.34 logMAR and increased significantly to 0.37±0.25 logMAR in the 12th month. The baseline mean BCVA in Group-2 was 0.69±0.34 logMAR and increased significantly to 0.35±0.18 logMAR at the 12th month. The baseline mean CMT in Group-1 was 432.13±114.55 µm and increased significantly to 291.23±62.21 µm at 12th month. The baseline mean CMT in Group-2 was 458.46±90.43 µm and increased significantly to 298.26±43.8 µm at 12th month. There was no significant difference between the increase in BCVA and the decrease in CMT between the two groups (p>0.05). The mean number of injections for 12 months was 7.2 (6-9) in Group-1, and 6.9 (68) in Group-2, and there was no statistically significant difference between the groups. (p> 0.05).

Conclusion: The efficacy of both drugs in the treatment of diabetic macular edema is similar.

Keywords: Aflibercept, Diabetic macular edema, Ranibizumab.

INTRODUCTION

Diabetic retinopathy is the leading cause of blindness among working-aged adults[1].

The most important cause of vision loss in diabetic retinopathy is diabetic macular edema (DME). Diabetic macular edema causes moderate vision loss. Vascular endothelial growth factor (VEGF) is secreted by the ischemic retina. VEGF leads to increased vascular permeability resulting in retinal edema and new blood vessel formation[2].

Treatment strategies are effective in 90% of cases to prevent severe visual loss. The most important factor in the medical management of diabetic retinopathy is good glycemic control[3]. Treatment options in DME are Laser therapy, Anti-VEGF drugs (bevacizumab, ranibizumab, aflibercept), corticosteroids (dexamethasone and fluocinolone Acetonide), and Surgery[4]. Several studies indicate that anti-VEGF drugs are more effective than focal laser. Intravitreal steroids are often used when the use of anti-VEGFs is contraindicated or when resistance to anti-VEGFs develops[5]. Surgical indications for diabetic macular edema are taut posterior hyaloid, epiretinal membrane (ERM), vitreomacular traction (VMT), and DME resistance to intravitreal injections. Nowadays, the most effective treatment method in the treatment of DME is intravitreal anti-VEGFs[6].

1- MD, Ümraniye Training and Research Hospital, Eye Clinic, Istanbul, Türkiye

2- Assoc. Prof., Ümraniye Training and Research Hospital, Eye Clinic, Istanbul, Türkiye

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Correspondence Adress:
Latif Tuncer
Ümraniye Training and Research Hospital, Eye Clinic, Istanbul, Türkiye

Phone:

E-mail: mltftuncer@yahoo.com

Intravitreal Aflibercept was approved by US Food and Drug Administration (FDA) in July 2014 based on VIVID-VISTA clinical trials in the treatment of DME[7]. Ranibizumab was approved by FDA in August 2012 based on RISE- RIDE clinical trials results in the treatment of DME[8]. Bevacizumab has off-label use worldwide in the treatment of DME[9].

The purpose of this study is, to compare the functional and anatomical results of patients who received intravitreal Ranibizumab or Aflibercept for diabetic macular edema in our clinic.

MATERIALS AND METHODS

The protocol of the present study conformed to the Declaration of Helsinki. Written informed consent was obtained from each patient after the risks, benefits, and alternatives of the treatment were explained to the patients. The study protocol was approved by Umraniye Training and Research Hospital Ethics Committee.

Study design

In this study, the medical records of patients who applied to the Retina department of our clinic between January 2016 and January 2020 and who were administered intravitreal ranibizumab or aflibercept injections for DME were reviewed retrospectively. Patients were divided into 2 groups. We included patients who received intravitreal ranibizumab injections in Group 1 and patients who received intravitreal aflibercept injections in Group 2.

Inclusion Criteria for Group-1 and Group-2

1- Patients with treatment-naive diabetic macular edema who were treated with intravitreal ranibizumab or aflibercept,

2- Patients treated with PRN regimen after 3 monthly loading doses,

3- Patients with follow up for at least 12 months,

4- Patients with an HbA1C value between %7-12 at the first examination,

5- Patients between the ages of 45-70 with Type 2 diabetes,

6- Patients with BCVA at the first examination between 0.1 and 0.5 decimal,

7- Patients with CMT between 300 µm and 600 µm at the first examination.

Exclusion Criteria for Group-1 and Group-2

1- Presence of type 1 diabetes,

2- Patients with other vascular retinal diseases (retinal vein occlusion…),

3- Patients who have previously received laser or intravitreal injections for the treatment of DME,

4- Patients with ocular trauma,

5- Presence of glaucoma, macular degeneration, ERM, VMT, or uveitis accompanying diabetic macular edema,

6- Patients with macular ischemia,

7- Patients with a history of ocular surgery.

Data collection

Patients' age, gender, BCVA measured with Snellen chart, biomicroscopic and dilated fundus examinations, intraocular pressure (IOP) measured with Goldman applanation tonometry, CMT measured with spectral-domain OCT, complications, and the total number of injections performed during 12 months were collected from patient records (at baseline, 1st, 3rd, 6th and 12th months). Both eyes were included in the study if they met the inclusion criteria.

Ophthalmic Examination

BCVAs of the patients were measured with the Snellen charts. Anterior segment examinations were performed with slit-lamp biomicroscopy and posterior segment examinations were performed with a 90D non-contact lens. Intraocular pressure (IOP) was measured with a Goldmann applanation tonometer. All examinations with color fundus photography and OCT (Optovue, RTVue 100, CA, USA) were performed at each visit. Fundus fluorescein angiography was performed at the 1st and 6th months.

Intravitreal Injection Technique

Intravitreal injection of 0.5 mg/0.05 mL ranibizumab (Lucentis; Genentech, USA, Inc., San Francisco, CA, USA) in Group-1 and intravitreal injection of 2 mg/0.05 mL aflibercept (Eylea; Regeneron Pharmaceuticals) in Group-2, NY, USA), was performed under sterile conditions in the operating room.

Outcome measurements

Best-corrected visual acuity (BCVA), central macular thickness (CMT), intraocular pressures (IOP), and a total number of injections at baseline, 1st, 3rd, 6th, and 12th-month controls were compared between the two groups.

Statistical analysis

For statistical evaluations, decimal BCVA values were converted to logMAR values. Our data were analyzed

using the SPSS 22.0 (SPSS Inc, USA) package program. Quantitative data are expressed as mean±standard deviation or median.min-max value], qualitative data as percentages, and data not normally distributed as Median (IQR, Inter QuntifierRatio, 25%75%). In data analysis, the distribution of continuous variables was determined by Kolmogorov-Smirnov and Shapiro-Wilk normality tests. The Student t-test was used for comparisons of two independent groups for data with normal distribution, and the ANOVA test was used for comparisons of more than two groups. Chi-square and Fischer exact tests were used for comparisons in qualitative data. Significance test and Mc-Nemar test were used for the difference between two percentages in addicted groups. Significance was evaluated as p<005.

RESULTS

We included 31 eyes in Group-1 and 35 eyes in Group-2. The mean age of patients in Group-1 was 63.45±6.31 and the mean age of patients in Group-2 was 61.89±6.38. Demographic and baseline characteristics of patient groups were given in Table 1.

The baseline mean BCVA in Group-1 was 0.64±0.34 logMAR and increased significantly to 0.37±0.25 logMAR at the 12th month. The baseline mean BCVA in Group-2 was 0.69±0.34 logMAR and increased significantly to 0.35±0.18 logMAR at the 12th month. In both groups, the increase in BCVA at the 1st, 3rd, 6th, and 12th months were statistically significant compared to baseline BCVA, and there was no significant difference between the two groups (p>0.05). The BCVA changes between the two groups are given in Figure 1.

The baseline mean CMT in Group-1 was 432.13±114.55 µm and decreased significantly to 291.23±62.21 µm at 12th month. The baseline mean CMT in Group-2 was 458.46±90.43 µm and decreased significantly to 298.26±43.8 µm at 12th month. In both groups, the decrease in CMT at the 1st, 3rd, 6th, and 12th months were statistically significant compared to baseline CMT, and there was no significant difference between the two groups (p>0.05). The CMT changes between the two groups are given in Figure 2.

The mean number of injections within 12 months was 7.2 (6-9) in Group-1, and 6.9 (68) in Group-2, and there was no statistically significant difference between the groups. (p> 0.05). Focal laser photocoagulation was applied to 4 patients (12.9%) in Group-1 and 5 (14.2%) patients in Group-2. Panretinal laser photocoagulation was applied to 5 (19,4%) patients in Group-1 and 9 (25.7%) patients in Group-2 There was no statistically significant difference between the two groups (p>0.05).

There was no increase in intraocular pressure requiring medical or surgical treatment in both groups during the 12-month follow-up. No serious ocular or systemic complications were observed in either group during the

Table 1. *Demographic and baseline characteristics of patients.*

	Group I (n=31)	Group II (n=35)	p-value
Age, mean ± SD	63.45±6.31	61.89±6.38	0.363
Gender, n (%)			
Female	15(48.4)	14(40)	0.493
Male	16(51.6)	21(60)	
HbA1c (%), mean ± SD	8,97±1,83	9.01±1.81	0.926
Duration of diabetes mellitus (year), mean ± SD	10.84±5.39	12.38±5.52	0,314
Hypertension, n (%)	11(32.9)	12(35)	0.870
Hyperlipidemia, n (%)	12(38)	15(42)	0.476
Renal failure and dialysis, n (%)	3(9.7)	4(11.3)	0.577
Baseline BCVA (logMAR), mean ± SD	0.64±0.34	0.69±0.34	0,078
Baseline CMT (µm), mean ± SD	432.13±114.55	458.46±90.43	0.201
Baseline IOP (mmHg), mean ± SD	17.29±2.91	17.74±3.52	0,471
Lens Phakic Pseudophakic	14(45.2) 17(54.8)	22(62.9) 13(37.1)	0.150

BCVA: best corrected visual acuity, CMT: central macular thickness, IOP: intraocular pressure
SD: standard deviation, LogMAR: Logarithm of the Minimum Angle of Resolution

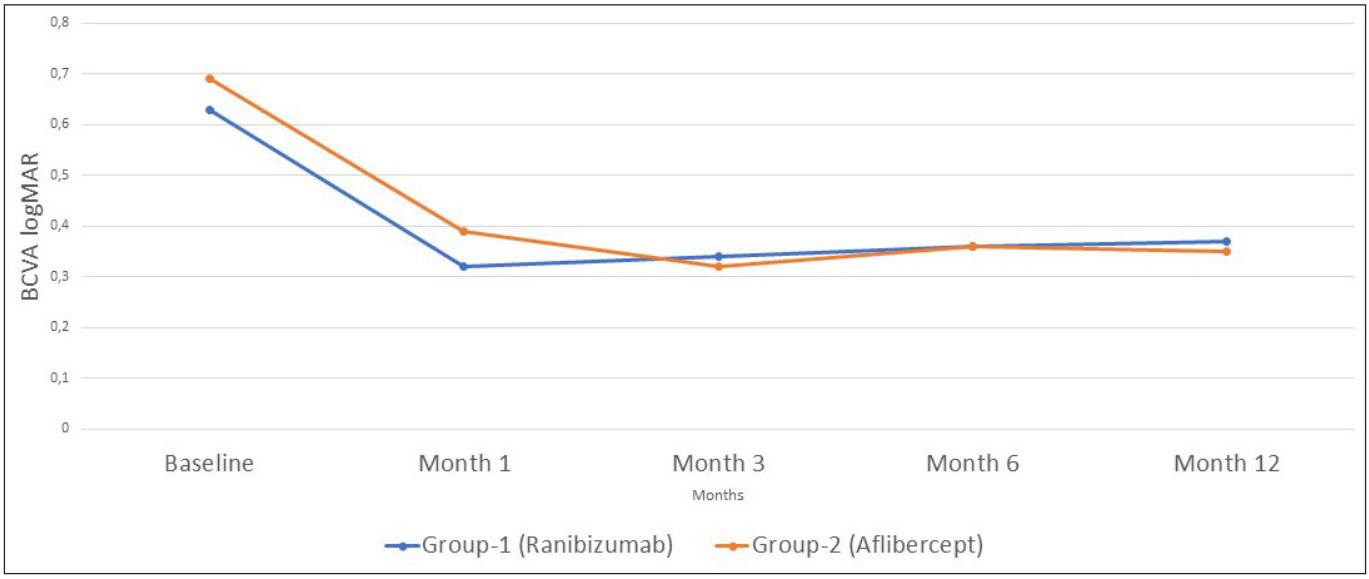

Figure 1: *The BCVA changes between two groups.*

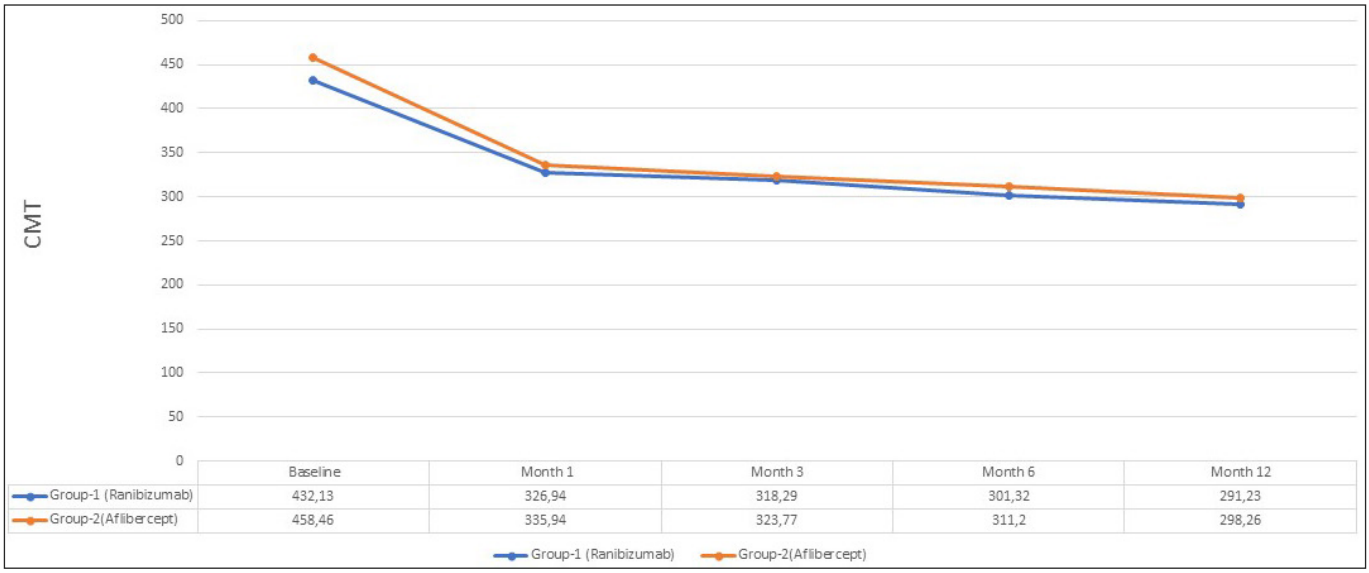

Figure 2: *The CMT changes between two groups.*

12-month follow-up period.

DISCUSSION

Diabetic macular edema is one of the most important causes of vision loss in patients with DRP[10]. Focal/grid laser applications have been used successfully for a long time in the treatment of diabetic macular edema[11]. When the role of VEGF was better understood in the pathogenesis of DME, intravitreal anti-VEGF agents became the first choice in the treatment of DME[12]. In this study, we compared the efficacy of intravitreal ranibizumab and aflibercept in DME. In the first year of treatment, BCVA increased and CMT decreased significantly in both groups. Improvement in BCVA and decrease in CMT were similar between both groups. The total number of injections in one year was slightly less in the aflibercept group, but there was no significant difference between the two groups.

The most important study which compares the efficacy of anti-VEGFs in the treatment of DME is the Protocol T study[13]. In Protocol T study when the whole patient group was examined, it had been determined that an average of 11.2, 9.7, and 13.3 letter gains were achieved in BCVA with ranibizumab, bevacizumab, and aflibercept in the 1st year. In patients with baseline BCVA of 20/50 or higher, BCVA increase was similar with all 3 anti-VEGF treatments. In patients with a baseline BCVA of 20/50 or less, the aflibercepttreated group had greater visual acuity improvement (18.9 letters with aflibercept, 14.2 letters with ranibizumab). However, in the 2nd year results of the Protocol T study, the visual acuity improvements obtained

with intravitreal ranibizumab and aflibercept were almost similar in patients with visual acuity less than 20/50 (18.1 letters with intravitreal aflibercept and 16.1 letters with intravitreal ranibizumab. In our study, we included patients with visual acuity less than 0.5 (20/40), but there was no statistically significant difference in visual acuity improvement between the intravitreal ranibizumab and intravitreal aflibercept groups at month 12.

Fouda et al.[14] followed up patients who received intravitreal aflibercept or ranibizumab for DME for 1 year. They reported aflibercept and ranibizumab have the same efficacy in the treatment of DME in eyes with moderate visual loss but with less drug re-injection and less treatment burden with aflibercept. Similarly, in our study, the number of injections was 7.2 (6-9) in the ranibizumab group and 6.9 (6-8) in the aflibercept group. However, there was no significant difference between the two groups.

Shimizu et. al.[15] compared the efficacy of intravitreal aflibercept to intravitreal ranibizumab injections in eyes with DME. They reported the BCVA of eyes with serous retinal detachment (SRD) was significantly better at 1 month after the intravitreal ranibizumab and at 1 month and 6 months after the intravitreal aflibercept. The BCVAs improved more significantly in the SRD+ group than in the SRD− group. The effects of intravitreal aflibercept persist longer than that of intravitreal ranibizumab. The effectiveness of both intravitreal ranibizumab and intravitreal aflibercept was not dependent on the presence of SRD.

Ozkaya et al.[16] compared the efficacy of intravitreal aflibercept and ranibizumab in patients with DME accompanied by subretinal fluid. They followed the patients for 12 months with the PRN treatment regimen after 3 loading doses. There was no difference in BCVA at 12 months between the two groups, but the regression rates in the subretinal fluid were higher in the intravitreal aflibercept group. They attributed this to the fact that aflibercept blocks placental growth factor (PGF), which also blocks inflammation.

In Ramos et al.'s [17] real-life study, the efficacy and safety of ranibizumab and aflibercept in the treatment of DME was examined. They reported there are no differences in efficacy and safety between ranibizumab and aflibercept in DME treatment. Similarly, no significant systemic or ocular side effects occurred with either agent in our study.

The limitations of our study; It is retrospective, the follow-up period is short, the efficacy of ranibizumab and aflibercept in different types of macular edema did not be compared, the proactive treatment regimen, treat and extend, is not used, and the number of patients is low.

In conclusion, both ranibizumab and aflibercept are effective in the treatment of diabetic macular edema. In patients with diabetic macular edema, intravitreal ranibizumab or aflibercept treatments can reduce vision loss and increase patients' quality of life.

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