Real-life outcomes of intravitreal ranibizumab, aflibercept, and dexamethasone implant administrations in patients with treatment-naïve diabetic macular edema

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ABSTRACT

PURPOSE: To investigate optical coherence tomography (OCT) biomarker data on visual recovery in treatment-naïve diabetic macular edema (DME) and follow the results of intravitreal ranibizumab (RNB), aflibercept (AFL), and dexamethasone (DEX) implant administration within the 1st year of the pro re nata treatment regimen.

METHODS: One hundred and twenty eyes of 102 patients were enrolled in the study. The patients medical records were analyzed retrospectively. Best-corrected visual acuity (BCVA), central macular thickness (CMT), type of DME, presence of subretinal fluid, number and localization of hyperreflective dots, vitreomacular interface disorders, disorganization of the retinal inner layer (DRIL), inner segment/outer segment (IS/OS) junction-external limiting membrane (ELM) status, intraretinal cyst diameter and localization, and subfoveal choroidal thickness were examined in all patients.

RESULTS: A statistically significant increase in BCVA and a decrease in CMT were detected in all treatment groups. When cases were evaluated in terms of BCVA before and after treatment, statistically significant differences were observed in the RNB and AFL groups at 1 and 4 months and in the DEX group during the 1st year. In terms of OCT biomarkers, visual recovery was obtained in cases of intact IS/OS-ELM and non-DRIL patients. In the serous macular detachment group, more visual gain was achieved with the RNB (1 and 4 months) and AFL (1, 4, and 6 months) agents compared to the DEX implant. On the other hand, in the group with cystoid macular edema, more visual gain was achieved with RNB compared to the DEX implant in all months, but more visual gain was achieved only in the 1st month with AFL administration.

CONCLUSION: Significant improvement was achieved for both BCVA and CMT in all treatment groups. We expect that OCT-based prognostic factors will become more important in the treatment of DME and will be determining factors in the choice of treatment.

Keywords: Aflibercept, dexamethasone, diabetic macular edema, optical coherence tomography biomarkers, ranibizumab

INTRODUCTION

Along with technological advances in the treatment of diabetic macular edema (DME), vascular endothelial growth factor inhibitors (anti-VEGF) and intravitreal steroid implants have become alternative therapies to laser photoablation and they are now the first choice of treatment for central involved DME.

Optical coherence tomography (OCT) has become an indispensable imaging method in the diagnosis and follow-up of DME. It objectively reveals the basic anatomical structures of the macula and various parameters associated with macular diseases. However, central macular thickness (CMT) is the most important OCT parameter, and it has been widely used in making the decision to re-treat in large-scale studies such as RISE/RIDE, RESTORE, and DRCR.net Protocol T.[1-3]
Recent studies have identified various OCT biomarkers with prognostic value and have emphasized that these biomarkers are important for drug selection in the initial stage of DME and/or in predicting future visual recovery.\textsuperscript{[4,5]} Therefore, this study aimed to investigate the effects of OCT biomarkers on anatomical and functional success in patients with untreated DME and to analyze the differences in the choice of treatment according to DME subtypes.

**Methods**

**Study population**

A total of 120 eyes of 102 patients with untreated DME were retrospectively analyzed. The study was carried out according to the principles of the Declaration of Helsinki after receiving the approval of the Local Ethics Committee.

**Patient selection**

The study included patients older than 18 years of age with type 1 or type 2 diabetes mellitus (DM), with best-corrected visual acuity (BCVA) ranging between 0.3 and 1.3 log MAR, and with DME involving the central macula according to OCT (CMT of >320 μm), with follow-up of patients in the study group who were administered three doses of ranibizumab (RNB) or aflibercept (AFL) monthly and on a pro re nata (PRN) treatment regimen afterward and of patients administered a PRN treatment regimen following a single dexamethasone (DEX) implant at baseline. During follow-up, in the event of BCVA of 0 log MAR or better and CMT of <320 μm according to OCT, no further treatment was applied for the patients. The exclusion criteria included age of <18 years, pregnancy, thromboembolic event history, uncontrolled DM (HbA1c of >12%), macular edema present other than diabetic retinopathy (DR), DME with neovascularization according to fundus fluorescein angiography, history of vitreoretinal surgery, history of glaucoma, and history of focal, grid, or pan-retinal laser photocoagulation. Patients with a previous history of intraocular injection and severe corneal opacification or dense cataracts that would affect retinal examination were also excluded from the study.

**Evaluation of patients**

Measurement of BCVA (converted to log MAR), slit-lamp examination, intraocular pressure measurement (Goldmann applanation tonometry), and posterior segment examinations with 90 D lenses were performed for all patients. Age, gender, duration of DM, and stage of DR were recorded. First, a total of 3 horizontal spectral-domain-OCT (SD-OCT) images (Heidelberg OCT Spectralis, version 1.7.0.0, Heidelberg Engineering, Heidelberg, Germany) were evaluated with a B-scan covering the fovea passing 500 μm above and 500 μm below the fovea. The value generated automatically by the device for CMT was saved. The patients were divided into three groups as having serous macular detachment (SMD), cystoid macular edema (CME), and diffuse retinal thickening (DRT). In subretinal fluid (SRF) evaluation, the patients with no reflection under the fovea and a hyporeflective cavity formed by the high reflection line at the base of the retina were considered SRF cases. Hyperreflective dot (HRD) evaluation revealed small and unshaded reflectivity of <40 μm. Patients with 2–10 HRDs were included in the “low” group, those with 11–20 HRDs in the “moderate” group, and those with ≥21 HRDs in the “high” group. In terms of localizations, those between the inner limiting membrane and the inner nuclear layer (INL) were included in the first group, those between the outer plexiform layer and the outer nuclear layer (ONL) in the second group, and those in the whole retina in the third group. In terms of vitreomacular interface diseases, patients were divided into three groups according to nontraction, vitreomacular traction (VMT), and the epiretinal membrane (ERM). For disorganization of the retinal inner layer (DRIL), an area of 1 mm in the foveal center was evaluated and analyzed. In inner segment/outer segment (IS/OS) junction-external limiting membrane (IS/OS-ELM) evaluation, the patients were divided into three groups as completely healthy, partially healthy, and completely damaged. The widest diameter of intraretinal cysts (IRC) was measured and defined in three categories as below 100, 100–200, and >200 μm. In the event of more than one cyst, the largest cyst was included in the study. The patients were grouped as having diffuse cysts covering the entire retina in the INL, in the ONL, and with localization of the cyst. The subfoveal choroidal thickness (SFCT) was measured as the distance between the posterior border of the retinal pigment epithelium and the choroid-scleral junction. OCT findings were evaluated without consideration of anatomic or functional results. These analyses were repeated before treatment and at 1, 3, 6, and 12 months after treatment.

**Statistical analysis**

Statistical analysis was performed with SPSS version 21 (IBM Corp., Armonk, NY, USA). ANOVA, Kruskal-Wallis, and Chi-square tests were used for the comparison of pretreatment groups. All patients were divided into three groups as those who acquired more than 10 letters, those who acquired fewer than 9 letters, and those who lost fewer than 9 letters; those who lost more than 10 letters compared to letter acquisitions at 1, 4, 6, and 12 months were also grouped. In this grouping, a 0.1 log MAR scale was used for every 5 letters. Preoperative OCT biomarkers of the three main groups were evaluated by logistic regression. The generalized estimating equations (GEE) method was used to analyze correlated data. The response variable was set to be visual acuity. The patients were evaluated according to the type of drug administered before the treatment and BCVA, CMT, and SFCT repeated measures were evaluated by ANOVA and the Friedman test. In terms of the type of DME and the presence of HRD, the response variable was evaluated as visual acuity by GEE analysis. Statistical significance was accepted as \( P < 0.05 \).

**Results**

**Study population**

The demographic data and BCVA, CMT, and SFCT values of the patients are summarized in Table 1. Baseline BCVA was
Evaluation of optical coherence tomography biomarkers

Patients were classified as having SMD, CME, and DRT according to the type of edema [Table 2]. Patients were grouped according to HRD, SRF, DRIL, and IRC. Four patients with VMT and six patients with ERM identified. Traction was not detected in the remaining 110 cases. In the 4th month, traction of 2 VMTs was found to be regressed. Patients were grouped according to treatment groups in terms of IS/OS-ELM. There was no significant difference between the groups.

The patients were divided into three groups according to visual acuity recovery and evaluated before treatment for the comparison of OCT biomarkers at 1, 4, 6, and 12 months. Patients with HRD before treatment had 2.21 times more visual recovery in month 12 compared to patients without HRD [Table 3].

When the RNB and AFL treatment groups were examined, healthy and partially healthy subjects in terms of IS/OS-ELM had statistically significant visual recovery in all months compared to damaged patients. Patients with DRIL had significantly less visual recovery in the entire year in the RNB group and at 4, 6, and 12 months in the AFL group [Tables 4 and 5].

In the DEX treatment group, healthy and partially healthy subjects in terms of IS/OS-ELM had statistically significant visual recovery in all months compared to damaged patients. Patients with DRIL had significantly less visual recovery at 1 month [Table 6].

When cases were evaluated in terms of BCVA before and after treatment, statistically significant differences were observed in the RNB and AFL groups at 1 and 4 months and in the DEX group during the 1st year [Figure 1]. There was a significant difference in CMT in all treatment groups in the 1st year compared to pretreatment. There was also a significant decrease in the RNB and DEX groups in the 1st year and in the AFL group at months 4 and 12. There was no significant difference in terms of HRDs according to the type of DME [Table 7 and Figure 2].

Average number of injections and injection-related adverse events

The mean number of injections administered during 1 year of treatment was 5.125 per patient in the RNB group, 4.85 in the AFL group, and 1.45 in the DEX group. Subconjunctival hemorrhage was the most common side effect after injection. There was no increase in IOP that could not be controlled by medical treatment in the DEX and other groups. Endophthalmitis, vitreous hemorrhage, retinal tear, and retinal detachment were not observed in any case. Anti-VEGF-related thromboembolic events and cardiovascular disease were not encountered during the 1-year treatment period.

Discussion

With the advances in OCT technology and current software, knowledge about OCT biomarkers is increasing day by day. Much more information on OCT biomarkers is obtained by SD-OCT and swept-source-OCT than time-domain (TD)-OCT. TD-OCT has been used in clinical trials such as RIDE/RISE, RESTORE, and DRCR.net Protocol I, in which the anti-VEGF treatment efficacy of DME was investigated.[1,2,6] Fewer studies in which SD-OCT is applied are available, such as VIVID/VISTA, DRCR.net Protocol T, and RETAIN, but they are rapidly increasing.[3,7,8] Qualitative features such as SRF and intraretinal cystoid fluid status, DRIL, IS/OS-ELM integrity, HRD, vitreomacular interface status, and SFCT change are now successfully shown by OCT. There are different results with

| Table 1: Patient demographics and baseline mean best corrected visual acuity, central foveal thickness and subfoveal choroidal thickness outcomes |
|---------------------|------------------|------------------|------------------|------------------|
|                   | RNB              | AFL              | DEX              | Total            |
| Age                | 62.25±8.33       | 60.25±8.16       | 60.7±6.72        | 61.06±7.75       |
| Gender (male/female)| 23/17            | 20/20            | 22/18            | 65/55            |
| DM duration (years)| 11.58±5.07       | 10.45±7.21       | 9.9±3.81         | 10.64±5.54       |
| BCVA (LogMAR)      | 0.64±0.33        | 0.70±0.39        | 0.93±0.49        | 0.76±0.42        |
| CMT (µm)           | 435.63±123.53    | 493.73±120.42    | 495.53±137.29   | 474.96±129.27    |
| SFCT (µm)          | 270.45±63.08     | 255.2±51.72      | 242.63±40.94    | 256.09±53.49     |

*R p value for RNB versus DEX: 0.0.16, RNB versus AFL: 0.549 and AFL versus DEX: 0.084. RNB: Ranibizumab, AFL: Aflibercept, DEX: Dexamethasone, DM: Diabetes mellitus, BCVA: Best corrected visual acuity, CMT: Central macular thickness, SFCT: Subfoveal choroidal thickness.

| Table 2: Classification of patients according to diabetic macular edema types |
|---------------------|------------------|------------------|
| DME types           | RNB (n=40), n (%)| AFL (n=40), n (%)| DEX (n=40), n (%)| Total (n=120), n (%)|
| SMD                  | 15 (37.5)        | 16 (40)          | 18 (45)          | 49 (40.8)          |
| CME                  | 21 (52.5)        | 13 (32.5)        | 18 (45)          | 52 (43.3)          |
| DRT                  | 4 (10)           | 11 (27.5)        | 4 (10)           | 19 (15.8)          |

RNB: Ranibizumab, AFL: Aflibercept, DEX: Dexamethasone, DME: Diabetic macular edema, SMD: Serous macular detachment, CME: Cystoid macular edema, DRT: Diffuse retinal thickening.
the choice of different intravitreal agents in the treatment of DME, and there is still no consensus on the optimal treatment. Steroids were largely reported as the second-line treatment for DME in the EURETINA recommendations. Steroid treatment has been proposed as the first-line treatment only for patients with a history of cardiovascular events. This is because those patients were excluded from all major anti-VEGF studies.

In a study conducted by Shimura et al.,[9] 143 patients were divided into groups according to the type of edema (17.5% SMD, 23.6% CME, 35% DRT, and 21% all groups) and bevacizumab was reported to have a better response in the DRT group than other groups. In our study, the classification included SMD (40.8%), CME (43.8%), and DRT (15.8%).

In the SMD group, more visual gain was achieved with the RNB and AFL agents when compared to the DEX implant at months 1 and 4 and at months 1, 4, and 6, respectively. On the other hand, in the CME group, more visual gain was achieved with RNB when compared to the DEX implant in all months, but more visual gain was achieved only in the first month with AFL. No significant difference was observed in the DRT group according to treatment choice. Therefore, we conclude that the lower baseline BCVA in the DEX group, a higher number of patients in the partially healthy IS/OS group, and lower baseline SFCT may have impacted the results.

The protective role of SRF was demonstrated by post hoc analysis in the RISE and RIDE studies. Although there was no difference in BCVA between the two groups at baseline, it was reported that at the end of the 1st year of the study, BCVA had improved more than patients without SRF at baseline.[10] Zur et al.[11] reported that patients with SRF had a better response to treatment at month 4 than those without SRF. Reznicek et al.,[12] however, found no statistically significant difference despite better visual recovery in the SRF group. Although this difference was not statistically significant in our study, when we evaluated all cases, we found more letter gain in the SRF group compared to the non-SRF group in months 1 and 12, with values of 1.49 and 1.11, respectively.

### Table 3: At the end of the 12th month, effect of baseline optical coherence tomography biomarkers on best corrected visual acuity gain analysis

|                      | BCVA gain ≥10 letters* (n=53) | BCVA gain <9 letters BCVA <loss 9 letters** (n=49) | BCVA loss ≥10 letters** (n=18) | P* | OR | 95% CI |
|----------------------|--------------------------------|---------------------------------------------------|--------------------------------|----|----|--------|
| Baseline BCVA        | 0.87±0.39                      | 0.66±0.45                                         | 0.68±0.40                      |    |    |        |
| Last BCVA            | 0.45±0.13                      | 0.63±0.47                                         | 1.10±0.38                      |    |    |        |
| Baseline CMT         | 485.2±812                      | 473.6±136.92                                      | 448±126.14                     |    |    |        |
| Presence of SRF      | (28±51) (52%)                  | 17 (51) (31%)                                     | 9 (54) (17%)                   | 0.77 | 1.11 | 0.54-2.30 |
| Absence of SRF       | 25 (60) (38%)                  | 32 (60) (48%)                                     | 9 (66) (14%)                   |    |    |        |
| Presence of HRD       | 37 (74) (50%)                  | 30 (74) (41%)                                     | 7 (74) (9%)                    | 0.04 | 2.21 | 1.02-4.80 |
| Absence of HRD       | 16 (46) (35%)                  | 19 (46) (41%)                                     | 11 (46) (24%)                  |    |    |        |
| HRD few              | 6 (15) (40%)                   | 8 (15) (53%)                                      | 1 (15) (7%)                    | 0.79 | 1.92 | 1.55-2.35 |
| HRD moderate         | 12 (25) (48%)                  | 10 (25) (40%)                                     | 3 (25) (12%)                   |    |    |        |
| HRD many             | 19 (34) (56%)                  | 12 (34) (35%)                                     | 3 (34) (9%)                    |    |    |        |
| HRD ILM-INL          | 2 (8) (25%)                    | 6 (8) (75%)                                       | 0 (8) (0%)                     | 0.18 | 1.35 | 1.22-1.56 |
| HRD OPL-ELM          | 12 (29) (41%)                  | 13 (29) (45%)                                     | 4 (29) (14%)                   |    |    |        |
| HRD all layers       | 23 (57) (62%)                  | 11 (37) (30%)                                     | 3 (37) (8%)                    |    |    |        |
| Absence of VMT       | 52 (110) (47%)                 | 42 (110) (38%)                                    | 16 (110) (15%)                 | 0.47 | 1.82 | 0.35-9.63 |
| VMT                  | 0 (4) (0%)                     | 3 (4) (75%)                                       | 1 (4) (25%)                    | 0.47 | 0.39 | 0.03-4.91 |
| ERM                  | 1 (6) (17%)                    | 4 (6) (66%)                                       | 1 (6) (17%)                    |    |    |        |
| Presence of DRIL     | 15 (37) (41%)                  | 14 (37) (38%)                                     | 8 (37) (21%)                   | 0.77 | 0.86 | 0.30-2.46 |
| Absence of DRIL      | 38 (83) (46%)                  | 35 (83) (42%)                                     | 10 (83) (12%)                  |    |    |        |
| IS/OS healthy        | 35 (76) (44%)                  | 31 (76) (41%)                                     | 10 (76) (12%)                  | 0.31 | 3.41 | 0.70-16.71 |
| IS/OS partially healthy | 12 (31) (41%)              | 14 (31) (44%)                                     | 5 (31) (15%)                   | 0.34 | 1.88 | 0.51-6.83 |
| IS/OS disrupted       | 5 (13) (38%)                   | 4 (13) (31%)                                      | 4 (13) (31%)                   |    |    |        |
| Presence of IRC      | 34 (73) (47%)                  | 30 (73) (41%)                                     | 9 (73) (12%)                   | 0.48 | 1.34 | 0.59-3.06 |
| Absence of IRC       | 18 (47) (38%)                  | 20 (47) (41%)                                     | 9 (47) (21%)                   |    |    |        |
| IRC small            | 3 (6) (50%)                    | 3 (6) (50%)                                       | 0 (6) (0%)                     |    |    |        |
| IRC medium           | 9 (23) (39%)                   | 12 (23) (52%)                                     | 2 (23) (9%)                    |    |    |        |
| IRC large            | 22 (44) (50%)                  | 15 (44) (35%)                                     | 7 (44) (15%)                   |    |    |        |
| IRC INL              | 10 (21) (48%)                  | 8 (21) (38%)                                      | 3 (21) (14%)                   |    |    |        |
| IRC ONL              | 19 (39) (48%)                  | 17 (39) (43%)                                     | 3 (39) (9%)                    |    |    |        |
| IRC diffuse          | 6 (13) (44%)                   | 5 (13) (39%)                                      | 2 (13) (17%)                   |    |    |        |
| SFCT                 | 252.5±44.61                    | 265.2±57.1                                        | 241.7±65.14                    |    |    |        |

*Logistic regression, **Based on the 0.1 logMAR Scale for each 5 letters. BCVA: Best corrected visual acuity, CMT: Central macular thickness, SRF: Subretinal fluid, HRD: Hyperreflective dot, ILM: Internal limiting membrane, INL: Inner nuclear layer, OPL: Outer plexiform layer, ELM: External limiting membrane, VMT: Vitreo-macular traction, ERM: Epiretinal membrane, DRIL: Disorganization of the retinal inner layer, IS/OS: Inner segment/outer segment, IRC: Intra retinal cyst, SFCT: Subfoveal choroidal thickness, ONL: Outer nuclear layer, OR: Odds ratio, CI: Confidence interval
There are different studies on the effect of HRDs on the visual outcomes after anti-VEGF treatment in DME. Kang et al.\textsuperscript{[13]} reported that the number of HRDs decreased and visual acuity increased in all layers with anti-VEGF treatment in cases of DME. In the SMD group, pretreatment HRD number was found to be higher, especially in the retinal outer layers, and the decrease in HRD number after treatment was reported to be significantly higher than in the other groups. In our study, there was no statistically significant difference between edema types for HRDs. When all patients were evaluated, we found that patients with HRDs achieved 2.08 times more letter acquisition in month 6 and 2.21 times more in month 12.

Ganglion cell loss, thinning of the INL, and hyalinization of the retinal capillary network are thought to be involved in the pathophysiology of DRIL. Balaratnasingam et al.\textsuperscript{[14]} reported a positive moderate correlation between the foveal avascular zone and DRIL in a study evaluating 95 eyes with DR and vein occlusion. Das et al.\textsuperscript{[15]} showed that there was a 6-letter decrease in BCVA in every 100 μm of DRIL and a correlation between DR severity and DRIL. In our study, there was a statistically significant negative effect on visual recovery at all months in the RNB group, at months 4 and 6 in the AFL group, and at month 1 in the DEX group.

In a study by Shin et al.\textsuperscript{[16]} that included 61 patients administered intravitreal triamcinolone acetonide, a statistically significant visual recovery was obtained in patients healthy and partially healthy in terms of IS/OS-ELM compared to the damaged group. In our study, it was found that the patients with healthy and partially healthy IS/OS-ELM layers had significantly better visual recovery in all drug groups and in all months compared to those with damaged layers. In our study, it was found that the patients with partially healthy IS/OS-ELM were more prevalent in the DEX group. This may be because anti-VEGF is preferred as first-line treatment in treatment-naive patients. This choice of treatment is consistent with the recommendations in the EURETINA guidelines, although it did make slight differences between the groups.\textsuperscript{[17]}

Pelosini et al.\textsuperscript{[18]} reported that there was a correlation between baseline BCVA and healthy neurosensory retinal volume and this correlation was lower when IRC was found between the inner and outer retinal layers. Gerendas et al.\textsuperscript{[10]} found a significant difference in terms of visual recovery in patients with cystoid cavity height >380 μm compared to smaller ones. In our study, there was no significant difference in the presence, size, or localization of IRC.

\textbf{Figure 1:} Changes in mean best corrected visual acuity with log MAR and central retinal thickness during the follow-up visits in three treatments modalities

\textbf{Figure 2:} Changes in central retinal thickness during the follow-up visits in three treatments modalities

\textbf{Table 4: The effect of baseline optical coherence tomography biomarkers on best-corrected visual acuity gain analysis in ranibizumab group}

|       | 1\textsuperscript{st} | 4\textsuperscript{th} | 6\textsuperscript{th} | 12\textsuperscript{th} |
|-------|------------------------|------------------------|------------------------|------------------------|
|       | P          | B          | P          | B          | P          | B          | P          | B          | P          | B          |
| SRF   | Presence   | -0.35      | 0.161      | -0.075     | 0.876      | 0.009      | 0.594      | 0.031      |
|       | Absence    |            |            |            |            |            |            |            |
| IRC   | Presence   | 0.183      | 0.067      | 0.792      | 0.017      | 0.926      | -0.006     | 0.834      | -0.014     |
|       | Absence    |            |            |            |            |            |            |            |
| IS/OS | Disrupted  | *          | *          | *          | *          | *          | *          |            |
|       | Healthy    | 0.002      | -0.403     | 0.012      | -0.396     | 0.008      | -0.419     | 0.016      | -0.403     |
|       | Partially healthy | 0.008     | -0.342     | 0.019      | -0.369     | 0.013      | -0.405     | 0.023      | -0.384     |
| DRIL  | Presence   | 0.001      | 0.326      | 0.005      | 0.277      | 0.010      | 0.254      | 0.003      | 0.292      |
|       | Absence    |            |            |            |            |            |            |            |
| VMI   | ERM        | *          | *          | *          | *          | *          | *          |            |
|       | VMT absence| 0.000      | 0.466      | 0.080      | 0.231      | 0.008      | 0.238      | 0.007      | 0.222      |
|       | VMT        | 0.000      | 0.427      | 0.015      | 0.349      | 0.006      | 0.360      | 0.011      | 0.345      |
| HRD   | Presence   | 0.438      | -0.036     | 0.615      | -0.027     | 0.582      | -0.029     | 0.617      | -0.027     |
|       | Absence    |            |            |            |            |            |            |            |

*Generalized estimating equations. B: Correlation coefficient, SRF: Subretinal fluid, IRC: Intraretinal cyst, IS/OS: Inner segment/outer segment, DRIL: Disorganization of the retinal inner layer, VMI: Vitreomacular interface, HRD: Hyperreflective dot, SFCT: Subfoveal choroidal thickness, ERM: Epiretinal membrane, VMT: Vitreo-macular traction.
In our study, a significant decrease in SFCT was detected in both anti-VEGF and DEX groups at months 4 and 12. In this study, a visual recovery of 0.03 log MAR was obtained with each increase of 10 μm baseline SFCT in the RNB group and 0.02 log MAR visual recovery in BCVA was obtained with every increase of 10 μm the AFL group. Patients with low baseline SFCT may be less responsive to anti-VEGF treatment because of lower VEGF secretion or ischemic macular edema. Yu et al.[19] reported that the pathogenesis of DME may also play a role in this examination, although they thought that SFCT thinning during DME treatment occurred with anti-VEGF treatment.

When the treatment groups were compared in our study, a rapid visual gain was observed in all treatment groups in the 1st month. In the DEX group, we saw that drug efficacy decreased after month 4, but increased efficacy was obtained after the second injection. We demonstrated that the greatest decrease in CMT was measured in the first month with the DEX implant, but it increased after month 4. In CMT analysis, we observed similar effects with the RNB and AFL agents in the 1st year. The best anatomic and functional outcomes with the RNB and AFL agents were observed in month 4, but they were observed in the 1st month with the DEX implant. The lower injection number in the DEX group was an important advantage in comparison to the RNB and AFL groups.

It has been shown that patients with DME who underwent anti-VEGF treatment in studies in which real-life data were evaluated had lower visual recovery compared to patients in randomized controlled studies. The authors explained that ischemia or atrophy-related DME may be more common in this group of patients, with systemic comorbidities being completely excluded in randomized controlled trials but generally included in studies analyzing real-life data. The mean number of injections for the 1st year was lower in the studies analyzing real-life data than the randomized controlled trials, and in our study, it was similar in terms of real-life data. In the Protocol I study, the visual recovery of the suboptimally responding group at week 12 compared to the group responding well at week 156 was similar. Therefore, we consider that the main contribution of our study lies in determining the response in the first 3–6 injection intervals in DME treatment to a large extent.

Intravitreal injection of anti-VEGF agents and the DEX implant may be associated with devastating complications including endophthalmitis, intraocular inflammation, rhegmatogenous retinal detachment, intraocular pressure elevation, and ocular hemorrhage.[22] For phakic eyes and in cases of glaucoma, DEX should be carefully considered during treatment selection for patients with DME. Iatrogenic crystalline lens injury may occur in eyes with intravitreal injections.[23]

Our study has several limitations. First, it was planned retrospectively. Second, there were patients in the DEX group who had a lower baseline BCVA compared to the RNB group. We think that this difference may be due to the first choice of anti-VEGF in patients with DME during treatment selection and DEX may be effective in patients with a history of cardiovascular disease. We also found that DEX was preferred for patients who could not be followed during treatment. DEX treatment is likely to pose a risk for glaucoma in such patients who cannot be followed regularly. Third, the higher number of partially healthy patients in the DEX group in terms of IS/OS-ELM may be considered as a disadvantage of our study. Failure to perform evaluations in terms of fundus fluorescein angiography in our study is another limitation. We suggest that VEGF secretion is lower or ischemic macular edema may be present in patients with low baseline SFCT and SFCT may provide a clue to the clinician in this regard.

Together with these limitations, the study has several strengths. It is one of the first studies in the literature in which three intravitreal agents used in the treatment of DME were evaluated together. In this study, RNB and AFL in the SMD group and RNB in the CME group provided better visual gain. Furthermore, the number of injections in the DEX group was lower than that in the anti-VEGF treatment group and this is the first option for patients with cardiovascular disease today.

**Conclusion**

The intensive treatment plan and the number of patient visits required to obtain visual recovery for patients outside of randomized controlled study groups are major challenges. When real-life data are evaluated, it is seen that the PRN
Table 6: The effect of baseline optical coherence biomarkers on best-corrected visual acuity gain analysis in dexamethasone group

|       | 1st | 4th | 6th | 12th |
|-------|-----|-----|-----|------|
|       | P   | B   | P   | B    | P   | B    |
| SRF   |     |     |     |      |     |      |
| Presence | 0.444 | -0.664 | 0.757 | -0.024 | 0.788 | -0.021 | 0.865 | 0.013 |
| Absence | 0.255 | 0.121 | 0.500 | 0.051 | 0.651 | 0.030 | 0.906 | 0.007 |
| IRC   |     |     |     |      |     |      |
| Presence | 0.043 | 0.198 | 0.189 | 0.121 | 0.133 | 0.152 | 0.140 | 0.136 |
| Absence | 0.674 | -0.029 | 0.398 | -0.058 | 0.840 | -0.015 | 0.841 | -0.016 |
| VMT   |     |     |     |      |     |      |
| ERM   |     |     |     |      |     |      |
| Presence | 0.309 | 0.001 | 0.365 | 0.001 | 0.347 | 0.001 | 0.388 | 0.001 |

*: Generalized estimating equations. B: Correlation coefficient, SRF: Subretinal fluid, IRC: Intraretinal cyst, IS/OS: Inner segment/outer segment, DRIL: Disorganization of the retinal inner layer, VMI: Vitreomacular interface, HRD: Hyperreflective dot, SFT: Subfoveal choroidal thickness, ERM: Epiretinal membrane, VMT: Vitreomacular traction.

Table 7: The effect of hyperreflective dot and treatment modalities on best-corrected visual acuity according to diabetic macular edema types

|       | 1st | 4th | 6th | 12th |
|-------|-----|-----|-----|------|
|       | P   | B   | P   | B    | P   | B    |
| SMD   |     |     |     |      |     |      |
| HRD   |     |     |     |      |     |      |
| RNB-DEX | 0.004 | -0.258 | 0.048 | -0.186 | 0.084 | -0.179 | 0.108 | -0.172 |
| AFL-DEX | 0.048 | -0.181 | 0.039 | -0.177 | 0.041 | -0.186 | 0.055 | -0.181 |
| RNB-AFL | 0.426 | -0.078 | 0.926 | -0.009 | 0.945 | 0.007 | 0.930 | 0.009 |
| CME   |     |     |     |      |     |      |
| HRD   |     |     |     |      |     |      |
| RNB-DEX | 0.007 | -0.217 | 0.015 | -0.204 | 0.022 | -0.211 | 0.028 | -0.219 |
| RNB-AFL | 0.491 | -0.057 | 0.282 | -0.096 | 0.273 | -0.115 | 0.254 | -0.131 |
| AFL-AFL | 0.041 | -0.160 | 0.141 | -0.107 | 0.209 | -0.097 | 0.276 | -0.088 |
| DRT   |     |     |     |      |     |      |
| HRD   |     |     |     |      |     |      |
| RNB-DX | 0.162 | 0.175 | 0.217 | 0.160 | 0.363 | 0.123 | 0.493 | 0.103 |
| RNB-AFL | 0.131 | -0.390 | 0.200 | -0.321 | 0.270 | -0.265 | 0.424 | -0.212 |
| AFL-DX | 0.551 | -0.147 | 0.542 | -0.142 | 0.471 | -0.165 | 0.544 | -0.146 |
| AFL-AFL | 0.109 | -0.243 | 0.265 | -0.179 | 0.539 | -0.100 | 0.734 | -0.066 |

*: Correlation coefficient, DME: Diabetic macular edema, HRD: Hyperreflective dot, RNB: Ranibizumab, AFL: Afibercept, DEX: Dexamethasone, SMD: Serous macular detachment, CME: Cystoid macular edema, DRT: Diffuse retinal thickening.

regimen is frequently used in the treatment of DME. Using CMT measurements in treatment in this protocol are not enough to predict visual recovery. We believe that HRD, SRF, DRIL, IRC, IS/OS, and ELM as evaluated by OCT can be used as biomarkers for DME and may be important in predicting visual prognosis. These biomarkers can give clinicians an idea about the choice of the treatment agent and treatment regimen, as well as the probable response of patients to treatment. Accordingly, it may be appropriate to change the treatment regimen for patients with suboptimal visual recovery after the first 3 intravitreal anti-VEGF injections. Moreover, we think that future randomized controlled trial analyses are important for the subsequent management of patients with limited baseline response to anti-VEGF treatment. We expect that treatment methods and processes will become more individualized with a better understanding of retinal morphology in patients with DME in future. In parallel with the advances in OCT technology, new biomarkers can be identified in this process.

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**Conflicts of interest**

There are no conflicts of interest.

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