Original Article

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Our 2-Year Real-Life Outcomes in Patients Who Received Ranibizumab Treatment for Diabetic Macular Edema (DME)

Gerçek Yaşam Klinik Uygulama Ortamlarında İki Yıl Takip Edilen Diyabetik Makula Ödemli (DMÖ) Gözlerde Tedavi Sonuçları

Ismail Umut Onur[1], Mehmet Fatih Asula[2], Ulviye Yigit[1], Ozan Sonbahar[1], Utku Furuncuoglu[3]

[1]*Bakirköy Dr. Sadi Konuk Training and Research Hospital, Department Of Ophthalmology*
[2]*Tosya State Hospital, Department Of Ophthalmology*
[3]*Kastamonu Training and Research Hospital, Department Of Ophthalmology*

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ABSTRACT

Objective: *To assess the real-life performance and clinical outcomes in patients with diabetic macular edema (DME).*
Method: *The chart records were retrospectively evaluated for 42 eyes of 42 patients with DME, who were followed for two years between October 2013 and October 2016 at the Retina Unit. The patients were treated using intravitreal ranibizumab (0.5 mg/0.05 ml) for two years.*
Results: *The Early Treatment of Diabetic Retinopathy Study (ETDRS) letter score indicated BCVA values of 71.1±22.4 letters at baseline, 74.1±19.1 letters at the sixth month, 76.2±16.2 letters at the first year, and 76.1±21.2 letters at the end of the second year. BCVA at the sixth month and first and second years were not significantly different from the baseline value (p=0.172, p=0.051, p=0.108). The mean CFT were 407.4±140.0 µm at the baseline, 375.5±141.5 µm at the 6th month, 357.0±129.1 µm at the 1st year, and 313.8±108.9 µm at the end of 2nd year. The change in mean CFT compared to the baseline value was not statistically significant at the 6th month, but were statistically significant at the 1st and the 2nd years (p=0.082, p=0.040, and p=0.000, respectively).The mean numbers of injections and follow-ups at the end of the second year were 3.7±2.5 and 9.1±3.1, respectively.*
Conclusion: *The BCVA did not change significantly compared to baseline. The BCVA eye scores improved by 15 or more letters, in agreement with findings of other multi-center studies. However, the eyes with a BCVA loss of 15 or more letters showed a significant difference, which might reflect the smaller number of injections given in the present study compared to the other studies.*

Keywords: *Diabetic macular edema, ranibizumab, real-life outcome*

ÖZ

Amaç: *Diabetik makula ödemi (DMÖ) nedeniyle retina birimimizce iki yıl takip ve tedavi altında tutulan olgularda gerçek yaşam performansı ve klinik sonuçlarının ortaya çıkarılması ve benzer çok merkezli başlıca randomize çalışmalardaki sonuçlarla kıyaslanmasıdır.*
Yöntem: *Ekim 2013-Ekim 2016 tarihleri arasında Göz Kliniği Retina biriminde DMÖ nedeniyle takip ve tedavisi gerçekleştirilen, intravitreal ranibizumab 0.5 mg/0.05 ml tedavisi uygulanan ve 2 yıl boyunca takipte kalan 42 hastaya ait 42 gözün dosya kayıtları retrospektif olarak incelendi ve parametreleri değerlendirildi.*
Bulgular: *ETDRS harf skorlamasına göre ilgili gözlerde EİDGK, enjeksiyon öncesi ortalama 71.1±22.4 harf, tedavi sonrası 6. ayda 74.1±19.1 harf, 1. yılda 76.2±16.2 harf, 2. yılın sonunda 76.1±21.2 harf olarak gerçekleşti. Altıncı ay, 1. yıl ve 2. yılın sonunda görme keskinlikleri başlangıç görme keskinliğine göre anlamlı bir değişim göstermemiştir. (p=0.172, p=0.051, p=0.108). Santral foveal kalınlıkla (SFK) ilgili olarak ortalama değerler başlangıçta 407,4±140.0 µm, 6.ayda 375.5±141.5 µm, 1. yılda 357.0±129.1 µm ve 2. yılın sonunda 313.8±108.9 µm idi. Başlangıç değeri ile karşılaştırıldığında SFK'daki değişim 6.ayda istatistiksel olarak anlamlı değil iken, 1. ve 2. yıl değerlerinde istatistiksel olarak anlamlıydı (p=0.082, p=0.040, ve p=0.000). Bunun yanında ortalama enjeksiyon sayımız 2. yılın sonunda 3.7±2.5, takip sayımız 9.1±3.1 olarak gerçekleşmiştir.*
Sonuç: *İkinci yılın sonunda görme keskinlikleri başlangıç görme keskinliğine göre anlamlı bir değişim göstermemiş iken,15 veya daha fazla harf kazanma oranı diğer çok merkezli çalışmalarla benzer oranda, 15 veya daha fazla harf kaybı oranımız ise diğer çalışmalara göre daha yüksek bulunmuştur. Bu sonuçta başlıca faktörün diğer çalışmalara göre düşük kalan enjeksiyon sayısı olduğu değerlendirilmiştir.*

Anahtar kelimeler: *Diabetik maküla ödemi, ranibizumab, gerçek yaşam sonuçları*

Corresponding Author:
✉ fatihasula@gmail.com

I.U. Onur 0000-0002-9028-2421
M.F. Asula 0000-0003-3856-9297
U. Yigit 0000-0003-0176-1509
O. Sonbahar 0000-0002-9103-7102
U. Furuncuoglu 0000-0003-0773-910X

INTRODUCTION

Diabetic macular edema (DME) is the leading cause of vision loss in patients with diabetes mellitus (DM) and it adversely affects quality of life [1-4]. If left untreated, DME can cause loss of visual acuity of more than two lines after two years [5]. The World Health Organization (WHO) predicts that patients with DME in Europe will likely increase in number from the 33 million reported in 2000 to 48 million by 2030, along with a similar increase in the prevalence of DME-related vision problems [6].

The cause of DME is a pathological increase in retinal vascular permeability [7], mediated primarily by the cytokine vascular endothelial growth factor (VEGF). Intraocular VEGF levels and DME show an association [8,9], suggesting that the blockage of VEGF signaling may serve to restore retinal anatomy [10,11], while also reversing vision loss due to macular edema [12].

One currently used anti-VEGF drug is ranibizumab (Lucentis; Novartis Pharma AG, Basel, Switzerland), a humanized monoclonal antibody Fab fragment that selectively binds to and inhibits all known active isoforms of VEGF-A. Ranibizumab was formulated especially for ocular use and is widely used at doses of 0.5mg/0.05 ml in more than 100 countries for the treatment of age-related macular degeneration (AMD), DME-related visual impairment, and macular edema due to retinal vein obstruction [13].

The aim of the present study was to assess the real-life performance and clinical outcomes of ranibizumab use in patients with DME. Our patients were followed in our retina unit for two years and we compared our results with those from similar randomized multicenterstudies.

MATERIAL and METHODS

The study was conducted in accordance with the tenets of the Declaration of Helsinki and was approved by the institutional ethical review board (Approval number: 2017/69). Informed consent was obtained from all individual participants included in the study.

Hospital records of 42 eyes of 42 patients with DME were retrospectively evaluated. All ipatients included in the study were treated between October 2013 and October 2016 with intravitreal ranibizumab (0.5 mg/0.05 ml) applications, and followed up for 2 years. The main inclusion criteria were clinically significant macular edema (CSME) according to the Early Treatment of Diabetic Retinopathy Study (ETDRS) classification, the absence of previous anti-VEGF treatments administered anywhere else, and the absence of any other ocular pathology that may cause vision loss. When both eyes were involved, the eye with the worse BCVA was selected in a one patient–one eye approach. Eyes that had previously undergone focal (grid) laser or panretinal laser photocoagulation (PRP) or underwent cataract surgery during the two years of follow-up were not excluded from the study. Application of PRP for severe non-proliferative (NPDR) or proliferative (PDR) diabetic retinopathy was also not an exclusion criterion. Major exclusion criteria in this study were history of uveitis, thromboembolic events or uncontrolled glaucoma in the affected eyes (intraocular pressure [IOP] >30 mmHg), the presence of vitreomacular traction (VMT), and uncontrolled hypertension.

The eyes were evaluated using color fundus photos and fundus fluorescein angiography images (FFA) (Kowa VX-10İ, Kowa Company Ltd. Tokyo, Japan). The central foveal thickness (CFT) was obtained with the MM5 protocol using optic coherence tomography (OCT) (RTVue Optovue Inc., Fremont, California, USA).

BCVA scores were obtained from hospital records and registered in data form following conversion to the ETDRS letter score. Intraocular pressure (IOP) measurements and biomicroscopic anterior segment and dilated fundus examination findings were all recorded in data form after reviewing the charts. In addition to primary outcome parameters, such as baseline, 6th (±1) month, 1st (±2 months) year, and 2nd (±2 months) year Best Corrected Visual Acuity (BCVA) and CFT, other parameters evaluated included the time between the first visit to FFA assessment (diagnosis-treatment decision), the completion time for the first three loading doses, the total number of injections, and the number of follow-up visits achieved in real-life conditions.

Before the treatment, the patients were informed in detail about the possible outcomes and side effects of intravitreal ranibizumab 0.5 mg, and provided written/oral consent. The patients received three monthly load-

ing doses of ranibizumab and then the eyes with DME were followed up at 4- to 6-week intervals. The ranibizumab injections were continued monthly until BCVA improved and/or CFT thinning were stabilized (change in BCVA <5 letters and change in SFT <10% from the last measurement). Cases with a decrease in BCVA (change ≥5 letters) and a ≥10% increase in CFT received a repeat injection. Focal laser therapy was applied to patients who were detected to have a leaking microaneurysm of 500 µm outside the foveola at baseline or at any follow-up visits, and PRP was applied to cases with severe NPDR and PDR. No specific protocol was adopted for the application of laser procedures at earlier or later timeframes.

The descriptive statistics included the mean, standard deviation, the lowest and the highest values, frequency, and ratio. The Kolmogorov-Smirnov test was used to assess the normality of the data distribution, and the Wilcoxon test was used for the assessment of dependent quantitative data. A value of P <0.05 was accepted as statistically significant. SPSS 22.0 (SPSS Inc. Chicago, USA) software was used for the statistical analyses.

RESULTS

In this study, 42 eyes of 42 patients were analyzed. Sixteen patients were males, 26 were females, and the mean age of all patients was 61.6±10.3 years. The mean duration of the DM diagnosis was 16.5±7.8 (2–33) years. The mean time interval from the first visit to the FFA imaging (which is mandatory for social security agency reimbursement) was 62.3±41.4 days. The patients received a mean number of 2.3±1.4 injections in the first year and 1.4±1.6 injections in the second year. The mean total number of injections at the end of the second year was 3.7±2.5. The mean number of follow-up visits in the first year was 5.1±2.1 and 4.0±1.8 at the end of the second year. The total number of follow-up visits at the end of the second year was 9.1±3.1, and the mean number of weeks to complete three loading doses was 40.4±25.1 weeks.

During the two-year follow-up period, 17 patients received only focal laser photocoagulation, 6 patients only PRP, and 5 patients both focal laser and PRP treatments. Only 10 patients (24%) had never previously received laser treatment at any time at any other center. During the two-year follow-up period, 3 patients had cataract surgery.

According to the ETDRS letter score, the mean BCVA for the eyes of concern was 71.1±22.4 letters at baseline, 74.1±19.1 letters at sixth month, 76.2 ± 16.2 letters at the first year, and 76.1±21.2 letters at the end of the second year. Compared with the baseline value, no significant difference was detected in visual acuity at the sixth month, first year, or second year (P=0.172, P =0.051, and P=0.108, respectively). The changes in BCVA are summarized in Table 1.

Table 1. Changes in the BCVA according to the ETDRS chart (letters)

	Q1-Q3	Med	Mean±Sd.	p
Baseline	50-89	77	71.1±22.4	
6th Month	59-89	80	74.1±19.1	0.172[w]
1st Year	64-89	83	76.2±16.2	0.051[w]
2nd Year	65-92	80	76.1±21.2	0.108[w]

[w]: Wilcoxon test
Med: Median
Q1-Q3: interquertile range
Sd: standard deviation
BCVA: Best corrected visual acuity

The number of eyes with a loss of 15 letters or more was 3 (7.1%) at the first year and 6 (14.2%) at the second year. Similarly, the number of eyes with an improvement of 15 letters or more was 12 (28.6%) at the first year and 13 (31%) at the end of second year.

The OCT measurements revealed a mean CFT of 407.4±140.0 at the baseline, 375.5±141.5 µm at the sixth month, 357.0±129.1 µm at the first year, and 313.8±108.9 µm at the end of the second year. The change in mean CFT compared to the baseline value was not statistically significant at the sixth month, but the differences were statistically significant relative to baseline at the first and the second years (P=0.082, P =0.040, and P=0.000, respectively). The changes in CFT are summarized in Table 2.

Table 2. Change in central foveal thickness (CFT) (µm)

	Q1-Q3	Med	Mean±Sd.	p
Baseline	302-465	372	407.4±140.0	
6th Month	302-465	334	375.5±141.5	0.082[w]
1st Year	302-465	336	357.0±129.1	0.082[w]
2nd Year	302-465	272	313.8±108.9	0.000[w]

[w]: Wilcoxon test
Med: Median
Q1-Q3: interquertile range
Sd: standard deviation
BCVA: Best corrected visual acuity

DISCUSSION

Ranibizumab is a humanized monoclonal antibody FAB fragment specifically designed for ocular use to selectively bind to and inhibit all known active isoforms of VEGF-A [13]. VEGF is the most significant factor that increases vascular permeability and leads to neovascularization in retinal diseases. VEGF also serves as a chemoattractant for macrophages and monocytes, and these cells play additional roles in increases in vascular permeability by producing proinflammatory molecules [14].

The ETDRS study for eyes with clinically significant macular edema (CSME) revealed a risk of loss of 15 or more letters at the end of the third year, but this risk was decreased by approximately 50% in a focal laser arm versus observation only. (24% vs. 12%) [15]. However, many known risks of laser treatment, including limited visual outcomes, collateral damage secondary to expansion of laser scars, occurrence of focal localized scotoma, impairment of color vision, permanent damage to the retinal pigment epithelium (RPE) and photoreceptors, secondary choroidal neovascularization (CNV), and RPE fibrous metaplasia, have prompted a serious search for other treatment options [16,17]. One of the first alternative treatments was the use of intravitreal corticosteroids. These drugs halt the destruction of the blood-retina barrier and lower the permeability by inhibiting VEGF and due to their anti-inflammatory effects [18]. Intravitreally administered steroids are efficacious for the treatment of DME, but they also cause complications that can include retinal detachment, intravitreal hemorrhage, increased IOP, development of cataract, pseudoendophthalmitis, and endophthalmitis (0.87%) [19]. Therefore, the current treatment for DME is predominantly focused on the suppression of VEGF-related effects.

The patients in the extended 24-month period of the multicenter, randomized, pilot RESTORE trial showed a mean letter gain of +7.9 letters after 24 months in the ranibizumab-only group and +6.7 letters in the ranibizumab-plus-laser-therapy group. The mean number of injections at the end of 2 years was 11.2 injections in both ranibizumab groups. The decreases in mean CFT were 140 µm vs. 133 µm [20]. Similarly, the RISE and RIDE trials, which were phase 3 trials for ranibizumab, showed visual gains of +11.9 and +12 letters, respectively, in the monthly 0.5 mg ranibizumab treatment arms, whereas the decreases in mean CFT at the end of 24 months were 253 µm and 270 µm, respectively [12]. The READ-2 trial compared ranibizumab and focal/grid laser treatments both head-to-head and in combination. The first group received 0.5 mg intravitreal ranibizumab at the first, third, and fifth months. The second group received focal/grid laser treatment at the baseline, with the treatment repeated at the third month, if necessary. The third group received the combination of 0.5 mg ranibizumab and focal/grid laser combination at the baseline, and the same treatment was repeated at the third month, if necessary. After the sixth month, the ranibizumab treatment was repeated in all groups when treatment was necessary. At the end of the two-year follow-up, the mean letter gain was +7.7 letters in the first, +5.1 letters in the second, and +6.8 letters in the third group, and the change from baseline was statistically significant for all three groups. At the end of the second year, the mean CFTs were 340 µm, 286 µm, and 258 µm, respectively. The mean number of injections in the groups were 9.3, 4.4, and 2.9, respectively. However, the visual outcomes in the second and third groups at the end of the second year were not significantly different from those of the first group. This finding suggests that the use of a focal or grid laser may significantly decrease the requirement for injections without compromising the visual acuity gain. In a relevant study, the greatest increase in visual gain was observed in the injection-only group [21]. The outcomes in our study are comparable with those of the second and the third groups of the READ-2 study with respect to the presence of a laser combination and the number of injections required.

The two-year extension of the independent, multicenter DRCR.net trial assessed 642 eyes of 526 patients in the following 4 groups: a sham injection plus laser, ranibizumab plus early laser (within a week), ranibizumab plus late laser (at the 24th week or later), and triamcinolone plus early laser (within a week). After 24 months of follow-up, the letter gains were +7 ± 13 letters in the ranibizumab-plus-early-laser group, +9 ±14 letters in the ranibizumab-plus-late-laser group, +2 ±19 letters in the triamcinolone-plus-laser group, and +3 ± 15 letters in the laser-only group. In the ranibizumab-plus-early-laser and ranibizumab-plus-late-laser groups, the median numbers of injections were 8 and 9 in the first year and 2 and 3 in the second year, respectively. At the end of second year, the visual outcomes were

similar in the ranibizumab-plus-early-laser and the ranibizumab-plus-late-laser groups; the results were significantly superior to those of the sham-injection-plus-laser and triamcinolone-plus-early-laser groups. Despite a significant difference in visual outcomes, the change in the CFT from baseline to the end of the second year was -145±141 µm in the sham-injection-plus-laser group, -126±162 µm in the ranibizumab-plus-early-laser group, -148±127 µm in the ranibizumab-plus-late-laser group, and -128±137 µm in the triamcinolone-plus-early-laser group. No significant differences were detected among the groups [22]. The letter gains reported for the ranibizumab-plus-early-laser group in protocol I of the DRCR.net study were also similar to the values obtained in our study.

Both gains and losses in visual acuity have been reported previously. For example, 39.2% of the eyes in the 0.5 mg ranibizumab group of the RISE trial gained 15 or more letters, whereas 45.7% of the eyes in the 0.5 mg ranibizumab group of the RIDE trial gained 15 or more letters. In a 2-year extension of DRCR.net protocol I trial, 29% of the eyes in the 0.5 mg ranibizumab-plus-early-laser group, 28% of the eyes in the 0.5 mg ranibizumab-plus-late-laser group, and 18% of the eyes in the sham-injection-plus-laser group gained 15 or more letters. These values agreed with our data. Indeed, 31% of the eyes gained 15 or more letters. The visual losses of 15 or more letters were detected in 2.4% of the eyes in the 0.5 mg ranibizumab group of the RISE trial and 3.9% of the eyes in the 0.5 mg ranibizumab group of the RIDE trial. In the two-year extension of DRCR.net trial, the corresponding rates of visual loss were 4% in the 0.5 mg ranibizumab-plus-early-laser group, 2% in the 0.5 mg ranibizumab-plus-late-laser group, and 10% in the sham-injection-plus-laser group, whereas our rate was 14.2% in the present study.

A multicenter, 2-year study from Portugal, which evaluated the real-life outcomes of ranibizumab, revealed a median number of 4 injections in the first year and 5 injections at the end of the second year. The baseline mean BCVA was 60 letters, which increased to 65 letters at the end of the second year. At that time, 21.4% of the eyes gained 15 or more letters, while 8.6% of the eyes lost 15 or more letters. The baseline median CFT was 443 µm, which decreased to 325.5 µm at the end of the second year [23].

In our study, the percentage of the patients who gained 15 or more letters was similar to the percentages reported in the previous trials, whereas our percentage of patients who lost 15 or more letters was higher than the relevant data reported previously. Our protocol was most similar to the the protocol used in combined laser-plus-ranibizumab groups analyzed in previous multicenter trials. When the clinical workload permitted, we also applied focal laser photocoagulation to the eyes with extrafoveally located edema and microaneurysms. However, the timing of the laser applications in our study was distributed between the early and late periods. Evaluation at the end of the 24-month follow-up demonstrated a median gain of +5.0±16.8 letters with intravitreal ranibizumab injection; however, the result was not statistically significant. This may be due to the high percentage of patients who lost 15 or more letters in our study. Our mean number of injections by the end of second year was 3.7±2.5, which was lower than that of the other trials. This may explain the reason for the high frequency of cases that lost 15 or more letters in visual acuity tests.

Conclusion

In summary, the accumulating trial data reporting real-life outcomes of DME treatments will greatly aid in the comparisons of the effectiveness of treatment protocols. The pharmaceutical industry may also accelerate its efforts in the field of drug formulations and treatment regimens by taking real-life outcomes into account. The development of customized treatment and follow-up protocols may also be proposed. Thus, patient motivation may be increased, and the goal of less frequent follow-ups/injections in low-risk patients and more frequent follow-ups/injections in high-risk patients may be achieved.

Ethics Committee Approval: Bakirköy Dr. Sadi Konuk Training And Research Hospital Clinical Studies Ethics Committee approval was received (29/5/2017; 2017-04-16).
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Informed Consent: Written consent was obtained from all patients participating in the study.

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