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Original Article

The real life data of ranibizumab use among the diabetic macular edema patients in Turkey: Documenting the improvement with clinical optimization during three consecutive years

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Abstract

Purpose: To report the 12 month real life outcomes of ranibizumab treated diabetic macular edema (DME) patients.
Methods: Treatment naïve DME patients treated with ranibizumab were included. Patients were divided into three groups according to their hospital admittance years (2013, 2014, and 2015) and were compared in regards to the treatment outcomes.
Results: The mean visual acuity change from baseline to month 12 was not statistically significant in 2013 at month 12. The mean BCVA change from baseline to month 12 was statistically better at month 12 in 2014 and 2015. There was a statistically significant difference among the three groups in regards to both mean visit and injection numbers. The mean visit number in 2013 and 2014 were both lower than 2015. The mean injection number in 2013 was lower than both 2014 and 2015.
Conclusions: It is effortful to obey the strict follow-up criteria of prospective studies in DME patients on a PRN regimen. However, optimizing the clinical processes of patient management may lead to improved clinical outcomes in real life.

Keywords: Diabetic macular edema, Intravitreal injection, Ranibizumab

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Introduction

Diabetic macular edema (DME) is the most frequent cause of visual loss among the diabetic retinopathy (DR) patients.[1–5] Different treatment options have been used in the treatment of DME.[2–5] Currently intravitreal injection of anti-vascular endothelial growth factors (Anti-VEGF) and steroids are the most preferred treatment modalities.[3–5] Ranibizumab has been found to be effective with various treatment regimens [i.e. monthly, pro re nata (PRN), treat and extend].[4–9] In pivotal multicenter studies, it was shown that, a mean of 8–9 ranibizumab injections were required in the first year of treatment. However, the mean injection number gradually decreased after the first year throughout the study period.[4–9]

In real life practice, it is not always possible to follow the strict follow-up and retreatment criteria proposed in prospective studies. Pro re nata regimen has been commonly used in Turkey in the treatment of DME.[10] Studies from our country have revealed that the real life practice in regards to the visit and injection numbers was far from ideal.[10–16] Indeed, the mean injection number for ranibizumab was 2.1 during the first 9–12 months of treatment and this is quite low in comparison to the higher injection numbers (up to 7.2) reported from Europe.[10,11]

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After revisiting our clinical practice in this regard and realizing that monthly visits were not performed regularly for DME patients who were on a PRN treatment regimen, we took some measures after 2013. In this study we aimed to report the 12 months real life outcomes of ranibizumab treated DME patients who were under follow-up in our clinic in 2013, 2014, and 2015, compare the outcomes among the three consecutive years, and summarize the measures taken for improving our visit and injection numbers.

Materials and Methods

In this retrospective case-control study, medical records of the patients who had DME and underwent intravitreal ranibizumab (IVR) treatment between January 2013 and December 2015 were analyzed. Newly diagnosed treatment naïve DME patients with non-proliferative DR, who completed a follow time of 12 months in our clinic were included. The patients with a history of any other treatment for DME, or showed proliferative DR at admission, or who were lost to follow-up, or received any other treatment for DME including focal or grid laser photocoagulation in the first 12 months during our follow-up were not included. A written informed consent was obtained from all patients before the treatment. The study adhered to the tenets of the Declaration of Helsinki, institutional review board approval was not required for this study according to our countries regulations, as this was a retrospective chart review study.

Data collected from the patients' records included age, gender, best corrected visual acuity (BCVA), central retinal thickness (CRT), and intraocular pressure (IOP) at baseline, and at months 3, 6, 9, and 12. Visit and injection numbers during the first 12 months were also recorded. Patients who admitted in 2013, 2014, and 2015 were grouped and compared in regards to the treatment outcomes, visit, and injection numbers.

Examinations

All patients underwent a standardized examination including measurement of BCVA via a projection chart in decimals at 4 meters, slit-lamp biomicroscopy, measurement of IOP via applanation tonometry, and biomicroscopic fundus examination. Fundus photography, fluorescein angiography (FA) (HRA-2; Heidelberg Engineering, Heidelberg, Germany), and optical coherence tomography (OCT) imaging (Spectralis; Heidelberg Engineering, Heidelberg, Germany) were performed before treatment. All examinations were repeated monthly, except for FA. Fluorescein angiography was repeated according to the physicians' discretion. Optical coherence tomography was used for detecting macular edema and measurement of CRT. Central retinal thickness, defined as the mean thickness of the neurosensory retina in a central 1 mm diameter area, was computed using OCT mapping software generated by the device. Diabetic macular edema was diagnosed via FA and OCT, and patients with a CRT of >300 microns were considered to have DME. The severity of non-proliferative DR, angiographic classification of DME, and ischemic status of macula were not assessed.

Injections

All injections were performed under sterile conditions after application of topical anesthesia, use of 10% povidone-iodine (Betadine; Purdue Pharma, Stamford, CT, USA) scrub was used on the lids and lashes, and 5% povidone-iodine was administered on the conjunctival sac. Intravitreal ranibizumab 0.5 mg/0.05 ml (Lucentis; Novartis, Basel, Switzerland) was injected through the pars plana at 3.5 mm posterior to the limbus with a 30 -gauge needle. Patients were instructed to admit back the hospital if they experienced decreased vision, eye pain, or any new arising symptoms.

Initially, all of the patients received a loading dose of three consecutive monthly injections. Then the patients were followed monthly, and a single injection of IVR was repeated when the VA decreased by one or more lines, or there was an increase of >100 microns in CRT in OCT images compared to the images obtained at the last visit.

Optimization process

In 2013 after reviewing the visit and injections frequency for DME patients in our clinic, we noticed that monthly visits were not performed on a regular basis and injection and follow-up visits were scheduled according to the availability of the calendar. The follow-up and treatment procedures of the DME patients was delayed and it took around 30–50 days to perform the first injection and 100 to 150 days to perform the third injection of the loading phase due to the heavy patient load and scheduling procedures. Therefore, we planned to make some improvements in the clinical processes. Before the optimization process, the DME patients were referred for examination in the retina clinic from the general outpatient and had their appointments in between 1 and 15 days. Similarly, a FA evaluation was performed in between 15 and 20 days, and the first injection was performed in between 15 and 30 days following FA. For those who required monthly follow-up visits, an appointment was scheduled for 40 days later instead of 30 days. As a result, the patient management process was slower than expected and all of the follow-up visits and injections were delayed. After detecting these issues, we planned to make some significant improvements in our clinical practice. Starting from the beginning of 2013, patients referred from the outpatient clinic were consulted and had their FA on the same day in the retina clinic. They received their first intravitreal injection in a maximum of 7–21 days and the next appointment was scheduled for 28 ± 7 later. By achieving these goals, we expected to increase our visit and injection numbers during the first year of treatment in DME patients.

Outcome measures

Primary outcome measure of this study was the change in BCVA and CRT. Secondary outcome measures were the change in CRT and the number of visits and injections.

Statistical analysis

Visual acuity was converted to the logarithm of the minimum angle of resolution (LogMAR) for statistical analysis.

Table 1. General characteristics of the groups.

	2013 Group	2014 Group	2015 Group	P
Mean age, years (range)	55.6 ± 9.7 (26–74)	58.9 ± 8.9 (42–79)	57.9 ± 8.6 (36–74)	0.1
Gender (F/M)	12/24	18/29	14/23	0.8
Baseline BCVA, Snellen	0.39 ± 0.24	0.30 ± 0.20	0.34 ± 0.14	0.1
Baseline CRT, Microns	480 ± 93	470 ± 124	471 ± 94	0.8

P, p value; F, female; M, male; BCVA, best corrected visual acuity; CRT, central retinal thickness.

Table 2. The mean best corrected visual acuity outcomes of the three groups at different time points.

	Baseline	Month 3	Month 6	Month 9	Month 12
2013 Group, in Decimals (LogMAR)	0.39 ± 0.24 (0.52 ± 0.37)	0.43 ± 0.27 (0.52 ± 0.49)	0.45 ± 0.28 (0.50 ± 0.48)	0.49 ± 0.25 (0.40 ± 0.38)	0.42 ± 0.27 (0.50 ± 0.43)
2014 Group, in Decimals (LogMAR)	0.30 ± 0.20 (0.65 ± 0.42)	0.39 ± 0.28 (0.56 ± 0.42)	0.40 ± 0.24 (0.49 ± 0.34)	0.37 ± 0.28 (0.59 ± 0.41)	0.38 ± 0.23 (0.52 ± 0.33)
2015 Group, in Decimals (LogMAR)	0.34 ± 0.14 (0.53 ± 0.29)	0.42 ± 0.24 (0.44 ± 0.27)	0.50 ± 0.26 (0.37 ± 0.30)	0.52 ± 0.27 (0.35 ± 0.29)	0.48 ± 0.24 (0.38 ± 0.28)

LogMAR, the logarithm of the minimum angle of resolution.

Table 3. The mean central retinal thickness values of the three groups at different time points.

	Baseline	Month 3	Month 6	Month 9	Month 12
2013 Group, microns	480 ± 93	412 ± 103	380 ± 104	402 ± 126	393 ± 110
2014 Group, microns	470 ± 124	398 ± 134	376 ± 93	382 ± 135	364 ± 118
2015 Group, microns	471 ± 94	366 ± 82	341 ± 83	336 ± 74	348 ± 115

Categorical variables were presented as numbers and percentages, while numerical variables were expressed as the mean and standard deviation. First, the data was analyzed in terms of normality using Kolmogorov-Smirnov test. As the distribution of the data was found to be normal, the visual acuity and the CRT values between baseline and the other time points were assessed with repeated measures test. The means within the groups were compared using independent sample t-test or one-way Anova test. Categorical variables were compared using chi-square test. A p value <0.05 was considered statistically significant.

Results

A total of 173 eyes of 120 patients were included. The mean age was 57.7 ± 8.8 years (range 26–79 years) and 44 patients (36.7%) were female, 76 patients (63.3%) were male. Fifty-three eyes (30.6%) were treated in 2013, 71 eyes (41.0%) were treated in 2014, and 49 eyes (28.3%) were treated in 2015. The general characteristics of the groups were summarized in Table 1.

The mean BCVA at baseline and months 3, 6, 9, and 12 of all groups were summarized in Table 2. The mean change in BCVA from baseline to month 12 was not statistically significant in 2013 at all of the time points ($p = 0.7$ for month 3, $p = 0.9$ for month 6, $p = 0.3$ for month 9, and $p = 0.3$ for month 12, respectively). The mean change in BCVA from baseline to month 12 was statistically better only at month 12 in 2014. ($p = 0.1$ for month 3, $p = 0.1$ for month 6, $p = 0.09$ for month 9, and $p = 0.02$ for month 12, respectively). The mean change in BCVA from baseline to month 12 was statistically better at all of the time points but month 3 in 2015 ($p = 0.2$ for month 3, $p = 0.001$ for month 6, $p < 0.0001$ for month 9, and $p = 0.004$ for month 12, respectively). The mean change in BCVA from baseline to month 12 was 0.6 ± 4.0 (range from −1.6 to 1.3) LogMAR lines in 2013, 1.3 ± 3.2 (range from −0.5 to 1.6) LogMAR lines in 2014, and 1.4 ± 3.2 (range from −0.7 to 0.9) LogMAR lines in 2015, respectively ($p = 0.4$).

The mean CRT at baseline and months 3, 6, 9, and 12 of all groups were summarized in Table 3. The mean CRT change from baseline to month 12 was statistically significant in 2013 at all of the time points ($p = 0.02$ for month 3, $p < 0.0001$ for month 6, $p = 0.004$ for month 9, and $p < 0.0001$ for month 12, respectively). The mean CRT change from baseline to month 12 was statistically significant in 2014 at all of the time points but month 3 ($p = 0.1$ for month 3, $p < 0.0001$ for month 6, $p = 0.002$ for month 9, and $p < 0.0001$ for month 12, respectively). The mean CRT change from baseline to month 12 was statistically significant in 2015 at all of the time points ($p < 0.0001$ for month 3, $p < 0.0001$ for month 6, $p < 0.0001$ for month 9, and $p < 0.0001$for month 12, respectively). The mean change from baseline to month 12 was not statistically different among the three groups ($p = 0.5$).

We used a cut-off value of 350 micrometers for CRT at month 12 for calculating the percentage of the patients who had inactivation of DME anatomically. At month 12, 32.1% of the patients in 2013 group, 54.9% in 2014, and 63.3% in 2015 group showed <350 micrometers of CRT which was statistically different among the three groups ($p = 0.02$) ($p = 0.03$ for 2013 versus 2014, $p = 0.01$ for 2013 versus 2015, and $p = 0.5$ for 2014 versus 2015, respectively). The percentage of the patients with a CRT < 350 micrometers was statistically lower in both 2014 and 2015 than 2013.

Mean number of visits and injections at month 12 in the three groups were summarized in Table 4. There was a statistically significant difference among the three groups in regards to both visit and injection numbers ($p < 0.0001$,

Table 4. The mean visit and injection numbers of the three groups.

	Visit number	Injection number
2013 Group (range)	4.3 ± 0.9 (2–7)	3.1 ± 1.5 (1–7)
2014 Group (range)	4.3 ± 0.9 (3–7)	4.0 ± 1.5 (1–8)
2015 Group (range)	5.1 ± 1.5 (3–8)	4.6 ± 1.2 (3–8)

and $p > 0.0001$). The mean visit number in 2013 and 2014 were both lower than both 2015 ($p = 0.9$ for 2013 versus 2014, $p = 0.001$ for 2013 versus 2015, and $p < 0.0001$ for 2014 versus 2015, respectively). The mean injection number in 2013 was both lower than 2014 and 2015 ($p = 0.003$ for 2013 versus 2014, $p < 0.0001$ for 2013 versus 2015, and $p = 0.1$ for 2014 versus 2015, respectively).

No injection-related endophthalmitis was noted after total of 685 injections.

Discussion

In this study, we evaluated the treatment outcomes and real life data of DME patients treated with ranibizumab during three consecutive years; 2013, 2014, and 2015. The randomized, controlled, multicenter studies on the outcomes of anti-VEGF treatments revealed very promising results in DME patients and this was astonishing for both the physicians and the patients considering that with laser photocoagulation which had been used for long periods before, we could only prevent the decrease in the visual acuity in patients with DME.[4–9] However, in real life setting, it was very difficult to obey the strict follow-up and treatment criteria of these studies especially with PRN treatment regimen.[10,12,14] The mean injection number of ranibizumab was reported to be between 2.1 and 7.2 in the previous reports during a mean follow-up period of 9–12 months.[10–16] Patrao et al., evaluated the visual and anatomical outcomes of ranibizumab treatment in diabetic macular edema patients in the United Kingdom National Health Service clinical setting.[11]The study consisted of 200 eyes of 164 patients. The mean visual acuity increased by 6.6 letters after a mean of 7.2 injections at month 12 and mean improvement in CRT was 133 microns. In the study, three loading injections of ranibizumab were given monthly, then a PRN treatment regimen was followed. The subgroup of the treatment naïve eyes in the study gained a mean of 4.8 letters. Also, 42.6% of the eyes had a CRT > 350 microns at month 12.[11]

In another study by Ghanchi and Hazel, 51 eyes of 41 South Asian DME patients treated with ranibizumab were evaluated throughout 12 months.[12] The mean BCVA increased by 8.5 letters from baseline to month 12 with a mean of 7 injections. In addition, the mean visit number was 10 during the 12 months period.[12] Another real life study conducted in Sweden included 59 DME patients and 12 months' outcomes of ranibizumab treatment were assessed.[13] The mean number of visits and injections were reported to be 14 and 5, respectively. The BCVA was improved by 5.2 letters from baseline to month 12 and the mean CRT decreased from 403 microns to 282 microns.[13] The PRIDE study from Italy evaluated the real life outcomes of ranibizumab treatment in DME patients.[14] A total of 515 patients were included and the mean number of injections during 18 months were 4.1 in unilaterally affected patients and 4.4 in bilaterally affected patients. In terms of decimal score, unilaterally affected patients gained 1.5 and bilaterally affected patients gained 1.2 lines of VA in the study. Perhaps one of the most interesting studies came from Denmark. Similar to our study, they evaluated the real life outcomes of anti-VEGF therapy in DME, retinal vein occlusion and neovascular age-related macular degeneration patients between 2012 and 2014.[15] The similarity was that the patients enrolled for the study were allocated to a half-year grouping, based on the month when the first intravitreal injection was performed. Then five groups were formed for each indication which were 2012/1, 2012/2, 2013/1, 2013/4, and 2014/1 groups, respectively. All patients in the groups were evaluated in regard to injection numbers. A total of 76 DME patients were enrolled and the mean injection numbers were 5.1, 3.6, 4.6, 5.2, and 5.9 from 2012/1 to 2014/1. Interestingly the mean injection number decreased from 5.1 to 3.6 in the first 6 months, but then gradually increased.[15]

A total of 173 eyes were included in our study and the patients were allocated to a yearly grouping based on the year when they were first admitted to our clinic. The visit and injection numbers increased from 2013 to 2015 and the number of visits increased from 4.3 to 5.1 and injections increased from 3.1 to 4.6. There was not a statistically significant difference in change in BCVA and CRT among the three groups. However, when groups were compared to their baseline, clinical improvements were remarkable especially in 2014 and 2015. In 2013, the change in mean BCVA was not statistically significant at any time points from baseline to month 12. However, in 2015, with an increase of 1.5 in the injection number (from 3.1 to 4.6), the change in BCVA was statistically better at months 6, 9, and 12 as compared to the baseline. Interestingly the change in BCVA was found to be improved only at one time point (month 12) in 2014. Also the percentage of the patients who had a CRT < 350 microns was statistically different among the three groups. It was 32.1% in 2013 (3.1 injections), increased to 54.9% in 2014 (4.0 injections), and to 63.3% in 2015 (4.6 injections). In our clinic, before the optimization process that we undertook, the mean injection and visit number in DME patients treated with ranibizumab was lower than most of the other countries.[10–16] Starting from the beginning of 2013, improvements were made in clinical processes as previously mentioned. After making all of these improvements, we were able to increase the first year ranibizumab injection number in DME patients from 3.1 (in 2013) to 4.6 (in 2015), and consequently visual results were improved when compared to baseline but, the most prominent outcome was the increase in the percentage of patients who had CRT < 350 microns at month 12.

The main limitation of this study is the relatively low number of included patients. Also we did not divide the patients according to the severity and stage of the non-proliferative DR as this was not one of the primary concerns of the study. However, all included patients had treatment naïve non-proliferative DR, thus forming a relatively homogenous group of patients. Our results have revealed some useful data for real life outcomes of ranibizumab treatment in DME cases throughout three consecutive years. Our study included both visual and anatomical outcomes, and also visit and injection numbers. In addition, a slight improvement in visual and anatomical outcomes was detected in parallel to the increase in the injection number that was an interesting result of our study.

Conclusions

In conclusion, it is well known that it is still very effortful to obey the strict follow-up and treatment criteria that were used in prospective studies while treating DME patients with anti-VEGFs especially in a PRN regimen in a real life setting. However, optimizing the clinical processes of patient management may lead to the improved clinical outcomes in real life.

Conflict of interest

The authors declared that there is no conflict of interest.

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