The effect of Visit Number on the Treatment of Diabetic Macular Edema with Ranibizumab in Real World

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Abstract

Purpose: To evaluate the effect of visit number on the treatment outcomes of ranibizumab in patients with diabetic macular edema (DME) on a pro re nata (PRN) regimen.

Methods: Retrospective, comparative study. Treatment naïve DME patients with non-proliferative DR and with a minimum follow time of 12 months were included. The patients were planned to be treated with ranibizumab on a PRN regimen after 3 monthly loading injections. To evaluate the effect of proper follow-up we divided the patients into 2 groups according to the visit number during the first year. Group 1 consisted of the patients who had a visit number < 6, and group 2 consisted of the patients who had a visit number of ≥ 6. Primary outcome measure of this study was the change in best corrected visual acuity (BCVA). Secondary outcome measures were the change in central retinal thickness (CRT) and the number of visits and injections.

Results: The mean visit number of group 1 and 2 during the 12 months follow-up period was 4.2 ± 0.7 (range 2 - 5) and 6.4 ± 0.5 (range 6-8), respectively (p < 0.0001). The mean injection number of group 1 and 2 during the 12 months follow-up period was 3.5 ± 1.1 (range 1 - 6) and 5.2 ± 1.5 (range 1 - 8), respectively (p < 0.0001). The change in BCVA was statistically better in group 2 than group 1 at month 6 and 12 (p = 0.09 at month 3, p = 0.01 at month 6, p = 0.3 at month 9, and p = 0.009 at month 12). The percentage of the eyes which gained ≥3 lines of vision was 19.2% in group 1 and 38.6% in group 2, respectively (p = 0.01). The change in CRT was statistically better in group 2 than group 1 at month 6 and 12 (p = 0.5 at month 3, p = 0.03 at month 6, p = 0.3 at month 9, and p = 0.005 at month 12).

Conclusion: Performing more frequent visits and injections may lead us to obtain better anatomical and visual outcomes in patients with DME who were treated with an anti-VEGF agent on a PRN regimen.

Keywords: Diabetes; Diabetic Retinopathy; Intravitreal Injection; Macular Edema; Ranibizumab

Introduction

Diabetic macular edema (DME) is the most frequent reason of visual deterioration among the diabetic retinopathy (DR) patients [1,2]. Several treatment options have been used in the treatment of DME [2-4] and most of them could only prevent the patients from loss of vision. Currently intravitreal anti-vascular endothelial growth factors (Anti-VEGF) and steroids are the most preferred agents in the treatment [2-5]. Ranibizumab and aflibercept are two approved drugs which both were found to be effective with various treatment regimens [i.e. monthly, pro re nata (PRN), treat and extend] [4-6]. In prospective, randomized, multicenter studies, it was shown that, a mean of 12 - 13 visits and 8 - 9 ranibizumab injections were required in the first year of treatment on a PRN treatment regimen [4-6]. However, it is not always possible to follow the strict follow-up and retreatment criteria proposed in prospective studies in real life. Pro re nata regimen has been commonly used in Turkey in the treatment of DME and other retinal diseases [7]. Studies from our country have revealed that the visit and injection numbers was far from ideal in real life practice [7-10]. 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 other countries [9,12]. Also, we have shown this weakness of PRN treatment regimen with ranibizumab in various diseases [7,13,14]. In addition, we tried to take some measures for improving our visit and injection numbers to overcome this negative side of PRN treatment regimen in our clinical practice [7]. It was shown that the increase in visit and injection numbers might improve the treatment outcomes [7]. Therefore, we conducted this study to evaluate the effect of visit number on the treatment outcomes of ranibizumab in patients with DME on a PRN regimen.

Materials and Methods

Patients

Medical records of the patients who had DME and underwent intravitreal ranibizumab (IVR) treatment between January 2013 and December 2015 were analyzed in this retrospective study. Treatment naïve DME patients with non-proliferative DR and with a minimum follow time of 12 months 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.

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.

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 were planned to receive 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.

Study Groups

Although the patients were planned to receive a loading dose of 3 monthly ranibizumab injections of ranibizumab and planned to be called for monthly follow-up visits. This was not possible as expected. To evaluate the effect of proper follow-up we divided the patients into 2 groups according to the visit number during the first year. Group 1 consisted of the patients who had a visit number < 6, and group 2 consisted of the patients who had a visit number of ≥ 6.

Outcome measures

Primary outcome measure of this study was the change in BCVA. 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. 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. Categorical variables were compared using chi-square test. A p value < 0.05 was considered statistically significant.

Results

A total of 143 eyes of 101 patients were included. The mean age was 57.5 ± 8.9 years (range 26 - 79 years) and 40 patients (39.6%) were female, 61 patients (60.4%) were male. The mean visit and injection number of the whole group was 4.9 ± 1.2 (range 2 - 8) and 4.0 ± 1.4 (range 1 - 8), respectively. There were 104 eyes (72.7%) in group 1, and 39 eyes (27.3%) in group 2. The baseline characteristics of the two groups was summarized in table 1.
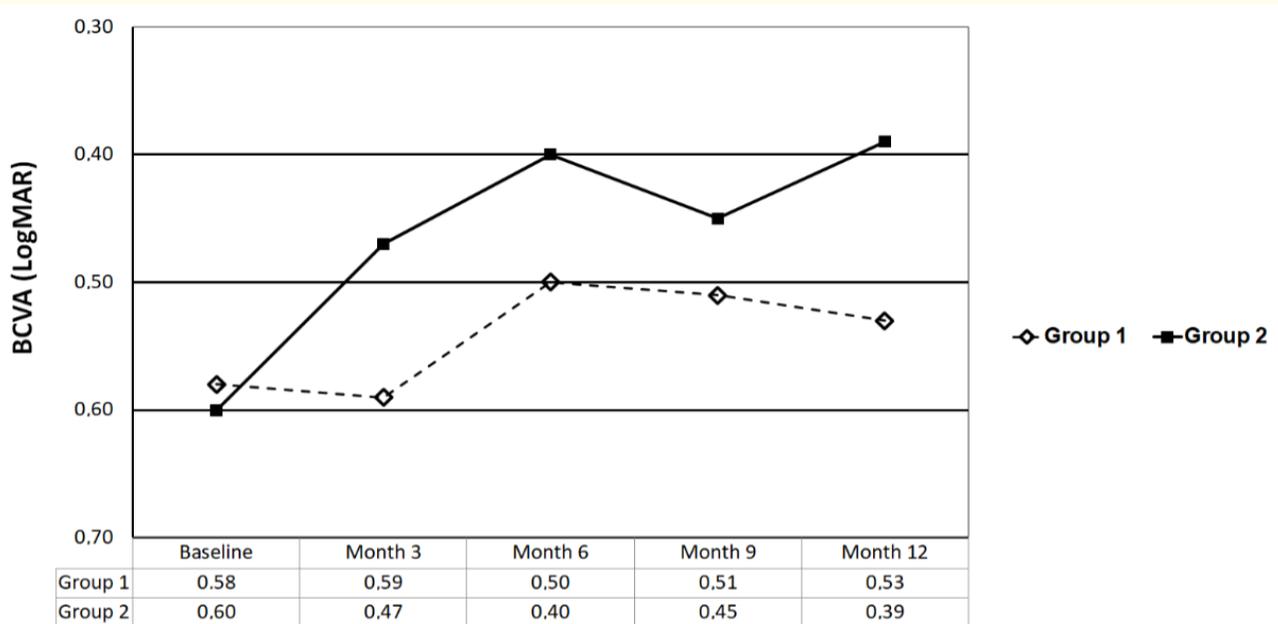
	Group 1	Group 2	P
Mean age, years (range)	57.9 ± 9.2 (26 - 79)	56.9 ± 8.7 (36 - 79)	0.9
Gender (F/M)	29/47	11/14	0.7
Baseline BCVA, Snellen	0.58 ± 0.29	0.60 ± 0.31	0.7
Baseline CRT, Microns	465 ± 99	501 ± 117	0.08

Table 1: *General characteristics of the groups.*

P: p Value; F: Female; M: Male; BCVA: Best Corrected Visual Acuity; CRT: Central Retinal Thickness.

The mean visit number of group 1 and 2 during the 12 months follow-up period was 4.2 ± 0.7 (range 2 - 5) and 6.4 ± 0.5 (range 6 - 8), respectively ($p < 0.0001$). The mean injection number of group 1 and 2 during the 12 months follow-up period was 3.5 ± 1.1 (range 1 - 6) and 5.2 ± 1.5 (range 1 - 8), respectively ($p < 0.0001$).

The mean baseline BCVA was 0.58 ± 0.29 LogMAR (range 0.30 - 1.30) and 0.60 ± 0.31 LogMAR (range 0.30 - 1.30) in group 1 and 2, respectively ($p = 0.7$). The BCVA outcomes of the two study groups were summarized in figure 1. The change in BCVA was statistically better in group 2 than group 1 at month 6 and 12 ($p = 0.09$ at month 3, $p = 0.01$ at month 6, $p = 0.3$ at month 9, and $p = 0.009$ at month 12). The percentage of the eyes which gained ≥ 3 lines of vision was 19.2% in group 1 and 38.6% in group 2, respectively ($p = 0.01$).

	Baseline	Month 3	Month 6	Month 9	Month 12
Group 1	0,58	0,59	0,50	0,51	0,53
Group 2	0,60	0,47	0,40	0,45	0,39

Figure 1: *The visual acuity levels of the two study groups at different time points.*

The mean baseline CRT was 465 ± 99 micrometers (range 304 - 704) and 501 ± 117 micrometers (range 312 - 759) in group 1 and 2, respectively ($p = 0.08$). The CRT outcomes of the two study groups were summarized in figure 2. The change in CRT was statistically better in group 2 than group 1 at month 6 and 12 ($p = 0.5$ at month 3, $p = 0.03$ at month 6, $p = 0.3$ at month 9, and $p = 0.005$ at month 12).
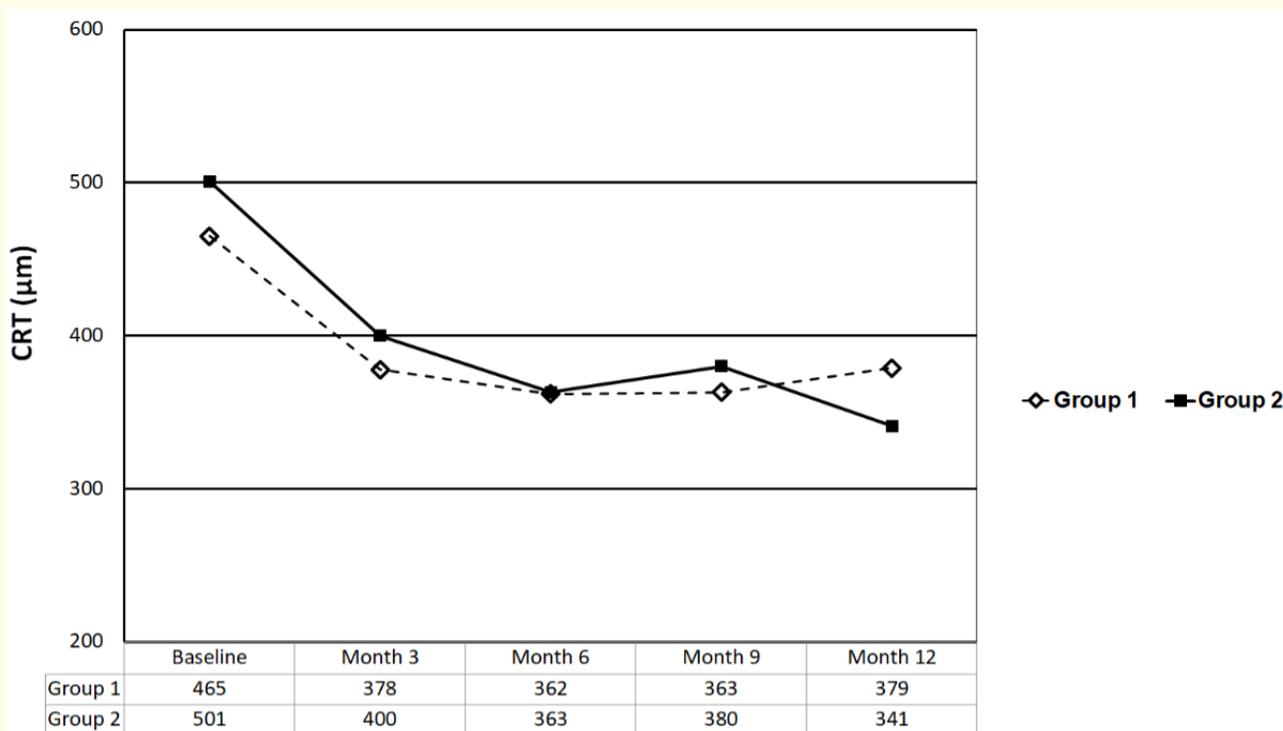
Figure 2: The central retinal thickness levels of the two study groups at different time points.

None of the patients in any of the groups showed injection-related endophthalmitis after any of the injections.

Discussion and Conclusion

We evaluated the effect of visit frequency on the functional and anatomical outcomes of ranibizumab on a PRN treatment regimen in patients with DME. The mean visit numbers were very low in both of the groups when compared with the randomized controlled trials. In an ideal PRN treatment regimen with an anti-VEGF agent the visit number has to be 12 - 13 during the first year of the treatment [4]. However, as shown in previous studies it is very hard to obtain these visit numbers in real life [7]. The mean visit number was 4.2 in group 1 and 6.4 in group 2. Parallel to these visit frequencies the mean injection number was 3.5 and 5.2 in group 1 and 2. The injection number of both of the groups were again lower than the randomized controlled trials [4-6]. In an ideal PRN treatment regimen with an anti-VEGF agent the mean injection number has to be 8 - 9 in the first year of treatment according to randomized controlled trials [4]. With this ideal treatment nearly one third of the patients showed ≥ 3 lines of increase in visual acuity, and the mean increase was 10 letters (2 lines) at the first year [4-6]. Whereas, only 19.2% of the eyes in group 1 of this study showed ≥ 3 lines of increase in visual acuity and the mean increase was only 0.5 lines in this group. Group 2 showed better outcomes than group 1 both in regards to visual and anatomical outcomes. More than one third of the eyes showed ≥ 3 lines of increase in visual acuity and the mean increase was only around 2 lines in this group.

There are several reasons which cause inadequate patient follow-up in real life. Some of them were elucidated in one of our previous real-life studies [7]. One of the main reasons was irregular scheduled monthly visits because of heavy patient load. Also delays in referrals to retina clinics and imaging scheduling may be the other reasons. In our clinic we faced all of these difficulties and took important measures for improving these real-life issues. We documented all these improvements in a study and showed the differences in our treatment outcomes during 2013, 2014, 2015 [7]. The mean visit number increased from 4.3 to 5.1 and the mean injection number increased from 3.1 to 4.6 from 2013 to 2015 which resulted in better visual and anatomical outcomes. Similar to our previous findings the current study also showed the importance of more proper visit and more frequent injection scheduling in the treatment of DME with anti-VEGF agents.

The main limitation of this study was its retrospective design and limited number of patients for a real-life study. However, all included eyes were treatment naïve non-proliferative DR eyes which led us to have a homogenous study population. Also, our results have revealed very useful data in regard to the importance of visit frequency in the treatment of DME with anti-VEGF agents in real life.

In conclusion, it is a known fact that it is very difficult to obey the monthly visit scheduling in the treatment of DME with anti-VEGF agents on a PRN regimen in real life. However, performing more frequent visits and injections may lead us to obtain better anatomical and visual outcomes.

Acknowledgements

Conflict of Interest

None.

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Volume 9 Issue 11 November 2018