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Original Article

Diabetic Macular Edema Patients with Poor Baseline Visual Acuity Treated with Ranibizumab in Real Life and Optical Coherence Tomography Based Predictor Factors for Visual Outcomes

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Abstract :

Purpose: We aimed to evaluate the real life outcomes of ranibizumab in the treatment of diabetic macular edema (DME) patients with a baseline visual acuity<0.05 in decimals.

Methods: Newly diagnosed DME patients with a visual acuity ≤0.05, treated with ranibizumab monotherapy, and completed a follow-up time of 12 months were included retrospectively. Patients were evaluated in regards to change in best corrected visual acuity (BCVA) and central retinal thickness, and the total visit and injection numbers.

Results: A total of 24 eyes of 24 patients were included. Mean BCVA at baseline, month 3, 6, 9, and 12 was, 0.04±0.01, 0.12±0.12, 0.12±0.11, 0.17±0.19, and 0.21±0.21 (p<0.05 for all), respectively. One eye (4.2%) had VA loss of ≥3 lines, and six eyes (25.0%) had stable vision (loss of <3 line, or remained stable, or gained <1 lines), and 17 eyes (70.8%) had VA gain of ≥3 lines at month 12.The mean visit number at month 12 was 4.8±1 and the mean injection number was 4.0 ±1.4.

Conclusion: Ranibizumab seemed to be effective in the treatment of DME patients with a low visual acuity in real life.

Introduction

Diabetic retinopathy (DR) is the most frequent retinal vascular disease and diabetic macular edema (DME) is an important cause of visual loss among the DR patients (1-5). Laser photocoagulation, vitrectomy, and intravitreal injections of different drugs were used in the treatment of DME (2-5). Intravitreal injection of anti-vascular endothelial growth (Anti-VEGF) agents is the most preferred treatment modality currently (4-9). Ranibizumab was proven to be effective in the treatment of DME with various treatment regimens which were monthly, pro re nata (PRN), treat and extend etc (4-9). In prospective multicenter studies it was reported that, a mean of 8-9 ranibizumab injections were required in the first 12 months of treatment; however, the mean injection number dramatically decreased after the first year and nearly no injections were needed at year 4 and 5 (4-7). It was not possible to follow the strict follow-up and retreatment criteria of these studies in real life especially when PRN regimen was preferred (8,9). Also, only the patients with a VA between 20/320 and 20/32-20/40 were included in these efficacy studies, and the patients with better or worse levels were not evaluated usually (4-8). In addition, it is a known fact that some optical tomography (OCT) markers such as the presence of an intact inner segment/outer segment (IS/OS) junction, disorganization of the retinal inner layers (DRILL), and the presence of subretinal fluid was found to be associated with the visual outcomes of DME treatment (10-17). Therefore in this study, we aimed to evaluate the efficacy of intravitreal ranibizumab (IVR) on a PRN treatment regimen in DME patients with a VA ≤ 0.05 in decimals and OCT based predictor factors for the treatment outcome.

Materials and Methods

In this retrospective study, medical records of the patients who had DME and underwent IVR treatment on a PRN treatment regimen between January 2013 and December 2015 were analyzed. Newly diagnosed treatment naïve DME patients with non-proliferative DR and a best corrected visual acuity $\leq$ 0.05 in decimals, and who completed a follow time of 12 months in our clinic were included. The patients with a history of any other treatment for DME at the first admission, or who were lost to follow-up, or received any other treatment for DME during the first 12 months of our follow-up were not included. A patient database of 1182 DME patients was reviewed for this study. A hundred and sixty-eight patients were treated with ranibizumab monotherapy and completed the minimum follow-up period of 12 months. Twenty-four eyes of 24 patients out of these 168 patients met the inclusion criteria and were included for this study. 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) at the baseline, and at month 3, 6, 9, and 12. Visit and injection numbers during the first 12 months were also recorded.

All patients underwent a standardized examination including measurement of BCVA via a projection chart in decimals at 4 meters, slit-lamp bio-microscopy, measurement of IOP via applanation tonometry, and bio-microscopic fundus examination. Fundus photography, fluorescein angiography (FA) (HRA-2; Heidelberg Engineering, Heidelberg, Germany), and 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 neuro sensory 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 was not assessed. The presence of macular ischemia was evaluated in the included eyes. Macular ischemia was diagnosed when the longest diameter of foveal avascular zone (FAZ) was >1000 µ measured via the built in caliper software of the device. On the contrary, FAZ was accepted normal FAZ if the longest diameter was <1000 µ with a regular and round/horizontally oval shape (18). The patients were divided into two groups in regard to the increase in BCVA at month 12. The first group consisted of the patients who had a gain in BCVA $\geq$3 LogMAR line, and the second group consisted of the patients who had a gain < 3 LogMAR line or lost vision. These two groups were compared in regards to OCT parameters which were the integrity of the IS/OS junction (10), the presence of cystic macular edema (11), DRILL (12), and subfoveal sensorial retinal detachment (10, 11, 13). Integrity of the IS/OS junction was classified into two subgroups semi quantitatively by eye examination; if the IS/OS junction was intact and clearly visible under the OCT section which trans-passed through the foveal depression then the IS/OS junction was called intact, if there was a definite continuity defect in the junction then it was called disrupted. The classification of DME subtype according to the intra retinal cyst patterns were divided into two groups; if the diameter of the largest intra retinal cyst was <300 micron then the DME was classified as spongiform edema, if the diameter of the largest intra retinal cyst was >300 microns then the DME was classified as cystic edema (11). Presence of DRILL, and subfoveal sensorial retinal detachment were all classified into two groups as present of absent (10-13). The patients were divided into two groups according to the increase in BCVA and the percentage of presence of the OCT parameters were compared between these two groups. The patients who gained $\geq$ 3 lines of vision were classified as group 1, and the patients who showed <3 lines gain in vision or lost

vision were classified as group 2.

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 prescribed 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 an increase of >100 microns in CRT in OCT images compared to the last visit.

Primary outcome measures of this study included the change in BCVA and CRT. Secondary outcome measure was the predictive factors in OCT for the visual improvement.

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 Shapiro-Wilk 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 24 eyes of 24 patients were included. The mean age was 59.2±9.3 years (range 36-73 years) and 15 patients (62.5%) were female; nine patients (37.5 %) were male. General characteristics of the patients were summarized in table 1.

The mean BCVA at baseline was 0.04±0.01 in decimals (range 0.01-0.05). The BCVA at month 3, 6, 9, 12 was 0.12±0.12 (range 0.01-0.5) (p=0.009), 0.12±0.11 (range 0.02-0.5) (p=0.002), 0.17±0.19 (range 0.02-0.8) (p<0.0001), and 0.21±0.21 (range 0.02-1.0) (p<0.0001), respectively. One eye (4.2%) had VA loss of $\geq$ 3 lines, and six eyes (25.0%) had stable vision (loss of <3 line, or remained stable, or gained <1 lines), and 17 eyes (70.8%) had VA gain of $\geq$ 3 lines at month 12. In regard to visual outcomes at month 12, 17 patients (70.8%) were included in group 1 and 7 patients (29.2%) were included in group 2. The IS/OS junction was intact in 13 of 17 eyes (76.5%) in group 1, and 3 of 7 eyes (42.9%) in group 2 (p=0.1). Cystic macular edema was detected in 15 of 17 eyes (88.2%) in group 1 and 6 of 7 eyes (85.7%) in group 2 (p=0.9). DRILL was detected in 11 of 17 eyes (64.7%) in group 1 and 4 of 7 eyes (57.1%) in group 2 (p=0.9). Subfoveal sensorial retinal detachment was present in 9 of 17 eyes (52.9%) in group 1 and in 1 of 7 eyes (14.4%) in group 2 (p=0.1). Macular ischemia was present in 4 of 17 eyes (23.5%) in group 1 and in 5 of 7 eyes (71.4%) in group 2 (p=0.02).

Mean CRT at baseline was 465±150 microns (range 320-759). The CRT at month 3, 6, 9, 12 was 364±119 (range 216-677) (p=0.1), 394±131 (range 233-754) (p<0.053), 383±121 (range 225-652) (p=0.1), and 330±102 (range 201-586) (p=0.004), respectively. At month 12, 14 of the 15 eyes (62.5%) had a CRT <350 microns.

The mean planned visit number at month 12 was 5.1±0.8 (range 4-7), and the number of completed visits were 4.8±1.0 (range 3-7) (94.3 % completion). The mean number of planned injections at month 12 was 4.2±1.7 (range 1-8), and the number of performed injections were 4.0 ±1.4 (range 1-7) (92.3% completion).

No injection related endophthalmitis was noted after a total of 96 injections.

Table 1 : General characteristics of the patients

Number of eyes	24
Age (years)	59.2±9.3
Gender (male/female)	9/15
Lens status (phakic/pseudophakic)	18/6
Baseline BCVA (in decimals)	0.04±0.01
Baseline CRT (microns)	465±150

BCVA : best corrected visual acuity; CRT: central retinal thickness.

Table 2 : The mean best corrected visual acuity and central retinal thickness levels at different time points.

	Baseline	Month 3	Month 6	Month 9	Month 12
BCVA, in decimals (LogMAR)	0.04±0.01 (1.41±0.24)	0.12±0.12 (1.05±0.37)	0.12±0.11 (1.03±0.36)	0.17±0.19 (0.95±0.42)	0.21±0.21 (0.84±0.41)
CRT, microns	465±150	364±119	394±131	383±121	330±102
Number of injections	-	-	-	-	4.0±1.4

BCVA, best corrected visual acuity; CRT, central retinal thickness

Table 3 : General data of the whole study population.

Patient no.	Gender	Age, years	Baseline VA	Month 3 VA	Month 6 VA	Month 9 VA	Month 12 VA	Baseline CRT, µ	Month 3 CRT, µ	Month 6 CRT, µ	Month 9 CRT, µ	Month 12 CRT, µ	Visit no.	Inj. no.	Severity of NPDR	Macula Ischemia	IS/OS	CME	DRILL	SRD
1	Female	66	0.02	0.02	0.02	0.05	586	439	469	754	603	586	5	6	Severe	+	Disrupted	+	+	-
2	Female	59	0.03	0.25	0.10	0.10	317	732	255	362	422	317	4	3	Severe	-	Normal	+	+	+
3	Male	56	0.05	0.05	0.16	0.50	252	320	294	288	276	252	5	3	Moderate	-	Normal	-	-	+
4	Male	55	0.01	0.16	0.20	0.10	344	346	333	449	444	344	5	2	Severe	+	Disrupted	+	+	-
5	Female	65	0.01	0.01	0.05	0.05	423	655	398	547	396	423	7	5	Severe	-	Normal	+	-	+
6	Female	63	0.01	0.40	0.20	0.40	231	499	322	294	283	231	3	5	Severe	-	Normal	+	+	+
7	Male	55	0.05	0.05	0.50	0.80	268	704	335	604	269	268	4	1	Moderate	-	Normal	-	-	-
8	Female	59	0.05	0.50	0.05	0.10	486	612	216	388	652	486	6	4	Severe	+	Disrupted	+	+	-
9	Female	73	0.05	0.05	0.05	0.05	320	324	343	366	384	320	4	3	Severe	+	Disrupted	+	+	-
10	Female	63	0.05	0.05	0.05	0.10	236	380	221	276	355	236	5	2	Severe	+	Normal	+	+	-
11	Male	68	0.05	0.05	0.10	0.05	310	370	372	350	313	310	5	3	Severe	-	Normal	+	-	-
12	Female	67	0.05	0.10	0.05	0.16	295	382	312	344	323	295	4	4	Moderate	-	Disrupted	+	-	-
13	Female	51	0.05	0.10	0.05	0.05	491	370	362	414	635	491	4	4	Moderate	+	Disrupted	+	-	-
14	Male	59	0.05	0.10	0.05	0.10	471	323	677	504	575	471	6	7	Severe	-	Normal	-	+	-
15	Female	73	0.05	0.05	0.05	0.05	407	330	396	284	316	407	4	3	Severe	+	Normal	+	+	-
16	Male	59	0.05	0.10	0.05	0.05	327	326	299	279	367	327	5	4	Severe	+	Disrupted	+	+	-
17	Female	56	0.05	0.05	0.05	0.02	201	368	227	270	225	201	5	2	Moderate	+	Disrupted	+	-	-
18	Female	55	0.05	0.05	0.20	0.40	233	412	275	233	441	233	6	5	Severe	-	Normal	+	-	-
19	Male	66	0.05	0.20	0.20	0.32	290	687	574	468	333	290	6	6	Moderate	-	Normal	+	+	+
20	Female	36	0.05	0.20	0.16	0.10	228	759	388	417	273	228	6	5	Severe	-	Normal	+	+	+
21	Female	62	0.05	0.25	0.32	0.20	284	392	607	611	304	284	4	6	Moderate	-	Normal	+	+	+
22	Male	68	0.05	0.05	0.05	0.16	298	343	402	356	350	298	3	4	Severe	-	Normal	+	+	+
23	Female	36	0.05	0.10	0.16	0.32	223	614	265	272	271	223	6	4	Moderate	-	Normal	+	+	+
24	Male	53	0.05	0.10	0.05	0.05	409	476	399	326	404	409	4	4	Moderate	-	Normal	+	-	+

Abbreviations: VA, visual acuity (in decimals); CRT, central retinal thickness; µ, micrometer; no, number; inj, injection; NPDR, non-proliferative diabetic retinopathy; IS/OS, inner segment-outer segment junction; CME, cystic macular edema; DRILL, disorganization of the retinal inner layers; SRD, sensorial retinal detachment

Figure 1 : Dot-blot diagram of visual acuity levels at different time points versus baseline, a) baseline visual acuity versus month 3, b) baseline visual acuity versus month 6, c) baseline visual acuity versus month 12. (VA, visual acuity; visual acuity levels were expressed in decimals)

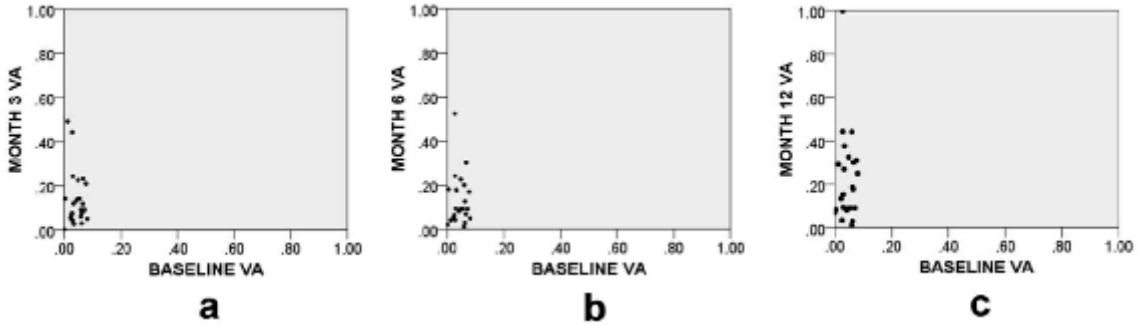
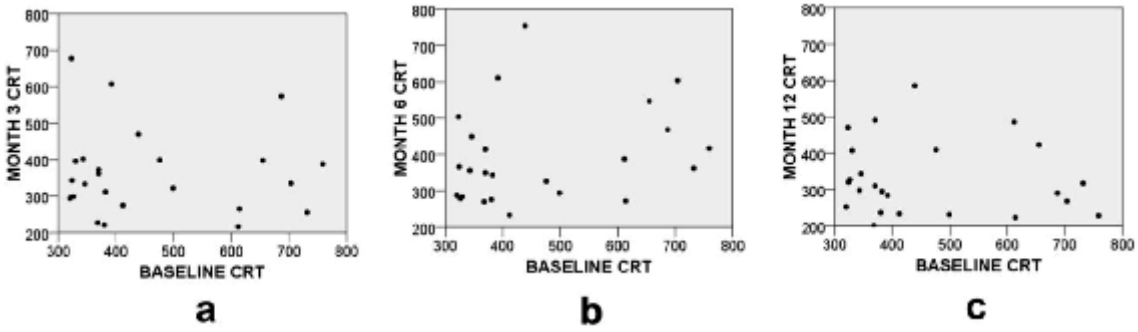


Figure 2: Dot-blot diagram of central retinal thickness levels at different time points versus baseline, a) baseline central retinal thickness versus month 3, b) baseline central retinal thickness versus month 6, c) baseline central retinal thickness versus month 12. (CRT, central retinal thickness; central retinal thickness levels were expressed in micrometers)



Discussion

There were a few studies in the literature regarding the outcomes of anti-VEGF treatment in neo vascular AMD patients with a poor visual acuity (14). However, a literature search from PubMED did not reveal such a focused study in DME patients.

In this study we evaluated the treatment outcomes, visit and injection numbers, and OCT parameters of ranibizumab treated DME patients with a poor baseline visual acuity. As our study was a real life practice the visit and injection numbers were very low in contrast to previous prospective studies. In spite of this low injection number the visual achievements were fairly good as 17 of 24 eyes (70.8%) gained >3 LogMAR lines of vision. The mean increase in BCVA was 1.7 Decimal lines in Decimals and 6.4 LogMAR which was also a satisfactory result. The decrease in mean CRT was statistically significant at least at the last visit at month 12. Several OCT markers were evaluated in the literature in regard to predict the visual outcomes of the DME patients (10-13,15-17). Seo et al, evaluated the visual and morphological outcomes of IVR treatment in patients with DME in regard to OCT based DME patterns (13). They classified the included 55 eyes into three subgroups as patients with diffuse retinal thickening, cystoid macular edema, and serous retinal detachment. They reported that the mean required injection numbers during the 12 months of follow up was different among the two groups. The cystoid macular edema group required 5.33, the serous detachment group required 5.03, and the diffuse thickening group required 3.69 injections. Also they mentioned that disruption of the photoreceptor integrity at baseline was found to be correlated with poorer visual outcome which was detected more frequently in serous detachment group. Sophie et al, investigated the predictors of functional and anatomical outcomes in DME patients treated with ranibizumab for 24 months of treatment (11). They evaluated several parameters in ranibizumab treated and sham treated patients and concluded that the presence of sub macular fluid, intra retinal cysts, severe macular thickening, and renal disease were the factors which were found to be associated with poor visual outcomes in sham treated patients and which responded well to ranibizumab treatment. The associations of DRILL with visual outcomes in DME patients were evaluated in a study by Radwan et al (12). They evaluated the visual outcomes of the macular edema patients who showed DRILL at the beginning of the treatment and graded these patients in regard to the change in DRILL length in central macular region after 8 months after the resolution of DME. The included patients were divided into two groups as the patients who showed resolution of DRILL, and who did not. The authors of the study concluded that the resolution of DRILL after treatment was associated with increased vision. In another study regarding the association between hyper reflective retinal spots and visual function after anti-VEGF treatment in DME patients, it was reported that hyper reflective retinal spots decreased after anti-VEGF treatment and this was found to be correlated with increased retinal sensitivity (17). In our study, the patients were divided into

2 groups in regard to their visual outcomes and several OCT parameters were compared between the two groups. The presence of an intact IS/OS band and subfoveal neuro sensory retinal detachment were both arithmetically more frequent in group 1, none of the OCT parameters did not show statistically significance. An intact IS/OS band was presence in 76.5% of the patients in group 1, and in 42.9% of the patients in group. Interestingly subfoveal sensorial retinal detachment was present in 52.9% of the patients in group 1, and in only 14.4% of the patients in group 2. Although the presence of macular ischemia was not a main outcome measure of the study, we evaluated it between the two groups and it was found statistically more frequent in group 2.

The main limitation of the study was the low patient number. The duration of diabetes and DME were not assessed. One other limitation was that we did not classify the patients according to the severity of non-proliferative DR. However, all patients were treatment naïve and we evaluated the patients with only low baseline visual acuity which were the strengths of the study. Also the study consisted of the real life data regarding about the patient compliance to visits and injections.

Conclusion

In conclusion ranibizumab seems to be effective in the treatment of DME patients with a low visual acuity. Although as needed treatment regimen seems to be insufficient in real life, both visual and anatomical outcomes were acceptable. However, under-treatment of these patients probably limited the visual success in this group of patients. None of the evaluated OCT parameters seemed to affect the visual outcomes of ranibizumab treatment. Only the presence of macular ischemia at the baseline might have a negative effect on visual outcomes. As a result this manuscript revealed some useful data which might be useful in the treatment of DME patients with low visual acuity which are; ranibizumab treatment may be beneficial in most of the patients in this subgroup, none of the evaluated OCT parameters do not seem to be associated with the visual outcomes, but macular ischemia seems to be associated with worse visual outcome.

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