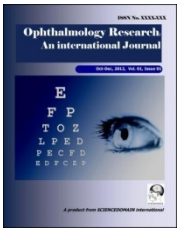

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The Effect of Required Injection Numbers during the First Year on the Clinical Course of Neovascular Age-related Macular Degeneration

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Authors' contributions

This work was carried out in collaboration between all authors. Author AO designed the study, wrote the protocol, and wrote the first draft of the manuscript. Author IY managed the literature searches, analyses of the study performed the spectroscopy analysis and authors ZA, YK managed the experimental process and author ATY identified the species of plant. All authors read and approved the final manuscript.

Original Research Article

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ABSTRACT

Aims: To evaluate the effect of injection number of ranibizumab on an as-needed treatment regimen during the first year of treatment on the clinical course of neovascular age-related macular degeneration (nAMD).
Study Design: Retrospective study.
Place and Duration of Study: Beyoglu Eye Training and Research Hospital. Department of Retina, between December 2009 and December 2011.
Methodology: The newly diagnosed nAMD patients who were treated with intravitreal ranibizumab on an as-needed treatment regimen with a follow-up period of at least 24 months were included in the study. The patients were divided into three groups according to the required injection numbers during the first year; group 1, 3 injections; group 2, 4-5 injections; group 3≥5 injections. Main outcome measures were the change in best corrected visual acuity (BCVA), and central retinal thickness (CRT). Secondary outcome measure was the number of injections during the second year.
Results: The study included 92 eyes of 87 patients. Group 1 consisted of 14 eyes (15.2%), group 2 consisted of 30 eyes (32.6%), and group 3 consisted of 48 eyes (52.2%). The visual outcomes seemed better in group 1; however, there was not a

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statistically significant difference among the three groups in regards of change in BCVA at all of the time points (p=0.4 for month 6, p=0.5 for month 12, p=0.6 for month 18, p=0.6 for month 24). There was not a statistically significant difference among the three groups in regards of change in CRT at all of the time points (p=0.2 for month 6, p=0.2 for month 12, p=0.1 for month 18, p=0.6 for month 24). The mean number of injections at month 12 and 24 was statistically different among the three groups (p<0.0001 for both).

Conclusion: This study did not show a relationship between injection numbers and treatment outcomes in patients with nAMD on an as-needed treatment regimen. However there was a difference among the three groups in regard of visual acuity which was not statistically significant.

Keywords: Age-related macular degeneration; as-needed treatment; ranibizumab; AMD.

1. INTRODUCTION

Neovascular age-related macular degeneration (nAMD) is a leading cause of severe visual loss among elderly population in developed countries [1,2]. Historically, different treatment options like laser photocoagulation, photodynamic therapy, and vitreoretinal surgery were studied for nAMD [3-9]. Currently, intravitreal anti-vascular endothelial growth factor (anti-VEGF) agents have become the gold standard for the treatment of nAMD [10,11]. Several studies showed that ranibizumab was effective to prevent VA loss up to 95% of the patients, and was effective to make an improvement in VA up to 40% of the patients both with monthly and flexible treatment regimens [11-15].

Ranibizumab treatment originally was introduced as a monthly treatment regimen [9,10]. Later, some clinical and optical coherence tomography based flexible treatment regimens were described [11-13]. PRONTO was one of the most important studies which showed similar results with the previous studies and the regimen used in PRONTO study became very popular in a very short time [11]. Then came a question, are flexible treatments really as effective as monthly treatment? This question was addressed in CATT study, and in both ranibizumab and bevacizumab arms of the study, there was not a statistically significant difference between flexible and monthly treatment regimens in regards of change in visual acuity and central retinal thickness [13]. However, the visual results of flexible regimens were not as good as the visual results of monthly regimens without statistically significance. In the flexible treatment regimens the patients are called for monthly visits and they are retreated if disease activity was detected. However, we cannot know the exact beginning time of the activity. For example if the disease becomes active a few days after the previous visit, then the patient may be left untreated for nearly three or four weeks. This phenomenon is may be the negative aspect of flexible treatment regimens. Also theoretically, higher injection number may mean increased disease activity. Therefore, increased disease activity may lead worse visual outcomes because the aforementioned possible negative aspect of flexible treatment. In PRONTO study, this correlation was evaluated indirectly and no relationship was found between injection number and visual outcomes [11]. In this study, we aimed to evaluate the effect of first year injection number on the functional and anatomical outcomes of patients with nAMD who were on an as-needed treatment regimen with ranibizumab.

2. MATERIALS AND METHODS

The clinical data of the patients who were treated with ranibizumab between 2009 and 2011 were retrospectively evaluated for this study. Inclusion criteria were age of 50 years or more, newly diagnosed nAMD, no treatments received other than ranibizumab alone, and a minimum follow-up period of 24 months. Patients were not included if they had any of the following criteria: retinal diseases other than nAMD, previous intravitreal injections, or a history of photodynamic therapy or laser photocoagulation. The tenets of the Declaration of Helsinki were followed throughout the study, and written informed consent for the treatment was obtained from all patients.

2.1 Data

Data collected from the patients' records included age, gender, type of choroidal neovascularization (CNV) (predominantly or minimally classic or occult), BCVA and central retinal thickness (CRT) before treatment, at month 6, 12, 18, and 24. The number of injections at month 12 and 24 were recorded for each patient. The patients were divided into three groups. Group 1 consisted of the patients who required only 3 injections, group 2 consisted of the patients who required 4 and 5 injections, and group 3 consisted of the patients who required >5 injections during the first year.

2.2 Examinations

All patients underwent a standardized examination including measurement of BCVA via the Early Treatment Diabetic Retinopathy Study (ETDRS) chart at 4 meters, slit-lamp biomicroscopy and fundus examination, and measurement of intraocular pressure (IOP) via applanation tonometry. Fundus photography, fluorescein angiography (HRA-2; Heidelberg Engineering, Heidelberg, Germany), and optical coherence tomography (OCT) imaging (Stratus OCT TM; Carl Zeiss Meditec Inc., Dublin, CA, USA) were performed before treatment. All examinations were repeated monthly, except fluorescein angiography, which was repeated only when the cause of visual acuity deterioration could not be clarified with the clinical examination and other imaging methods. OCT was used for detecting subretinal fluid and measurement of CRT, the latter being defined as the mean thickness of the neurosensory retina in the central 1mm diameter region, computed via OCT mapping software provided with the device.

2.3 Injection Method

All injections were performed under sterile conditions after topical anesthesia and 10% povidone-iodine scrub (Betadine; Purdue Pharma, Stamford, CT, USA) was used on the lids and lashes, and then 5% povidone-iodine was administered on the conjunctival sac. Intravitreal bevacizumab (Avastin; Genentech, South San Francisco, CA, USA) or ranibizumab (Lucentis; Novartis, Basel, Switzerland) was injected with a 27-gauge needle through the pars plana at 3.5 mm to 4 mm posterior to the limbus. Patients were then instructed to consult the hospital if they experienced decreased vision, eye pain, or any new symptoms.

2.4 Treatment Schedule

For the first three months of treatment, all patients received monthly doses of ranibizumab (0.5mg/0.05ml). The patients were then examined monthly and were retreated if they met any of the following criteria: a) Visual loss of 1 or more lines, b) Newly developed macular hemorrhage, c) Evidence of CNV enlargement on examination or fluorescein angiography, d). Any amount of persistent subretinal fluid one month after an injection.

2.5. Data Analysis

Visual acuity was converted to logarithm of Minimum Angle of Resolution (LogMAR) for statistical analysis. One-way ANOVA test and following post-hoc test was used to compare categorical variables and $\chi 2$ test/Fisher's exact test for nominal parameters. A p value of less than 0.05 was considered to be statistically significant. The statistical analysis was performed using SPSS version (Version 15.0, SPSS Inc., Chicago, IL, USA).

3. RESULTS

Nine-two eyes of 87 patients met the inclusion criteria for the study. The mean age of the patients was 73.5±7.8 years (range 53-89 years). Forty-two patients (48.3%) were male, 45 patients (51.7%) were female. Predominantly classic CNV was present in 21 eyes (22.8%), and occult/minimally classic CNV was present in 71 eyes (77.2%). The mean number of injections at month 12, and 24 was 5.4±1.5 (range 3-8), and 8.0±2.9 (range 3-15). There were 14 eyes (15.2%) in group 1, 30 eyes in group 2 (32.6%), and 48 eyes (52.2%) in group 3. The general characteristics of the patients were summarized in Table 1.

Table 1. General characteristics of the patients

	Overall
Mean age, years	71.4 ± 8.2
Gender (Male/Female)	36/43
Laterality (Right /Left eye)	38/41
Lens status (Phakic/Pseudophakic)	59/19
CNV type (classic/occult)	23/56
Mean baseline VA	0.85±0.41 LogMAR
VA at month 12	0.72±0.46 LogMAR
Mean VA at month 24	0.73±0.49 LogMAR
Mean injection number at month 12	5.4±1.5
Mean injection number at month 24 Mean	8.0±2.9

CNV: choroidal neovascularization; VA: visual acuity.

The mean BCVA of the patients at different time points in the three groups were listed in Table 2 and showed in Fig. 1. The change in mean BCVA from baseline to month 6, 12, 18, and 24 was statistically better in all of the three groups ($p<0.05$, for all). Although the visual outcomes seemed better in group 1, there was not a statistically significant difference among the three groups in regards of change in BCVA at all of the time points ($p=0.4$ for month 6, $p=0.5$ for month 12, $p=0.6$ for month 18, $p=0.6$ for month 24).

Table 2. Mean LogMAR visual acuity of the groups at different time points

	Group 1	Group 2	Group 3	P value
Baseline, LogMAR	0.70±0.26	0.86±0.40	0.89±0.44	0.2
Month 6, LogMAR	0.55±0.25	0.67±0.41	0.82±0.47	0.08
Month 12, LogMAR	0.48±0.29	0.69±0.44	0.80±0.49	0.07
Month 18, LogMAR	0.46±0.23	0.74±0.52	0.79±0.50	0.09
Month 24, LogMAR	0.47±0.21	0.73±0.52	0.81±0.51	0.08

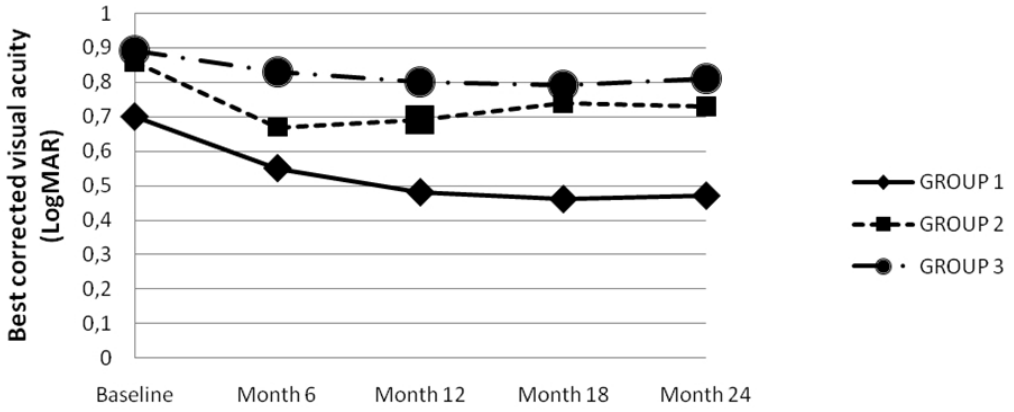

Fig. 1. The changes in mean visual acuity in the three groups. The graph shows the mean LogMAR visual acuity levels from baseline to month 24. The change in mean best corrected visual acuity from the baseline to month 6, 12 18, and 24 was not statistically different among the three groups (p>0.05 for all)

At month 24, 5 of the 14 patients (36%) in group 1, 15 of the 30 patients (50 %) in group 2, and 16 of the 48 patients (33%) in group 3 gained VA≥3 lines. Fourteen of the 14 patients (100%) in group 1, 27 of the 30 patients (90%) in group 2, and 37 of the 48 patients (77%) in group 3 had stable or improved vision (loss of<3 line, or remained stable, or gained≥1 lines). None of the patients in group 1, 3 of the 30 patients (10%) in group 2, and 11 of the 48 patients (23%) in group 3 had VA loss≥3 lines.

The mean CRT at different time points in the three groups were listed in Table 3 and showed in Fig. 2. The change in mean CRT from baseline to month 6, 12, 18, and 24 was statistically better in all of the three groups (p<0.05, for all). There was not a statistically significant difference among the three groups in regards of change in CRT at all of the time points (p=0.2 for month 6, p=0.2 for month 12, p=0.1 for month 18, p=0.6 for month 24).

Table 3. Mean central retinal thickness of the groups at different time points

	Group 1	Group 2	Group 3	P value
Baseline, microns	342±89	354±88	304±97	0.06
Month 6, microns	257±58	274±93	262±70	0.7
Month 12, microns	261±62	256±71	253±58	0.9
Month 18, microns	232±40	261±70	257±64	0.3
Month 24, microns	235±36	267±80	266±73	0.3

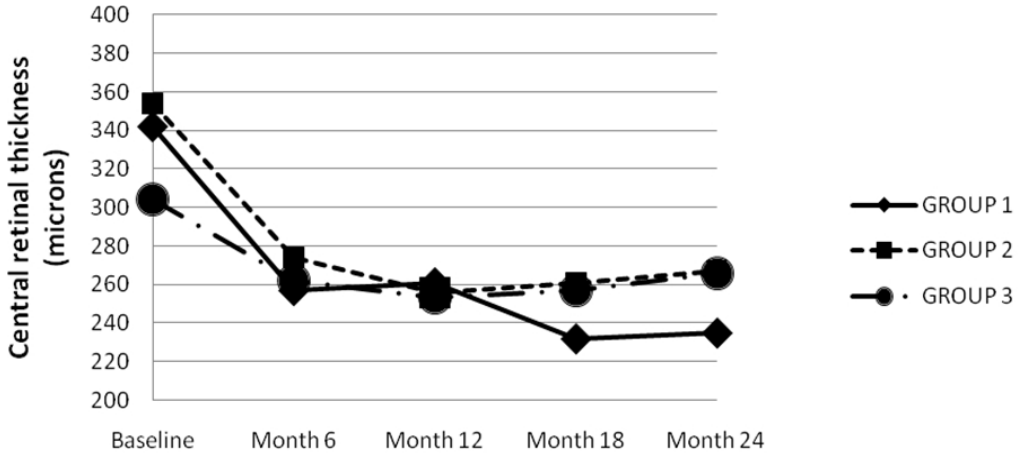

Fig. 2. The changes in mean central retinal thickness in the three groups. The graph shows the mean central retinal thickness levels from baseline to month 24. The change in mean central retinal thickness from the baseline to month 6, 12 18, and 24 was not statistically different among the three groups (p > 0.05 for all)

The mean number of injections of the groups at month 12 and month 24 was summarized in Table 4.

Table 4. Mean number of injections of the groups at month 12 and 24

	Group 1n, injection	Group 2	Group 3	P value
Month 12, microns	3.0±0	4.6±0.4 (range 4-5)	6.6±0.7 (range 6-8)	<0.0001
Month 24, microns	3.7±1.2 (range 3-7)	7.2±1.5 (range 5-11)	9.8±2.3 (range 6-15)	<0.0001

n: number.

No serious systemic or ocular complications were detected in any of the patients. Only mild complications like punctate keratitis, subconjunctival hemorrhage, and transient mild anterior uveitis were observed.

4. DISCUSSION

The predictive factors for the treatment outcomes of nAMD were evaluated in many studies [16]. Single nucleotide polymorphism in the complement factor H gene, increasing age, poorer visual acuity at baseline, larger CNV at baseline, previous PDT, presence of PED at baseline, a delay for the treatment was found to be negative predictive factors for the treatment of nAMD [16]. On contrast, the presence of a foveal pit, absence of a fibrous tissue under the fovea, a normal retinal layer configuration on OCT, presence of a vital RPE on autofluorescence imaging was reported to be positive predictors [16].

The number of injections was not evaluated in a detailed fashion before as a predictive factor for the treatment outcomes of nAMD. In PRONTO study, the influence of reinjections on the change in visual acuity was evaluated. The relationship was assessed with two

different statistical analyses, although no statistically significant correlation was found with either analysis, the authors mentioned about a trend towards a possible correlation between more frequent injections and worse visual outcome [11]. Ozkaya et al. reported that the nAMD patients who did not require additional ranibizumab injections after the initial 3 injections during the first year of treatment was found to be associated with better visual outcomes [17].

In this study mean overall injection number 5.4 at month 12 and 8.0 at month 24 which was comparable with PRONTO study [11]. Also the rate of the patients who received only 3 loading injections were similar (15.2% in our study and 17.5% in PRONTO study) [11]. In addition 32.6% of the patients required 4-5 injections and 52.2% patients required >5 injections during the first year. The change in VA at month 12 was 2.2, 1.7 and 0.9 lines in group 1, 2, and 3, respectively, and the change at month 24 was 2.3, 1.3 and 0.8 lines, respectively. The functional and anatomical outcomes were not statistically different among the three groups, but there was a trend towards a lower increase in visual acuity in group 3. Also the rate of the patients who lost ≥3 lines of VA supported the phenomenon, none of the patients lost ≥3 lines of VA in group 1; in contrast 23% of the patients lost ≥3 lines of VA in group 3. However, we could not support this data because of the low number of patients.

Clinically it is obvious that the group of nAMD patients who require more frequent ranibizumab injection on an as-needed treatment regimen represents the group of patients with an increased disease activity. More active disease may lead to more cellular damage and may cause worse visual and anatomical outcomes. In this study, we tried to evaluate this possible relationship. However, we could not obtain statistically significant results because of low number of patients which was the most important limitation of this study. In addition we did not evaluate the CNV type and size among the three groups, and another important limitation was the retrospective design.

5. CONCLUSION

In conclusion, this study did not show a possible relationship between injection numbers and treatment outcomes in patients with nAMD on an as-needed treatment regimen. However, the visual and anatomical results seemed better in the group of patients who required less ranibizumab injections without a statistically significance. Therefore, we think that this study may give rise to a further study that will evaluate the effects of injection number and injection frequency on the treatment outcomes of nAMD in a larger group of patients.

CONSENT

A waiver of informed consent was obtained given that this study posed less than minimal risk to all participants and did not affect patient welfare.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by theappropriate ethics committee and have therefore been performed in accordance with theethical standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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