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Intravitreal ranibizumab for choroidal neovascularization secondary to angiod streaks. Comparison of the 12 and 24-month results of treatment in treatment-naïve eyes

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Abstract. – OBJECTIVE: Our aim study was to compare 12 and 24-month results of intravitreal ranibizumab therapy in the management of choroidal neovascularization (CNV) secondary to angioid streaks (ST). This could be of clinical importance helping us planning optimal dosing strategies.

PATIENTS AND METHODS: Over a 7-year period, a consecutive series of treatment-naïve eyes with macular CNV due to AS were treated with intravitreal ranibizumab (0.5 mg). The main outcome measure was changed in best-corrected visual acuity (BCVA) at 12 and 24 months as compared to baseline.

RESULTS: Twenty eyes completed 24-month therapy and regular follow-up visits. BCVA improved at 12 (0.42 ± 0.26 logMAR) and 24 months (0.44 ± 0.22 logMAR) as compared to baseline (0.75 ± 0.26 logMAR) ($p < 0.001$), but did not change between the 12 and 24-month follow-up ($p = 0.48$). BCVA improved in 15 (75%) and 16 (80%) of the eyes, but in 5 (25%) and 4 eyes (20%) remained unchanged ($p = 0.71$) at 12 and 24 months, respectively.

CONCLUSIONS: These results suggest that during the first year of intravitreal ranibizumab therapy for patients with macular CNV due to AS, BCVA improved in most of the eyes, and was maintained during the second year.

Key Words: Angioid streaks, Choroidal neovascularization, Ranibizumab, Anti-VEGF.

Introduction

Angioid streaks (AS) are calcified, crack-like disruptions of Bruch's membrane, spreading radially outward from the peripapillary area. They may be idiopathic or associated with systemic disorders such as pseudoxanthoma elasticum (PXE), Ehlers-Danlos syndrome, Paget disease, and hemoglobinopathies, i.e., beta-thalassemia, sickle cell anemia (SCA)[1].

Macular choroidal neovascularization (CNV) is the most serious complication of AS, occurring at least in one eye in 72-86% of the patients[2,3]. It has a poor natural course, usually resulting in central visual loss and legal blindness. In the past, laser photocoagulation, photodynamic therapy with Verteporfin, and submacular surgery have been used with poor results for the treatment of CNV in patients with AS[4].

Recently, intravitreal injections of vascular endothelial growth factor inhibitors (anti-VEGF) drugs (bevacizumab, ranibizumab) have been used for the treatment of macular CNV secondary to AS. Published studies have shown that it is currently the most effective treatment[4]. All published case series, report the final effect of anti-VEGF therapy on best corrected visual acuity (BCVA) at one, and two years of follow-up. Although it is clinically important, no study has compared the functional outcomes, i.e., BCVA, by the end of the first and second year of therapy. These data could help in a better understanding on the efficacy of anti-VEGF in this disease and planning the best mode of therapy of these patients. Therefore, the primary aim of our study was to investigate BCVA changes by the end of 12 and 24-month active treatment and follow-up.

Patients and Methods

Patients

Over a 7-year period (December 2007-June 2013) we carried out a prospective, open-label, interventional clinical study of treatment in eyes wi-

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th macular CNV secondary to AS; all 19 patients (20 eyes) had a regular follow-up visits until the completion of the study at 24 months. Two additional patients were excluded from the study as they failed to present at the scheduled follow-up examinations. Among these 19 patients, we included PXE, SCA and idiopathic cases. Skin biopsies were not performed to confirm the diagnosis of PXE. We used patient's medical history and clinical criteria so as, to classify the etiology of the AS. Therefore, we cannot exclude the possibility that a small number of our cases with AS secondary to PXE could have been misdiagnosed, as idiopathic.

Patients who had any previous treatment for the disease, as well as, those who had BCVA of less than 20/200 (< 0.1 logMAR) at baseline, were excluded from the study. All 20 eyes completed 24 months therapy and regular follow-up (Supplementary Table). The study protocol was approved by the hospital Ethics Committee. It was conducted according to the Helsinki Declaration for Human Rights, and informed consent was obtained from all patients.

Examinations and Injection Protocol

Fifteen of the 20 eyes have been described in our previous one-year follow-up study, including the time-table of injections, the injection procedure and the ocular examinations which our patients had undergone before every injection[5]. Briefly, intravitreal injections of 0.5 mg ranibizumab (Lucentis, Novartis, Athens, Greece) were administered to each eye at baseline and week 4, 8, 12; patients were instructed to return for examination, at six weeks. If there were no signs of CNV activity at week four, such as new hemorrhage, edema, or subretinal fluid, patients were injected and instructed to return at eight weeks. Patients with no signs of CNV activity in the next follow-up examinations were re-injected at three-, four- and five-month intervals, ending treatment after a total of 24-month follow-up. Patients who returned to the office presenting new hemorrhage or signs of exudation, after the initial four injections, were injected and instructed to return at the same time interval, as the one before the previous injection (modified "inject and extend" protocol)[5,6]. At every visit, each patient underwent complete ocular examination, including BCVA (Snellen charts), contact lens fundus biomicroscopy, optical coherence tomography (OCT) imaging (Stratus, v. 4.0, OCT v. 4, Carl Zeiss Meditec, Jena, Germany), color and red free photography. Digital fluorescein angiography (Topcon Imagenet 2000 Digital Imaging System with a TRC-50 IA fundus camera, Topcon Europe Medical B.V., LJ Capelle Aan Den ISssel, The Netherlands) was performed at baseline, at 12 weeks and in the case of CNV recurrence.

Calculations and Definitions

For calculations, BVCAs were converted from the Snellen to the logarithm of the minimal angle of resolution (logMAR) scale[7]. At 12 and 24 months follow-up, improved BCVA was defined as a decrease of ≥ 0.2 logMAR units, worsening BCVA as an increase of ≥ 0.2 logMAR units and stable BCVA as $\pm$ 0.1 logMAR units, as compared to baseline measurements. Changes of the central retinal thickness of more than 10% at 12 and 24 months, as compared to pretreatment values were classified as "increase" or "decrease"[8,9].

Statistical Analysis

Data were analyzed by the statistical package Statgraphics Centurion XV, v15.1.02 (StaPoint Technologies Inc., Warrenton, VA, USA). Numerical data in the text and tables are presented as mean $\pm$ 1SD or median with range as appropriate. BCVA at baseline, one and two-year follow-up, as well as central retinal thickness were compared by Student's two-sided, pair-t-test. Chi square test was also used to compare differences between 12 and 24 months in a number of eyes: 1. With improvement, worsening or stabilization of BCVA and 2. With changes (increase, decrease) of central retinal thickness. A p value of < 0.05 indicated statistical significance.

Data in figures are presented as box-and-whisker plots. The box includes 50% of the results falling between the 25th and the 75th percentile. The median value is represented as a horizontal line inside the box. Outliers, i.e., points more than 1.5 times the interquartile range from the end of the box, are shown as open squares.

Results

The demographic data and clinical characteristics of the 19 patients (20 eyes) are shown in Table I. The duration of symptoms before entering the study was 1-3 months. During the initial 12 months, each eye received a median of 7 (range: 7-10) injections and during the second year 2 (1-5) injections. In the 24-month study period, each eye received 9 injections, except one eye (5%) which had 15 injections, because of several

Table I. Epidemiological data of the 19 patients (20 eyes) included in the study.

Gender (male/female)	8/12
Age (years) (mean, range)	59.25, 46-78
Systemic diseases (No of eyes)	
Pseudoxanthoma elasticum (PXE)	3
Sickle cell anemia (SCA)	2
Idiopathic	15
Location of choroidal neovascularization (CNV) (No of eyes)	
Subfoveal	6
Juxtafoveal	7
Extrafoveal	7
Type of CNV (No of eyes)	8
Predominantly classic	
Classic	9
Occult (including also minimally classic cases)	3

recurrences of CNV activity. BCVA was significantly improved at 12 (0.42±0.26 logMAR) and 24 months (0.44±0.22 logMAR) as compared to baseline values (0.75±0.26 logMAR) (pair-t = 4.74, $p < 0.001$ and pair-t=4.94, $p<0.001$, respectively). However, there was no statistically significant difference between the 12 and 24-month follow-up (pair-t = 0.72, $p = 0.48$) (Figure 1, Supplementary Table). Figure 2 shows the percentage of eyes with improvement, worsening or stabilization of BCVA at 12 and 24 months as compared to baseline logMAR values, as well as, respective percent changes between 12 and 24 months. In 15 (75%) and 16 (80%) of the eyes BCVA improved and in 4 (20%) and 3 (15%) remained unchanged (x^2=0.18, Df=2, p=0.92) at 12 and 24 months, respectively. However, in 17 (85%) of eyes BCVA was stabilized, in 2 (10%) improved and 1 (5%) deteriorated between 12 and 24-month follow-up. Central retinal thickness (OCT- measured) was calculated in all cases from the automated measurements generated by the software of the OCT (Macular thickness map). There was no case where the algorithm failed. Central retinal thickness was significantly reduced at 12 (287 ± 87 μm) and 24 months (322 ± 98 μm) as compared to baseline values (382 ± 96 μm) (pair-t = 4.73, $p < 0.001$ and pair-t = 6.44, $p < 0.001$, respectively). However, there was not any statistically significant difference between the 12 and 24-month follow-up (pair-t = 1.55, $p = 0.14$) (Figure 3). Central retinal thickness was decreased by more than 10% to baseline in 17 (85%) and 15 (75%) eyes, while in 3 (15%) and 5 (25%) remain unchanged (x^2= 0.63, Df = 1, $p = 0.43$) at 12 and 24 months, respectively. However, the central retinal thickness was unchanged in 12 (60%) eyes, in 2 (10%) decreased and in 6 (30%) increased at between the 12 and 24th month of follow-up.

Nor drug- or injection-related complications were recorded during the 24-month treatment and follow-up period of the study.

Discussion

Angioid steaks complicated with macular choroidal neovascularization is a rare disorder[10]. If untreated, may lead to severe visual impairment and legal blindness. Published results of thermal

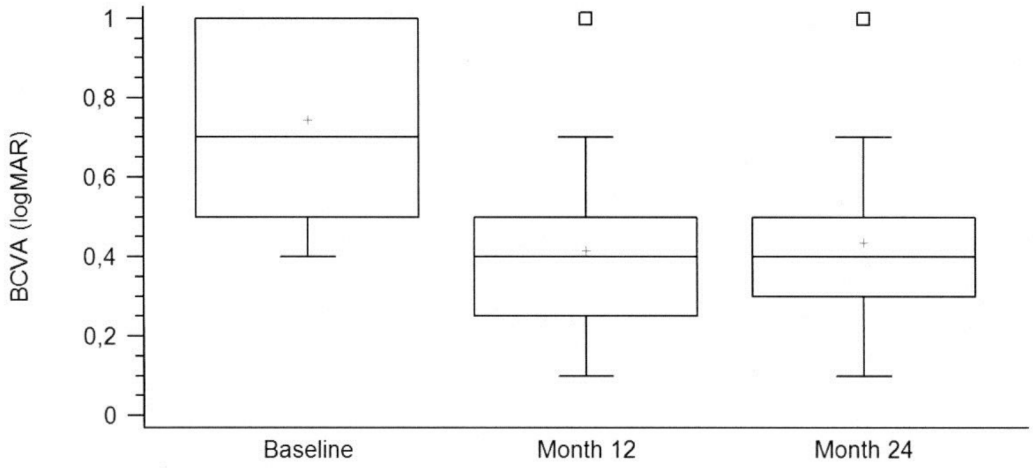

Figure 1. Outcome of BVCA of 20 eyes treated with intravitreal ranibizumab for macular choroidal neovascularization secondary to angioid streaks. There was a significant improvement of BCVA at 12 and 24 months as compared to baseline values (pair-t=4.74, $p<0.001$ and pair-t=4.94, $p<0.001$, respectively), but not between the 12 and 24-month follow-up (pair-t=0.72, p=0.48).

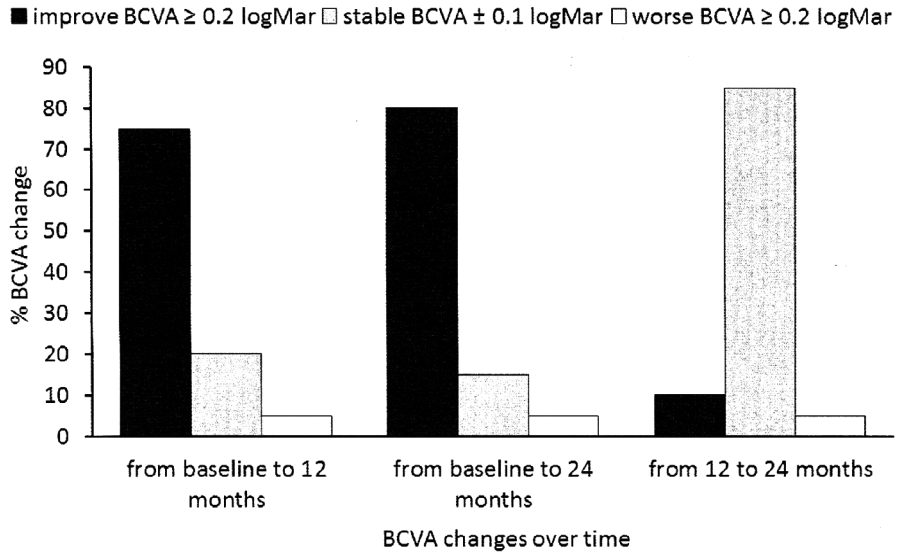

Figure 2. Percentage of eyes with improvement, stabilization or worsening of BCVA at 12 and 24 months as compared to baseline logMAR values, as well as, respective percent changes between 12 and 24 months. All 20 eyes had intravitreal ranibizumab for macular choroidal neovascularization secondary to angioid streaks. Improved BCVA was defined as a decrease of ≥0.2 logMAR units, worsening BCVA as an increase of ≥0.2 logMAR units and stable BCVA as ±0.1 logMAR units, as compared to baseline measurements There is no significant difference of the percent outcome at 12 or 24 months (x^2=0.14, Df=2, p=0.71).

laser photocoagulation, photodynamic therapy and submacular surgery have been disappointing[4]. Intravitreal injections of anti-VEGF agents are currently the treatment of choice for macular CNV due to AS, since they improve or stabilize the BCVA in the majority of the cases over a follow-up period of about two years[4]. However, published studies assessing the efficacy of anti-VEGF to treat macular CNV due to AS are relatively few and half of them, have either a short (6-16 months) follow-up period or include small number of eyes[11-16], due to the rarity of the disease. In addition, certain studies include only treatment-naïve eyes, while others also include eyes which had previously undergone other treatments before the anti-VEGF therapy. Also, investigators have used various injection protocols, making the comparison between different studies difficult.

There are only seven published reports with an extended follow-up to about two years (Table II), but they do not separately report on the results of the first and second year of therapy on BCVA[8,9,17-21]. As a result, clinicians are not aware whether there are any differences of the effectiveness of anti-VEGF on BCVA during the first and second year treatment and follow-up.

Table II. Efficacy of VEGF inhibitors in macular CNV secondary to AS in studies including more than 9 eyes with a follow-up period of about two years.

Reference	No of eyes	Treatment naive	Type of study	VEGF inhibitor	Follow-up (months) (mean, range)	No of injections (median, range)	BCVA	
							improved (%)	stabilized (%)
Current study	20	20/20	Pro*	R*	24	9 (9-15)	80	20
Wiegand (17)	9	9/9	Retro*	B*	19 (10-28)	4 (2-7)	44.4	44.4
Neri (18)	11	11/11	Pro	B	24 (20-29)	3 (2-6)	90.9	9.1
Sawa (8)	15	15/15	Retro	B	19 (12-24)	4 (1-9)	33	54
Shah (19)	12	12/12	Retro	R	22 (1-54)	4 (2-15)	25	66.7
Myung (20)	9	3/9	Retro	B/R	29 (24-31)	6 (1-17)	56	44
Finger (21)	16	13/16	Retro	B	28 (16-39)	4 (1-22)	43.8	50
Mimoun (9)	35	11/35	Retro	R	24 (6-37)	4 (2-14)	11.4	74.3

Pro*: prospective, Retro*: retrospective, R*: Ranibizumab, B*: Bevacizumab

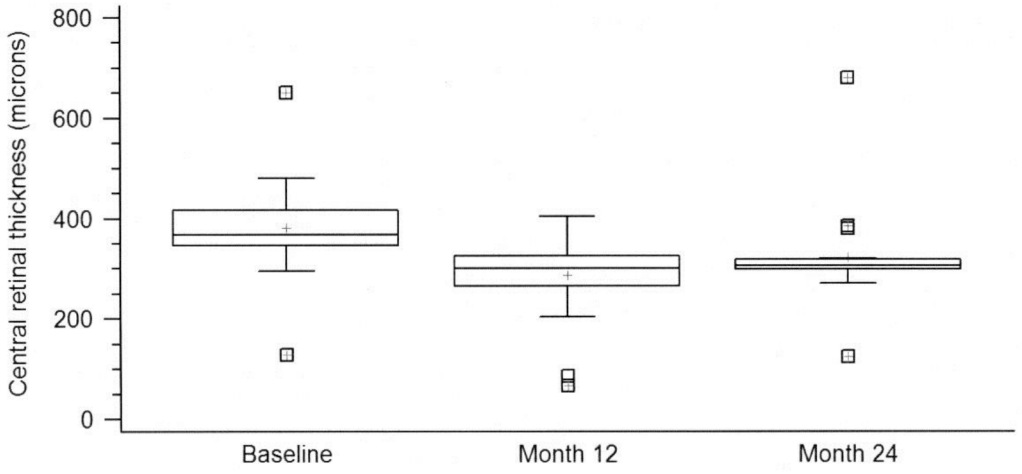

Figure 3. Outcome of the central retinal thickness (OCT) of 20 eyes treated with intravitreal ranibizumab for macular choroidal neovascularization secondary to angioid streaks. There was a significant reduction of the size of the central retinal thickness at 12 and 24 months as compared to baseline values (pair-t=4.73, $p<0.001$ and pair-t=6.44, $p<0.001$, respectively), but not at between the 12 and 24 month follow-up (pair-t=1.55, $p=0.14$).

Our study included a reasonable number of eyes (n=20), which had all completed 24-month active treatment and follow-up. This is the first study to clearly show that our intravitreal injection protocol improves BCVA, during the first year of therapy and stabilizes it, during the second year of maintenance therapy in the majority of patients. It is of note that during the second year, the time-interval between examinations and injections was increased according to our modified "inject and extend" protocol.

When comparing the other studies (Table II)[8,9,17-21] and our case series, there are important differences among them. Firstly, our patients had the highest median number of intravitreal injections (n=9) within two years, followed by

Supplementary Table. Demographic, functional and morphologic data of studied eyes.

Eye	Gender	Age (years)	No of injections	Macular thickness (μm) OCT[2]		BCVA[1]	
				Baseline	Final[3]	Baseline	Final[3]
1	m	65	9	443	320	1.00	0.70
2	f	78	9	367	310	0.70	0.70
3	f	68	9	357	318	1.00	0.40
4	f	70	9	387	306	1.00	0.50
5	f	70	9	395	298	0.70	0.30
6	m	57	9	398	304	1.00	0.20
7	m	52	15	650	680	0.50	1.00
8	f	52	9	339	299	0.40	0.10
9	m	57	9	437	296	0.50	0.40
10	m	48	9	367	305	0.40	0.20
11	f	46	9	345	303	0.40	0.30
12	f	54	9	356	307	1.00	0.50
13	m	49	9	329	311	1.00	0.70
14	f	52	9	362	297	1.00	0.40
15	f	65	9	128	125	1.00	0.40
16	m	73	9	460	380	1.00	0.50
17	f	61	9	346	320	0.70	0.50
18	m	63	9	295	270	0.50	0.30
19	f	49	9	480	385	0.40	0.20
20	f	56	9	392	305	0.70	0.40

[1]BCVA: Best corrected visual acuity; [2]OCT: optical coherence tomography; [3]Final: At 24 months.

the Myung et al[20] series with 6 injections over the same time period. This is probably explained by the fact that the eyes of our patients had been scheduled to receive 7 injections within the first 12 months, irrespective of having a quiescent eye disease, while most studies used an "according to need" treatment regimen. Secondly, three of the studies (Table II)[9,20,21] included eyes which had previously received other therapies, such as laser photocoagulation or photodynamic therapy. Mimoun et al[9] treated 11 treatment-naïve, out of 35 eyes and found no differences in the number of injections and BCVA outcomes, between the treatment-naïve and previously treated eyes. However, this was a retrospective study having the lowest rate of BCVA improvement among the seven published studies (Table II). Thirdly, our case series and that of Neri et al[18] are the only prospective clinical trials having a follow-up of 24 months, but using a different injection protocol. Their findings showed the highest rate of improved BCVA among the studies of Table II. It is possible that other factors could affect the treatment outcome, such as the underlying systemic disease (PXE, Ehlers-Danlos syndrome, Paget disease, SCA) or idiopathic[8], the location (sub-, juxta-, extra-foveal) and the type of macular CNV (classic, predominantly classic, occult) and the severity of the eye lesions. It has been suggested that the most favorable results were obtained in patients with less advanced disease[21], indicating that the onset of treatment should be as early as possible[4]. However, a multivariate analysis including all of the above factors would need a large prospective study, which is not possible to perform due to the rarity of the disease.

In our case series, the central retinal thickness was significantly reduced at 12 and 24 months as compared to baseline, but there were no significant differences between the 12th and 24th month measurements. Indeed, the central retinal thickness was reduced by more than 10% in the majority (75-80%) of the eyes, as compared to pretreatment values and in 60% of the eyes, it was unchanged at between the 12th and the 24th month. These percentages are similar to those of BCVA stabilization-improvement, at the same time intervals. These data are in agreement with those of Wiegand et al[17], Neri et al[18], Myung et al[20] and Finger et al[21], but not with those of Shah and Amoaku[19] and Mimoun et al[9], who found no significant difference of central retinal thickness after treatment, as compared to baseline values. This discrepancy among studies is difficult to explain, but could be related to the above-mentioned co-factors possibly affecting the treatment outcome.

Our work has the inherent limitations of a prospective cohort study, lacking a control group with randomized eyes. Despite that, taking into account the rarity of the disease, we have included a reasonable number of treated eyes, all completing 24 months of treatment and follow-up. Moreover, central retinal thickness values of all CNV lesions, independently of their location, were included in the analysis. Even though an extrafoveal CNV may not affect the central retinal thickness, to the same extent as a subfoveal CNV, it is noteworthy that central retinal thickness decreased in most cases by the end of the follow-up.

Conclusions

Our 24-month prospective study has clearly shown that intravitreal injections of ranibizumab in patients with macular CNV secondary to AS improves visual acuity during the first year and stabilizes it, during the second year of therapy. We suggest that this could be attributed to the treatment during the first year, that leads to a functional and anatomical improvement while, during the second year, treatment mainly preserves the first-year results.

Conflicts of interest

The authors declare no conflicts of interest.

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