Long-Term Follow-Up of Choroidal Neovascularization due to Angioid Streaks with pro re nata Intravitreal Anti-VEGF Treatment

Long term follow-up of choroidal neovascularization due to angioid streaks with PRN intravitreal anti-VEGF treatment

Running title: anti-VEGF in angioid streaks: long term results

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Abstract

Purpose: To evaluate the long-term outcomes of intravitreal anti-VEGF drugs with a “pro re nata” (PRN) regimen in the treatment of choroidal neovascularization (CNV) secondary to angioid streaks (AS).

Methods: Retrospective, multicenter, non comparative case series of consecutive AS eyes affected by treatment-naïve CNV. A complete ophthalmologic examination was performed every 30-45 days after the loading phase including fluorescein angiography and/or optical coherence tomography.

Results: 52 eyes of 39 patients were treated with intravitreal bevacizumab and/or ranibizumab and followed for a mean of 33.8 months. Baseline best corrected visual acuity was 20/40 and deteriorated by an average of 6.8 ETDRS letters per year ($p<0.001$). We performed an average of 5.1, 6.5 and 6.8 injections at 1, 2 and 3-year follow-up respectively.

Conclusions: Intravitreal anti-VEGF drugs in a PRN regimen, with close monitoring, appear to slow the progression of CNVs in AS, but don’t prevent from a progressive visual loss.

Conflict of interest:

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INTRODUCTION

Angioid streaks (AS) represent breaks in a calcified and thickened Bruch's membrane and appear as irregular, reddish or dark lines typically radiating from the optic disc. [1-3] The disease can be isolated or associated with systemic disorders such as pseudoxanthoma elasticum (PXE), [4-5] PXE-like syndromes,[6] beta-thalassemia,[7] sickle cell disease [8] and Paget disease.[9] The occurrence of choroidal neovascularization (CNV) into the subretinal space complicates the disease and frequently results in legal blindness especially in middle-aged patients. Until now laser photocoagulation, surgical approaches, trans-pupillary thermotherapy (TTT) and photodynamic therapy (PDT) with verteporfin have achieved just a short-term reduction in the lesion activity and often intensive follow-up and frequent retreatments have only allowed a delay in disease progression.[10-22]

Currently intravitreal Vascular Endothelial Growth Factor (VEGF) inhibitors are the most effective therapy for CNV due to AS: treatment with bevacizumab or ranibizumab was found to cause stabilization or an increase of Best Corrected Visual Acuity (BCVA) in the majority of patients. [23] Encouraging anatomical results were achieved in all studies except one,[24] and report a reduction or at least a stabilization of the central retinal thickness (CRT) measured by optical coherence tomography (OCT).[25-42] It was also shown that combination therapies do not give better results than monotherapy.[28, 43-45] At present, in a chronically active AS-related CNV, the available treatments do not prevent the functional loss but rather limit it.[23,46] In this context, analysis of long-term functional and anatomical outcomes is helpful to corroborate these findings. The aim of our study is to retrospectively evaluate the efficacy of intravitreal anti-VEGF drugs administered with a “pro re nata”(PRN) regimen (bevacizumab and/or ranibizumab) in the treatment of CNV secondary to AS over a long-term follow-up.

MATERIALS and METHODS

This study is a retrospective, multicenter, non comparative case series. All the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) and with the Helsinki Declaration. An informed consent was obtained in all patients and before each injection. We reviewed patients with CNV secondary to angioid streaks (AS); treatment began with intravitreal bevacizumab and/or ranibizumab between January 2008 and August 2013. The inclusion criteria were: 1) angioid streaks (AS), 2) naïve CNV (absence of any previous treatment) with a subfoveal or non-subfoveal (>1μm

from the fovea) location, 3) active neovascular membrane (leakage in fluorescein angiography, FA), 4) treatment with bevacizumab and/or ranibizumab intravitreal injections, 5) minimum follow-up of 12 months, 6) absence of neovascular membrane due to other causes, such as age-related macular degeneration, pathologic myopia, etc.

All patients were treated with intravitreal injections of bevacizumab (1.25 mg/0.05 mL) and/or ranibizumab (0.5 mg/0.05 mL) according to a PRN regimen, that is a first loading phase of three monthly injections and then maintenance with single injections as needed.

A complete ophthalmologic examination including measurement of BCVA using Early Treatment Diabetic Retinopathy Study (ETDRS) charts and fluorescein angiography (FA) with lesion size analysis were recorded at baseline and at 1 month after the last injection of the loading phase. The same data were recorded at 6, 12, 24 and 36 months from baseline. The lesion size, defined as the Greatest Linear Diameter (GLD, mm), was measured on the FA image through an image analyzer software (Visupac Zeiss FF450). Follow-up visits with a complete ophthalmic examination, BCVA measurement and fundus observation were carried out every 30-45 days after the first injection. At the time, FA and/or optical coherence tomography scan (OCT 3D-1000 Topcon) were also performed if necessary.

In the cases of recurrence (new retinal hemorrhages or retinal edema on biomicroscopic examination, angiographic leakage or increase in lesion size on FA associated or not with visual acuity loss) or persistence (new retinal hemorrhages or retinal edema on biomicroscopic examination, angiographic leakage or increase in lesion size on FA associated or not with visual acuity loss despite the first loading phase of three injections), a single intravitreal injection of ranibizumab or bevacizumab and scheduled checks every 30-45 days (BCVA measurements, ophthalmic examination and, if any, additional FA and/or OCT) were repeated. Re-treatment decision was made by a single physician in each Institute.

Outcome measures were the mean number of injections, the mean change in BCVA and the mean change in lesion size (GLD, mm). BCVA data were extracted in logMAR, since this is a suitable scale in statistical analyses, while means were converted to Snellen ratio and differences were converted to ETDRS letters for clarity. A secondary outcome was the maintenance of BCVA $\geq$ 20/63 at the end of the follow-up. Univariate regression analyses were conducted. Data were analyzed using Stata 13.1 software (StataCorp, College Station, TX), using linear mixed models to account for correlated data within the individual. A p-value $< .05$ was considered the threshold for significance.

RESULTS

We included 39 patients (52 eyes), affected by CNV due to AS, with a mean age of 53.0 years (SD: 7.8 years). Twenty patients were women and 19 were men. Thirty-four eyes (65%) were affected by subfoveal CNV while 18 eyes (35 %) had an extrafoveal CNV location. Follow-up was at least 12 months and reached 36 months only in 23 eyes (mean of 33.8 months, SD:19.6).

Treatment pattern

Thirteen eyes received only bevacizumab injections, 33 only ranibizumab doses, and in 6 cases we administered both drugs. All eyes received a loading phase of three initial anti-VEGF injections. We performed an average of 3.7 injections (SD: 0.7) at 6-months, 5.1 injections (SD:2.0) and 6.5 injections (SD:4.0) at 1 and 2 years respectively. Overall we administered 160 doses of bevacizumab and 166 of ranibizumab with a mean of 6.8 (SD:1.7) injections in the first 3 years of follow-up.

CNV persistence was observed in 4/52 eyes (8%) and at least one recurrence in 36/52 eyes (69%), with the first recurrence after the last injection of the loading phase appearing after a mean of 6.2 months (SD:5.2). Five out of 18 eyes (28%) progressed from a non-subfoveal to a subfoveal location.

Visual and anatomic outcome

Mean logMAR BCVA values and a regression-based estimate of their linear trend during the follow-up are illustrated in **Figure 1**. There was progressive deterioration from a mean baseline BCVA of 20/40 Snellen ratios, by an average of 6.8 ETDRS letters per year ($p<0.001$), or rather approximately a mean loss of 20.4 ETDRS letters at three years. In 23 patients followed at 3 years, 9 (39%) lost less than 15 ETDRS letters although 16/23 eyes (70%) maintained a visual acuity of ≥ 20/63.

The mean GLD was 2.1 mm (SD: 0.4) at baseline and slightly increased during follow-up (linear trend 0.13 mm per year $p=0.003$).

Treatment with intravitreal ranibizumab and/or bevacizumab was very well tolerated in all patients without adverse ocular or systemic side-effects over the whole 3-year follow-up.

Predictors of visual outcome

Baseline BCVA, GLD and CNV location were statistically associated and they were shown to be significant predictors of visual outcome, too. In fact, compared to 24 eyes with baseline BCVA ≥20/40, 28 eyes with lower vision had a larger CNV at baseline (median 1.2 mm vs 1 mm,

p=0.017) and have more commonly a subfoveal CNV (18/28 vs. 0/24, p<0.001) . At 3 years, eyes with better baseline BCVA showed a modest loss from a mean baseline value of 20/25 to 20/40 Snellen. Conversely, eyes with worse baseline BCVA markedly lost vision from a mean value of 20/50 to a value of 20/320 Snellen at 3-year follow-up.

Subfoveal CNV consistently lost more vision during follow-up (11 versus 3 ETDRS letters per year, p<0.001). There was no statistically significant difference between the number of injections performed on eyes with non-subfoveal CNV compared to eyes with subfoveal neovascular membrane (p=0.37).

Restricting the analysis at eyes followed for 36 months or more, 10 eyes with extrafoveal CNV lost 0.18 logMAR while 13 eyes with subfoveal CNV lost 0.59 logMAR; although the difference in BCVA change at 36 months was not statistically significant due to small sample size, the linear trend in visual acuity was significant (p<0.001) suggesting a worse outcome for eyes with subfoveal lesions. (**Figure 2**)

Case report

F.S. (male, 49 years) was bilaterally affected by AS complicated by a subfoveal CNV in the right eye and an extrafoveal neovascular membrane in the left eye. In the right eye BCVA was 20/50 Snellen ratios and the lesion size was 1.4 mm at baseline. We performed the loading phase of three intravitreal injections of bevacizumab maintaining a stable value of BVCA until 18 months (1.5-year follow-up). BCVA deteriorated to 20/100 at 19-month follow-up and slightly improved to 20/63 at 2-year follow-up after six administrations of the drug. Visual acuity deteriorated again to 20/200 at 3-year 3-month follow-up and remained stable after 14 intravitreal injections of bevacizumab overall. GLD remained unchanged until 3-year 3-month follow-up when it increased to 2.02 mm. **(Figure 3)** On the contrary the left eye presented an extrafoveal CNV that did not affect the visual acuity because the lesion did not involve the subfoveal area. In fact baseline BCVA of 20/20 and baseline GLD of 0.8 mm remained unchanged throughout the whole 3-year 6-month follow-up after three intravitreal injections of bevacizumab. **(Figure 4)**

DISCUSSION

CNV is a severe complication of angioid streaks that leads to dramatic visual impairment in middle-aged patients. There is no general consensus about the most appropriate treatment because of the high recurrence rates and poor visual outcomes. Anti-VEGF intravitreal injections were found to be effective, obtaining good anatomical and functional results but there is no agreement on the appropriate dosing strategy (PRN, treat and extend, fixed). [25-42] Furthermore long-term data has not yet been published, except for a little sample recently reported by Martinez-Serrano et al [46]. Our study presents the largest retrospective case series reported to date concerning the treatment of CNV secondary to angioid streaks using intravitreal bevacizumab and/or ranibizumab.

Comparing our study with previous studies, in our case series eyes with baseline BCVA value > 20/40 showed a deterioration of BCVA from 20/25 to 20/40, which is a result comparable to the one reported by Battaglia Parodi et al [42] which evaluated the effects of intravitreal bevacizumab injections in the treatment of non-subfoveal CNV due to AS at 1-year follow-up. Furthermore we found progressive deterioration over time of BCVA both in eyes with extrafoveal CNV and high baseline visual acuity (> 20/40 Snellen ratios), and in eyes with subfoveal CNV and/or low baseline visual acuity (≤ 20/40). There was less deterioration in eyes with higher baseline BCVA over time than there was in the other group. These data are partially in agreement with those obtained by Battaglia Parodi et al[42] that showed a substantial stability of functional outcomes. Similar results with a longer follow-up were reported by Martinez-Serrano et al in 14 eyes.[46] In contrast our data disagrees with the data obtained by Sawa et al,[31] Finger et al,[34] El Matri et al,[35] Mimoun et al,[37] Ladas et al[38] and Shah et al[41] who demonstrated a trend of improvement or stability of functional and anatomical outcomes in their case series. In the study by Ladas et al, eyes were treated according to a treat and extend protocol showing beneficial results with a mean of 7.1 injections over a 16-month period. Our data showed an average of 3.7 injections (SD: 0.7) at 6-months and 5.1 injections (SD:2.0) at 1-year follow-up. In the second and in the third year further injections were performed reaching a total number of 6.5 injections (SD:4.0) and 6.8 injections (SD:1.7) respectively. Our data showed a lower number of injections: this could be explained by the PRN regimen used in our case series vs the different retreatment protocol used by Ladas et al. We think that a treat and extend protocol may allow better visual and anatomical results, nevertheless, undergoing patients to a higher burden of intravitreal treatments.

Explaining these differences in the results is difficult but we think that a different selection criteria of cases (naïve/not naïve, extra/juxta/subfoveal CNV), the different length of follow-up and the different treatment regimen used (PRN protocol, [31,34,35,37,41,46] single injection followed by PRN,[42] treat and extend protocol [38]) certainly played an important role in this case. In fact our results show a high tendency towards relapse and confirm the difficulties in controlling a

disease that deteriorates long-term despite a close follow-up, especially in the case of subfoveal CNV and in eyes with low baseline visual acuity.

In the face of the deterioration in BCVA we found a growing trend of the lesion size (GLD) which does not seem to have a statistically significant influence on the trend of visual acuity. In our opinion this statement can be explained on the one hand by possible invasion of the fovea, as observed in 5/18 cases of extrafoveal CNV in our case series, and on the other by the phenomena of atrophy of the retina overlying a subfoveal CNV that may occur during a longer follow-up.

Furthermore our study is additionally significant due to the long follow-up period and to the greater sample number than the other case series reported to date in literature. We recognize that this study has the limitations of any retrospective case series with its inherent selection bias, including the absence of a control group and the choice of a PRN treatment regimen with a follow-up of 30-45 days. Another limitation was represented by the execution of FA and OCT only in the cases of suspected recurrence during follow-up: if used monthly, OCT could highlight a possible recurrence earlier with subsequent, more frequent re-treatments and better anatomical and functional results.

It is clear that the major problem in managing CNV in eyes with angioid streaks is its recurrence, as also shown in our case series. It is possible that a different treatment regimen with a greater number of injections may achieve better results, preventing recurrences and slowing down the deterioration of the lesion in agreement with the data obtained by Ladas et al.[38]

Even in the presence of a progressive deterioration our data show that CNV with an extrafoveal location and/or a good baseline visual acuity, in particular if treated at an early stage, is characterized by a level of visual function in the context of normal vision (30.4%) or moderate low vision (39.2%) in a not-negligible percentage of eyes (69.6%) for at least 3 years after the beginning of the therapy with anti-VEGF drugs.

These findings indicate the importance of periodic monitoring of patients with angioid streaks complicated by CNV treated with bevacizumab and/or ranibizumab: this appears to be a safe treatment resulting in a slower progression of the disease. Further prospective, randomized studies with a larger sample size and longer follow-up are needed to confirm our results.

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