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

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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

Giacomelli Giovanni¹, Finocchio Lucia¹, Biagini Ilaria¹, Sodi Andrea¹, Murro Vittoria¹, Introini Ugo², Varano Monica³, Bandello Francesco², Menchini Ugo¹

¹*Department of Translational Surgery and Medicine, Eye Clinic, University of Florence, Florence, IT*

²*Department of Ophthalmology, San Raffaele Scientific Institute, University of Milan, Milan, IT*

³*GB Bietti Eye Foundation IRCCS, Rome, IT*

Corresponding author: Giovanni Giacomelli, Department of Translational Surgery and Medicine, Eye Clinic, University of Florence, Italy; Viale Morgagni 85, Florence 50134, Italy; phone: +39 055 2758008 ; fax: +39 055 7949718. E-mail: giovanni.giacomelli@unifi.it

Keywords: macular diseases; neovascular membranes; anti-VEGF

1 **Abstract**

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

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

8 **Results:** 52 eyes of 39 patients were treated with intravitreal bevacizumab and/or ranibizumab and
9 followed for a mean of 33.8 months. Baseline best corrected visual acuity was 20/40 and deteriorated
10 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
11 injections at 1, 2 and 3-year follow-up respectively.

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

14

15 **Conflict of interest:**

16 None: all the authors have no proprietary, financial, professional or other personal interests of any
17 nature or kind in any product, service and/or company that could be construed as influencing the
18 position presented in, or the review of, the present manuscript.

19

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22

1 INTRODUCTION

2

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

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

25

26 MATERIALS and METHODS

27

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

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

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

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

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

25 Outcome measures were the mean number of injections, the mean change in BCVA and the
26 mean change in lesion size (GLD, mm). BCVA data were extracted in logMAR, since this is a
27 suitable scale in statistical analyses, while means were converted to Snellen ratio and differences
28 were converted to ETDRS letters for clarity. A secondary outcome was the maintenance of BCVA
29 $\geq 20/63$ at the end of the follow-up. Univariate regression analyses were conducted. Data were
30 analyzed using Stata 13.1 software (StataCorp, College Station, TX), using linear mixed models to
31 account for correlated data within the individual. A p-value $< .05$ was considered the threshold for
32 significance.

33

34 **RESULTS**

1
2 We included 39 patients (52 eyes), affected by CNV due to AS, with a mean age of 53.0
3 years (SD: 7.8 years). Twenty patients were women and 19 were men. Thirty-four eyes (65%) were
4 affected by subfoveal CNV while 18 eyes (35 %) had an extrafoveal CNV location. Follow-up was
5 at least 12 months and reached 36 months only in 23 eyes (mean of 33.8 months, SD:19.6).

6 7 *Treatment pattern*

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

14 CNV persistence was observed in 4/52 eyes (8%) and at least one recurrence in 36/52 eyes
15 (69%), with the first recurrence after the last injection of the loading phase appearing after a mean
16 of 6.2 months (SD:5.2). Five out of 18 eyes (28%) progressed from a non-subfoveal to a subfoveal
17 location.

18 19 *Visual and anatomic outcome*

20 Mean logMAR BCVA values and a regression-based estimate of their linear trend during
21 the follow-up are illustrated in **Figure 1**. There was progressive deterioration from a mean baseline
22 BCVA of 20/40 Snellen ratios, by an average of 6.8 ETDRS letters per year ($p<0.001$), or rather
23 approximately a mean loss of 20.4 ETDRS letters at three years. In 23 patients followed at 3 years,
24 9 (39%) lost less than 15 ETDRS letters although 16/23 eyes (70%) maintained a visual acuity of \geq
25 20/63.

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

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

30 31 *Predictors of visual outcome*

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

1 p=0.017) and have more commonly a subfoveal CNV (18/28 vs. 0/24, p<0.001) . At 3 years, eyes
2 with better baseline BCVA showed a modest loss from a mean baseline value of 20/25 to 20/40
3 Snellen. Conversely, eyes with worse baseline BCVA markedly lost vision from a mean value of
4 20/50 to a value of 20/320 Snellen at 3-year follow-up.

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

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

14

15

16 *Case report*

17

18 F.S. (male, 49 years) was bilaterally affected by AS complicated by a subfoveal CNV in the
19 right eye and an extrafoveal neovascular membrane in the left eye. In the right eye BCVA was
20 20/50 Snellen ratios and the lesion size was 1.4 mm at baseline. We performed the loading phase of
21 three intravitreal injections of bevacizumab maintaining a stable value of BVCA until 18 months
22 (1.5-year follow-up). BCVA deteriorated to 20/100 at 19-month follow-up and slightly improved to
23 20/63 at 2-year follow-up after six administrations of the drug. Visual acuity deteriorated again to
24 20/200 at 3-year 3-month follow-up and remained stable after 14 intravitreal injections of
25 bevacizumab overall. GLD remained unchanged until 3-year 3-month follow-up when it increased
26 to 2.02 mm. **(Figure 3)** On the contrary the left eye presented an extrafoveal CNV that did not
27 affect the visual acuity because the lesion did not involve the subfoveal area. In fact baseline BCVA
28 of 20/20 and baseline GLD of 0.8 mm remained unchanged throughout the whole 3-year 6-month
29 follow-up after three intravitreal injections of bevacizumab. **(Figure 4)**

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33 **DISCUSSION**

34

1 CNV is a severe complication of angioid streaks that leads to dramatic visual impairment in
2 middle-aged patients. There is no general consensus about the most appropriate treatment because
3 of the high recurrence rates and poor visual outcomes. Anti-VEGF intravitreal injections were
4 found to be effective, obtaining good anatomical and functional results but there is no agreement on
5 the appropriate dosing strategy (PRN, treat and extend, fixed). [25-42] Furthermore long-term data
6 has not yet been published, except for a little sample recently reported by Martinez-Serrano et al
7 [46]. Our study presents the largest retrospective case series reported to date concerning the
8 treatment of CNV secondary to angioid streaks using intravitreal bevacizumab and/or ranibizumab.

9 Comparing our study with previous studies, in our case series eyes with baseline BCVA
10 value $> 20/40$ showed a deterioration of BCVA from 20/25 to 20/40, which is a result comparable
11 to the one reported by Battaglia Parodi et al [42] which evaluated the effects of intravitreal
12 bevacizumab injections in the treatment of non-subfoveal CNV due to AS at 1-year follow-up.
13 Furthermore we found progressive deterioration over time of BCVA both in eyes with extrafoveal
14 CNV and high baseline visual acuity ($> 20/40$ Snellen ratios), and in eyes with subfoveal CNV
15 and/or low baseline visual acuity ($\leq 20/40$). There was less deterioration in eyes with higher
16 baseline BCVA over time than there was in the other group. These data are partially in agreement
17 with those obtained by Battaglia Parodi et al[42] that showed a substantial stability of functional
18 outcomes. Similar results with a longer follow-up were reported by Martinez-Serrano et al in 14
19 eyes.[46] In contrast our data disagrees with the data obtained by Sawa et al,[31] Finger et al,[34] El
20 Matri et al,[35] Mimoun et al,[37] Ladas et al[38] and Shah et al[41] who demonstrated a trend of
21 improvement or stability of functional and anatomical outcomes in their case series. In the study by
22 Ladas et al, eyes were treated according to a treat and extend protocol showing beneficial results
23 with a mean of 7.1 injections over a 16-month period. Our data showed an average of 3.7 injections
24 (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
25 year further injections were performed reaching a total number of 6.5 injections (SD:4.0) and 6.8
26 injections (SD:1.7) respectively. Our data showed a lower number of injections: this could be
27 explained by the PRN regimen used in our case series vs the different retreatment protocol used by
28 Ladas et al. We think that a treat and extend protocol may allow better visual and anatomical
29 results, nevertheless, undergoing patients to a higher burden of intravitreal treatments.

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

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

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

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

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

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

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

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1 **REFERENCES**

2

3 ¹ Matonti F, Conrath J. Angioid streaks. *J Fr Ophthalmol* 2012; 35(10):838-45.

4 ² Connor PH, Juergens JL, Perry HO, Hollenhorst RW, Edwards JE. Pseudoxanthoma elasticum and
5 angioid streaks: a review of 106 cases. *Am J Med* 1961; 30:537-43.

6 ³ Jensen OA. Bruch's membrane in pseudoxanthoma elasticum. Histochemical, ultrastructural, and
7 x-ray microanalytical study of the membrane and angioid streaks areas. *Albrecht Von Graefes Arch*
8 *Klin Exp Ophthalmol* 1977; 203:311-320.

9 ⁴ Finger RP, Charbel ISSA P, Ladewig MS Götting C, Szliska C, Scholl HP, Holz FG.
10 Pseudoxanthoma elasticum: genetics, clinical manifestations and therapeutic approaches. *Surv*
11 *Ophthalmol* 2009; 54:272-285.

12 ⁵ Gliem M, De Zaeytijd J, Finger RP, Holz FG, Leroy BP, Charbel Issa P. An update on the clinical
13 phenotype in patients with pseudoxanthoma elasticum. *Front Genet* 2013; 4:14.

14 ⁶ Vanakker OM, Martin L, Gheduzzi D, Leroy BP, Loeys BL, Guerci VI, Matthys D, Terry
15 SF, Coucke PJ, Pasquali-Ronchetti I, De Paepe A. Pseudoxanthoma elasticum-like phenotype with
16 cutis laxa and multiple coagulation factor deficiency represents a separate genetic entity. *J Invest*
17 *Dermatol* 2007; 127:581-587.

18 ⁷ Aessopos A, Stamatelos G, Savvides P, Kavouklis E, Gabriel L, Rombos I, Karagiorga M,
19 Kaklamanis P. Angioid streaks in homozygous beta thalassemia. *Am J Ophthalmol* 1989;108: 356-
20 359.

21 ⁸ Aessopos A, Voskaridou E, Kavouklis E, Vassilopoulos G, Rombos Y, Gavriel L, Loukopoulos
22 D. Angioid streaks in sickle-thalassemia. *Am J Ophthalmol* 1994; 117:589-592.

23 ⁹ Dabbs TR, Skjodt K. Prevalence of angioid streaks and other ocular complications of Paget
24 disease of bone. *Br J Ophthalmol* 1990; 74:579-582.

25 ¹⁰ Gelisken O, Hendrikse F, Deutman AF. A long-term follow-up study of laser coagulation of
26 neovascular membranes in angioid streaks. *Am J Ophthalmol* 1988; 105:299-303.

27 ¹¹ Clarkson JG, Altman RD. Angioid streaks. *Surv Ophthalmol* 1982; 26:235-246.

28 ¹² Brancato R, Menchini U, Pece A, Davi G, Capoferri C. Laser treatment of macular subretinal
29 neovascularizations in angioid streaks. *Ophthalmologica* 1987; 195:84-87.

30 ¹³ Pece A, Avanza P, Galli L, Brancato R. Laser photocoagulation of choroidal neovascularization
31 in angioid streaks. *Retina* 1997; 17:12-16.

- 1 ¹⁴ Mennel S, Schimdt JC, Meyer CH. Therapeutic strategies in choroidal neovascularizations
2 secondary to angioid streaks. *Am J Ophthalmol* 2003; 136:580-582.
- 3 ¹⁵ Ehlers JP, Maldonado R, Sarin N, Toth CA. Treatment of nonage-related macular degeneration
4 submacular diseases with macular translocation surgery. *Retina* 2011; 31:1337–1346.
- 5 ¹⁶ Roth DB, Estafanous M, Lewis H. Macular translocation for subfoveal choroidal
6 neovascularization in angioid streaks. *Am J Ophthalmol* 2001; 131:390–392.
- 7 ¹⁷ Aras C, Başer T, Yolar M, Yetik H, Artunay O, Guzel H, Ozkan S. Two cases of choroidal
8 neovascularization treated with transpupillary thermotherapy in angioid streaks. *Retina* 2004;
9 24:801–803.
- 10 ¹⁸ Ozdek S, Bozan E, Gurelik G, Hasanreisoglu B. Transpupillary thermotherapy for the treatment
11 of choroidal neovascularization secondary to angioid streaks. *Can J Ophthalmol* 2007; 42:95–100.
- 12 ¹⁹ Menchini U, Virgili G, Intorini U, Bandello F, Ambesi-Impiombato M, Pece A, Parodi MB,
13 Giacomelli G, Capobianco B, Varano M, Brancato R. Outcome of choroidal neovascularization in
14 angioid streaks after photodynamic therapy. *Retina* 2004; 24:763–771.
- 15 ²⁰ Browning AC, Chung AK, Ghanchi F, Harding SP, Musadiq M, Talks SJ, Yang YC, Amoaku
16 WM. Verteporfin photodynamic therapy of choroidal neovascularization in angioid streaks: one-
17 year results of a prospective case series. *Ophthalmology* 2005; 112:1227–1231.
- 18 ²¹ Lee JM, Nam WH, Kim HK. Photodynamic therapy with verteporfin for choroidal
19 neovascularization in patients with angioid streaks. *Korean J Ophthalmol* 2007; 21:142-145.
- 20 ²² Arias L, Pujol O, Rubio M, Caminal J. Long-term results of photodynamic therapy for the
21 treatment of choroidal neovascularization secondary to angioid streaks. *Graefes Arch Clin Exp*
22 *Ophthalmol* 2006; 244:753-757.
- 23 ²³ Gliem M, Finger RP, Fimmers R, Brinkmann CK, Holz FG, Charbel Issa P. Treatment of
24 choroidal neovascularization due to angioid streaks. A comprehensive review. *Retina* 2013;
25 33:1300-1314.
- 26 ²⁴ Mimoun G, Tilleul J, Leys A, Coscas G, Soubrane G, Souied EH.. Intravitreal ranibizumab for
27 choroidal neovascularization in angioid streaks. *Am J Ophthalmol* 2010; 150:692–700 e691.
- 28 ²⁵ Teixeira A, Moraes N, Farah ME, Bonomo PP. Choroidal neovascularization treated with
29 intravitreal injection of bevacizumab (Avastin) in angioid streaks. *Acta Ophthalmol Scand* 2006;
30 84:835–836.
- 31 ²⁶ Bhatnagar P, Freund KB, Spaide RF, Klancnik JM Jr, Cooney MJ, Ho I, Fine HF, Yannuzzi LA..

1 Intravitreal bevacizumab for the management of choroidal neovascularization in pseudoxanthoma
2 elasticum. *Retina* 2007; 27:897–902.

3 ²⁷ Rinaldi M, Dell'Omo R, Romano MR, Chiosi F, Cipollone U, Costagliola C.. Intravitreal
4 bevacizumab for choroidal neovascularization secondary to angioid streaks. *Arch Ophthalmol* 2007;
5 125:1422–1423.

6 ²⁸ Donati MC, Virgili G, Bini A, Giansanti F, Rapizzi E, Giacomelli G, Menchini U Intravitreal
7 bevacizumab (Avastin) for choroidal neovascularization in angioid streaks: a case series.
8 *Ophthalmologica* 2009; 223:24–27.

9 ²⁹ Wiegand TW, Rogers AH, McCabe F, Reichel E, Duker JS. Intravitreal bevacizumab (Avastin)
10 treatment of choroidal neovascularisation in patients with angioid streaks. *Br J Ophthalmol* 2009;
11 93:47–51.

12 ³⁰ Neri P, Salvolini S, Mariotti C, Mercanti L, Celani S, Giovannini A. Long-term control of
13 choroidal neovascularisation secondary to angioid streaks treated with intravitreal bevacizumab
14 (Avastin). *Br J Ophthalmol* 2009; 93:155–158.

15 ³¹ Sawa M, Gomi F, Tsujikawa M, Sakaguchi H, Tano Y. Long-term results of intravitreal
16 bevacizumab injection for choroidal neovascularization secondary to angioid streaks. *Am J*
17 *Ophthalmol* 2009; 148:584–590 e582.

18 ³² Myung JS, Bhatnagar P, Spaide RF, Klancnik JM Jr, Cooney MJ, Yannuzzi LA, Freund KB.
19 Long-term outcomes of intravitreal antivascular endothelial growth factor therapy for the
20 management of choroidal neovascularization in pseudoxanthoma elasticum. *Retina* 2010; 30:748–
21 755.

22 ³³ Teixeira A, Mattos T, Velletri R, Teixeira R, Freire J, Moares N, Bonomo PP. Clinical course of
23 choroidal neovascularization secondary to angioid streaks treated with intravitreal bevacizumab.
24 *Ophthalmic Surg Lasers Imaging* 2010; 41:546–549.

25 ³⁴ Finger RP, Charbel Issa P, Schmitz-Valckenberg S, Holz FG, Scholl HN. Long-term
26 effectiveness of intravitreal bevacizumab for choroidal neovascularization secondary to angioid
27 streaks in pseudoxanthoma elasticum. *Retina* 2011; 31:1268–1278.

28 ³⁵ El Matri L, Kort F, Bouraoui R, Karim B, Chebil A, Chaker N. Intravitreal bevacizumab for the
29 treatment of choroidal neovascularization secondary to angioid streaks: one year of follow-up. *Acta*
30 *Ophthalmol* 2011; 89:641–646.

31 ³⁶ Vadalà M, Pece A, Cipolla S, Monteleone C, Ricci F, Boscia F, Cillino S.. Angioid streak-related

1 choroidal neovascularization treated by intravitreal ranibizumab. *Retina* 2010; 30:903–907.

2 ³⁷ Mimoun G, Tilleul J, Leys A, Coscas G, Soubrane G, Souied EH. Intravitreal ranibizumab for
3 choroidal neovascularization in angioid streaks. *Am J Ophthalmol* 2010; 150:692–700 e691.

4 ³⁸ Ladas ID, Kotsolis AI, Ladas DS, Niskopoulou M, Georgalas I, Papakonstantinou D, Rouvas AA.
5 Intravitreal ranibizumab treatment of macular choroidal neovascularization secondary to angioid
6 streaks: one-year results of a prospective study. *Retina* 2010; 30:1185–1189.

7 ³⁹ Carneiro AM, Silva RM, Veludo MJ, Barbosa A, Ruiz-Moreno JM, Falcão MS, Brandão
8 EM, Falcão-Reis FM. Ranibizumab treatment for choroidal neovascularization from causes other
9 than age-related macular degeneration and pathological myopia. *Ophthalmologica* 2011; 225:81–
10 88.

11 ⁴⁰ Finger RP, Charbel Issa P, Hendig D, Scholl HP, Holz FG. Monthly ranibizumab for choroidal
12 neovascularizations secondary to angioid streaks in pseudoxanthoma elasticum: a one-year
13 prospective study. *Am J Ophthalmol* 2011; 152:695–703.

14 ⁴¹ Shah M, Amoaku WM. Intravitreal ranibizumab for the treatment of choroidal neovascularisation
15 secondary to angioid streaks. *Eye (Lond)* 2012; 26:1194–1198.

16 ⁴² Battaglia Parodi M, Iacono P, La Spina C, Berchicci L, Scotti F, Leys A, Introini U, Bandello F.
17 Intravitreal bevacizumab for nonsubfoveal choroidal neovascularization associated with angioid
18 streaks. *Am J Ophthalmol* 2014; 157:374-377.

19 ⁴³ Pece A, Russo G, Ricci F, Isola V, Introini U, Querques G. Verteporfin photodynamic therapy
20 combined with intravitreal triamcinolone for choroidal neovascularization due to angioid streaks.
21 *Clin Ophthalmol* 2010; 4:525-530.

22 ⁴⁴ Spaide RF, Sorenson J, Maranan L. Photodynamic therapy with verteporfin combined with
23 intravitreal injection of triamcinolone acetonide for choroidal neovascularization. *Ophthalmology*
24 2005; 112:301-304.

25 ⁴⁵ Artunay O, Yuzbasioglu E, Rasier R, Sengul A, Senel A, Bahcecioglu H. Combination treatment
26 with intravitreal injection of ranibizumab and reduced fluence photodynamic therapy for choroidal
27 neovascularization secondary to angioid streaks: preliminary clinical results of 12-month follow-up.
28 *Retina* 2011; 31:1279-1286.

29 ⁴⁶ Martinez-Serrano MG, Rodriguez-Reyes A, Guerrero-Naranjo JL et al. Long-term follow-up of
30 patients with choroidal neovascularization due to angioid streaks. *Clin Ophthalmol.* 2016 Dec
31 19;11:23-30.

