Artigo Original

Efficacy and progression of macular atrophy after seven years of treatment with ranibizumab: the myopic CNV seven-up

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RESUMO

Objectivo: Determinar a eficácia da injeção intra-vítrea de ranibizumab (IVR) a sete anos, no tratamento da neovascularização coroideia miópica (NVCm), e estimar a progressão da atrofia macular.
Material e Métodos: Estudo retrospetivo com avaliação cross-sectional. Foram analisados os registos médicos de altos míopes com NVCm tratados com injeção IVR, com tempo mínimo de *follow-up* de 84 meses. A avaliação *cross-sectional* final incluiu melhor acuidade visual corrigida (MAVC), retinografia, tomografia de coerência ótica spectral-domain (OCT- SD) e autofluorescência (FAF).
Resultados: Foram incluídos treze olhos de 13 doentes com *follow-up* médio de 96.6±5.4 meses. Após um número médio de 8.5±4.5 injeções IVR, a MAVC no baseline e na última visita foi 48.4±16.7 letras (L) e 45.2±26.8 L, respetivamente (p=0.6). A AV melhorou até ao terceiro ano (56.7±21.0 L), tendo diminuído desde então. Em relação à última visita, 4 doentes (30.8%) alcançaram ganho visual significativo (MAVC>5 L), 2 doentes (15.4%) mantiveram AV (variação entre -5 e 5 L), e em 7 doentes (53.8%) verificou-se perda superior a 5 L. Em relação à área de atrofia macular, verificou-se um aumento significativo durante o *follow-up*, em média 4,6±3,2 mm^2, traduzindo progressão significativa da mesma (p=0,002). A espessura macular central média variou de 304.9±116.5 µm no baseline para 360.5±89.1 µm na última visita (p>0.05).
Conclusões: O ranibizumab é um fármaco eficaz no tratamento da NVCm, secundária a miopia patológica, mantendo ou mesmo melhorando a MAVC. Contudo parece não evitar o desenvolvimento de atrofia macular, que poderá estar associada à perda progressiva de AV.

Palavras-chave
Miopia patológica; neovascularização coroideia; atrofia macular; ranibizumab; acuidade visual.

ABSTRACT

Purpose: To assess the efficacy of intravitreal ranibizumab (IVR) in the treatment of myopic choroidal neovascularization (mCNV) after 7 or more years of follow-up, and to estimate the progression of macular atrophy.

Material and Methods: Retrospective study with cross-sectional evaluation. The medical records of highly myopic patients with mCNV treated with IVR and with minimum follow-up of 84 months were analysed. A final cross-sectional evaluation was performed including best corrected visual acuity (BCVA), colour fundus photography (CFP), spectral-domain optical coherence tomography (SD-OCT) and fundus autofluorescence (FAF) imaging.
Results: Thirteen eyes of 13 patients with an average follow-up of 96.6 ±5.4 months were included. The mean number of IVR injections was 8.5 ±4.5. BCVA at baseline was 48.4±16.7 letters (L) and in the last visit was 45.2 ±26.8 L (p=0.600). BCVA improved up to the third year (56.7±21.0 L, p>0.05) but decreased ever since. Regarding the last visit, 4 patients (30.8%) reached significant visual gain (BCVA >5 L), 2 patients (15.4%) maintained visual acuity (range between -5 and 5L), and in 7 patients (53.8%) more than 5 L loss was reported. Concerning macular atrophy area, we found an average increase of 4.6 ±3.2mm^2 during follow-up, which was significant (p=0.002). The mean central macular thickness ranged from 304.9±116.5 µm at baseline to 360.5 ± 89.1 µm on the last visit (p>0.05).
Conclusions: Ranibizumab is effective in the treatment of CNV secondary to pathologic myopia in the long-term, stabilizing or even improving vision. However it does not seem to prevent subsequent macular atrophy which could be an important factor in progressive VA loss.

Key-words
Pathological myopia; choroidal neovascularization; macular atrophy; ranibizumab; visual acuity.

INTRODUCTION

The prevalence of myopia in the adult population is estimated to be 20% to 40%, and around 2% has pathological myopia. High myopia is defined by an excessive increase in axial length (≥ 26.0 mm), and/or a refractive error equal or less negative than -6.00 diopter, depending on the authors.[1-3] Myopic related changes in the posterior segment include: posterior staphyloma, diffuse and patchy atrophy, development of lacquer cracks, choroidal neovascularization (mCNV), and macular atrophy.[4,5]

Myopic CNV develops in nearly 10% of cases, it may be bilateral, and is an important cause of irreversible vision loss and blindness in young adults, due to fibrosis and central chorioretinal atrophy development around the regressed mCNV.[3,5-8] Reported factors associated with increased risk of mCNV and poor visual prognosis include: greater axial length, subfoveal location and larger area of mCNV, lower VA at baseline, age under 40 years old, greater duration of symptoms, and previous photodynamic therapy (PDT).[3,5,9] Patients with mCNV in one eye, also have greater probability of developing mCNV in the fellow eye (around 30-35% in 8 years).[5,10] Non treated mCNV usually has poor visual prognosis because the natural evolution is one of fibrosis and chorioretinal atrophy development.[3] Studies have shown that after 10 years of *follow-up*, 96% of patients with non-treated mCNV feature visual acuity (VA) of less than 20/200.[10] Hayashi *et al*,[11] analyzed 806 highly myopic eyes, and showed progression of myopic maculopathy in 40% of eyes, after a mean *follow-up* of 12.7 years. They also reported development of macular atrophy in eyes with CNV, which led to significant visual decline.

Ranibizumab (Lucentis, Genentech, USA; Novartis, Europe) is licensed for the treatment of mCNV in Europe, Japan, Australia and Canada. An initial single 0.5 mg injection is recommended, followed by monthly assessment and retreatment as needed.[10,12,13]

The purpose of this study is to determine the effectiveness of IVR in the long-term treatment of mCNV, to estimate the progression of macular atrophy, and to realize their impact on visual prognosis.

MATERIAL AND METHODS

Retrospective study with *cross-sectional* evaluation, performed at the Ophthalmology Department of Centro Hospitalar e Universitário de Coimbra and at the Association for Innovation and Biomedical Research on Light and Image.

Informed consent was obtained from all patients and the study followed the assumptions of the Helsinki Declaration.

Inclusion and exclusion criteria

Patients were included based on the following criteria: 1)

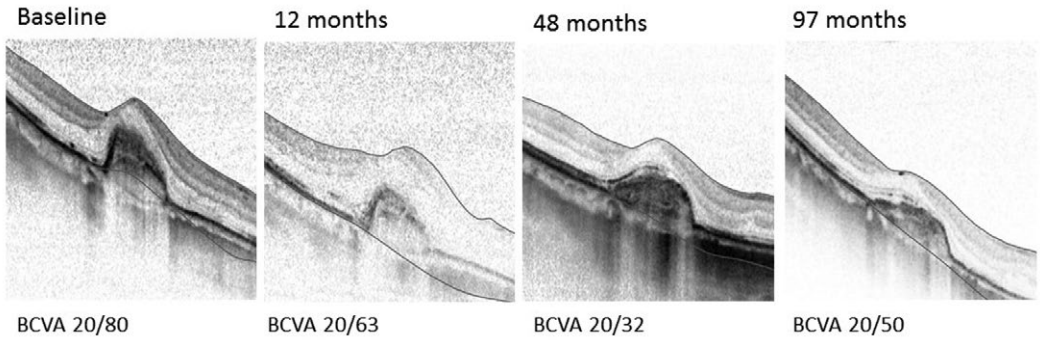


Fig. 1 | SD-OCT of a 60-year-old woman affected by myopic CNV and treated with 6 IVR injections. Central macular thickness decreased from 360 µm at baseline to 302 µm after 97 months of *follow-up*.

highly myopic eyes, defined as having a spherical equivalent (SE) refractive error equal or less negative than –6.00 diopter and/or axial length (AL) equal or greater to 26.0 mm; 2) mCNV treated with IVR, with or without previous treatments with PDT; 3) *follow-up* time equal or greater than 84 months. The exclusion criteria comprised CNV previously treated with laser photocoagulation and eye diseases that could compromise visual acuity, such as history of amblyopia, glaucoma, uveitis, dense cataract, diabetic retinopathy or other retinal vascular diseases, and surgical procedures such as vitreoretinal surgery.

Treatment with IVR

All treated eyes were always evaluated with Fluorescein angiography (FA) and OCT before starting treatment for myopic CNV. During *follow-up*, IVR retreatment was performed when clinically active myopic CNV was suspected and based on the presence of fluid in the OCT, BCVA loss associated with metamorphopsia, and/or evidence of macular hemorrhage. FA was also performed before IVR retreatment when necessary.

Study population and ophthalmologic evaluation

The medical records of highly myopic patients with mCNV treated with IVR and with a minimum *follow-up* of 84 months were analysed. Thirteen eyes of 13 high myopic patients with mCNV met the inclusion criteria and the records were reviewed for data including: demographic characteristics, BCVA evolution during *follow-up* assessed with Early Treatment of Diabetic Retinopathy Study (ETDRS) charts, axial length, spherical equivalent, phakic status, number and type of treatments for mCNV. Colour fundus photographs at baseline were also selected for longitudinal analysis of macular atrophy progression.

A cross-sectional evaluation was performed in all patients at the end of *follow-up*, including BCVA using ETDRS charts, slit lamp examination, and dilated fundus stereoscopic examination. Colour fundus photography (CFP), spectral-domain optical coherence tomography (SD-OCT) with Spectralis OCT (Heidelberg Engineering, Heidelberg, Germany) (Figure 1), and fundus autofluorescence (FAF) imaging (Heidelberg Engineering, Heidelberg, Germany), were also performed for macular atrophy development and progression analysis.

Macular atrophy and Central Retinal Thickness analysis

The area of macular atrophy was measured on colour fundus photography images, using the semiautomatic software RetmarkerAMD® (Retmarker, SA, Portugal). (Figure 2) This software allows to overlap a circular grid centered on the fovea, which comprises 1, 3, and 6 mm concentric circles, similar to the ETDRS-style macular grid.[14,15] The central field overlaps the central macula. The grader

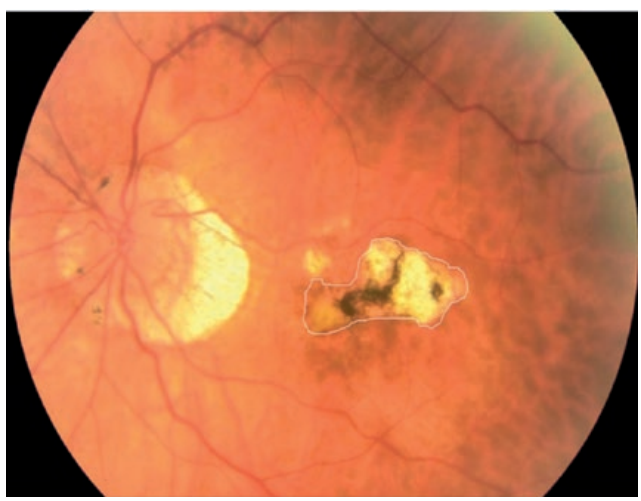


Fig. 2 | Measurement of the area of macular atrophy in the CFP, using the semiautomatic software RetmarkerAMD®.

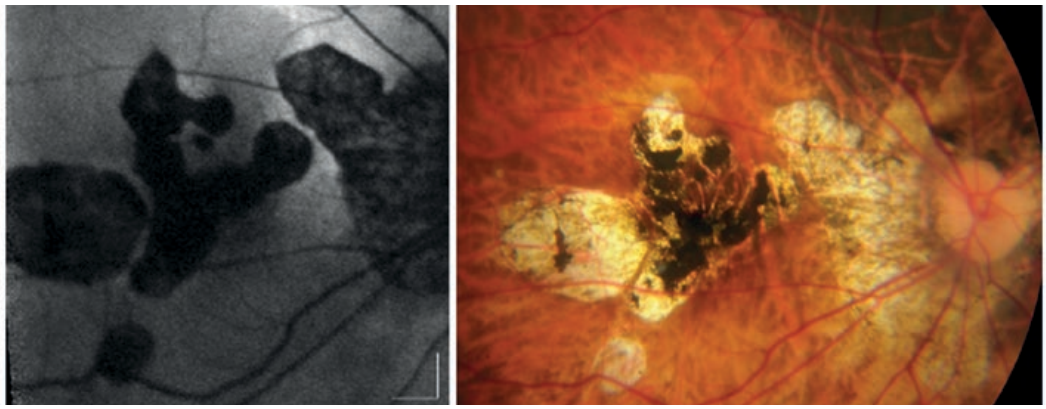


Fig. 3 | Autofluorescence and colour fundus photography of a 44-year-old woman, at the end of *follow-up*. Atrophic areas are comparable in both exams.

manually delineates the area of atrophy and the software automatically gives the corresponding area in mm^2.

The hypoautofluorescent areas in FAF images in the last visit, corresponding to atrophic areas, were also measured, using the same software, and the obtained values were compared with those from the colour fundus photography. (Figure 3). In case of discrepancies between the 2 methods the macular areas of atrophy were reanalysed.

The central retinal thickness (CRT) was obtained by automated thickness map on SD-OCT, with segmentation errors manually corrected whenever necessary.

Statistical analysis

Statistical analysis was performed using the IBM SPSS *statistics*® 23.0 (SPSS Inc, Chicago, IL, USA). Data were described and analysed statistically. Linear correlation between variables was analysed using Pearson's correlation coefficient. Correlations between parameters were tested using the Spearman correlation coefficient. Wilcoxon test was used to test for statistically significant differences between parameters with non-normal distribution, and the t-test used for parameters with normal distribution. Results were considered statistically significant to a level of statistical significance <0.05 (p value).

RESULTS

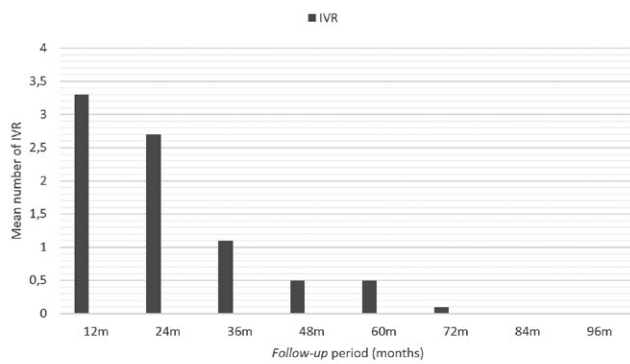
Demographic Data

We included 13 eyes of 13 patients (11 females and 2 males) with myopic CNV. The mean age at the end of *follow-up* was 61.9 ± 15.8 years (range 29 – 88 years) and the average *follow-up* time was 96.6 months (± 5.4).

The initial mean axial length was 29.4 ± 1.9 mm and the refractive error in phakic eyes was -15.9 ± 5,7 diopter (range, -8.5, -25.4). The mCNV was subfoveal in all the sample.

Two eyes (15.4%) were pseudophakic and PDT for mCNV had been performed in 61.5% (n=8) of the included eyes, before switching to treatment with IVR (range, 1 to 6 sessions).

The mean number of IVR injections performed during *follow-up* was 8.5 ± 4.5. The Diagram 1 shows the mean number of IVR injections annually.



Diag. 1 | Mean number of IVR injections during *follow-up*.

Patient demographic data is summarized in Table 1.

Progression of macular atrophy

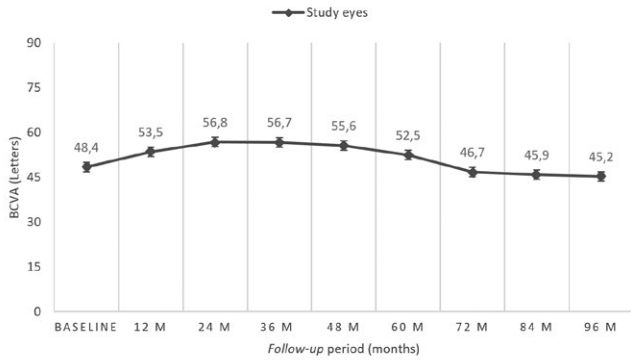
At the beginning of the study 38.5% (n=5) of the eyes had macular atrophy, with bilateral involvement in 4 patients (30.8%). At the end of *follow-up* the rate of macular atrophy increased to 92.3% of eyes (n=12), and bilateral involvement occurred in 9 patients (69.2%).

The progression of macular atrophy was quantified through measurement of the area in CFP, as explained previously. The area of macular atrophy ranged from 2.9 ± 7.4 mm2 at baseline, to 7.5 ± 8.9 mm^2 in the final visit. This

Table 1 | Summary of patients demographic data.

Parameters	Study eye
Number	13 patients 13 eyes
Final age, years	61.9 ± 15.8
Gender (male:female)	2:11
Follow-up period (months)	96.62 ± 5.4
Spherical equivalent (D)	-15.9 ± 5,7
Pseudophakia	2
Previous PDT	8

PDT photodynamic therapy with verteporfin.



Diag. 2 | BCVA annually during *follow-up*.

progression in size was statically significant, p = 0.002. Also, the area of atrophy was greater than 1 mm^2 in 30.8% of the eyes at baseline, but increased to 69.2% of the eyes in the final visit.

Macular atrophy areas measurements in CFP were highly comparable with hypoautofluorescent areas measured in FAF (r = 0.749; p < 0.005).

The colour fundus photography in Figure 4 demonstrates macular atrophy progression in a patient with mCNV, after 90 months of *follow-up*.

Progression of the area of atrophy showed no correlation with age, degree of myopia, axial length, refractive error or number of performed injections (p > 0.05).

Visual Acuity Evolution

The mean change of BCVA was not statistically significant, varying from 48.4 ± 16.7 letters (L) at baseline to 45.2 ± 26.8 L on the last visit (p=0.60). A more detailed analysis on the BCVA evolution revealed that it increased up to the second year of *follow-up* (56.8 ± 21.0 L; p>0.05), decreasing thereafter, as illustrated in Diagram 2.

Regarding the last visit, 3 patients (23.1%) showed significant visual gain (BCVA > 15L); 2 patients (15.4%) maintained visual acuity (range between -5 and 5L), and 2 patients (15.4%) lost more than 15 L, as illustrated in Table 2. No

Table 2 | Visual acuity outcomes in the end of *follow-up*.

Number of letters	n (eyes)	% (eyes)
<-15	2	15.4
-15 to -5	5	38.5
-5 to + 5	2	15.4
+5 to +15	1	7.7
>+15	3	23.1
VA decline	7	53.8
VA improvement	6	46.2

VA - Visual acuity.

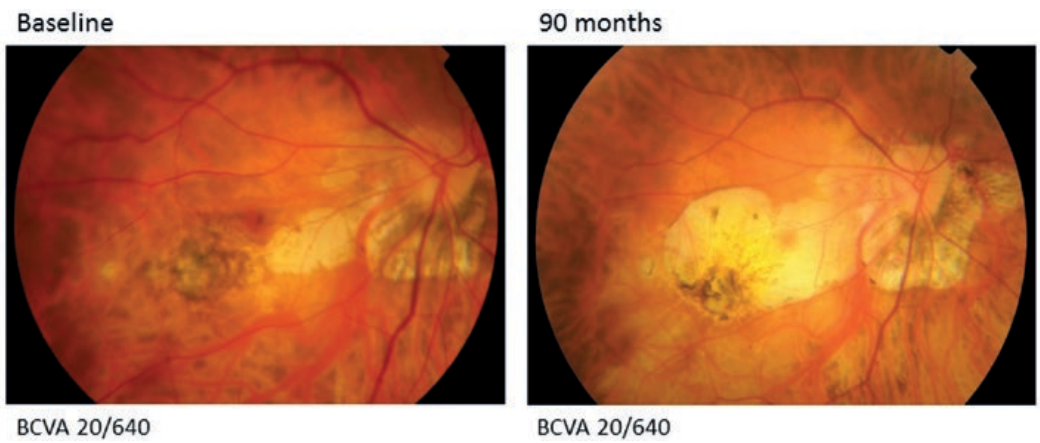
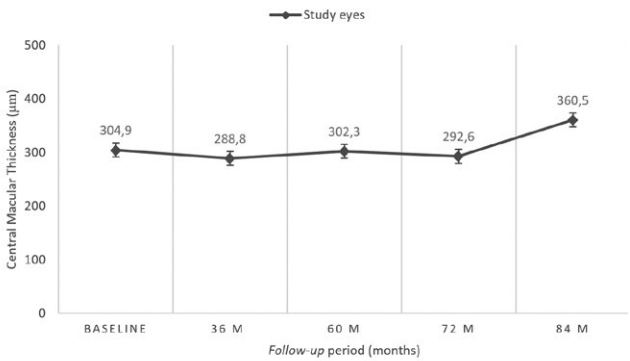


Fig. 4 | CFP at *baseline* and after 90 months of *follow-up*, of a 60-year-old woman affected by myopic CNV and treated with 5 IVR injections. In spite of treatment, subsequent progression and enlargement of macular atrophy around the regressed CNV, limited the visual outcome in the long-term.

significant correlation between BCVA and age or number of administered injections was found ($p > 0.10$). Additionally no correlation was found between BCVA decline and the enlargement of macular atrophy ($r = -498$, $p = 0.08$).

Central macular thickness

The mean central macular thickness ranged from 304.9 ± 116.5 µm at baseline to 360.5 ± 89.1 µm in the last visit ($p > 0.05$), and the evolution by year of follow- up is presented in Diagram 3.



Diag. 2 | Central macular thickness evolution during follow-up.

DISCUSSION

The effectiveness of anti-VEGF to 6 years *follow-up* in pathological myopia had previously been published.[16] Nevertheless our study is the first to assess ranibizumab effectiveness to more than 7 years *follow-up*, in addition to determine the progression of macular atrophy.

Long-term natural history of myopic CNV remains doubtful, and the precise aetiology of chorioretinal atrophy is still unknown. Vascular Endothelial Growth Factor (VEGF) contributes to the CNV pathogenesis and therefore the use of intravitreal anti-VEGF agents has been increasing in the last years.[1,3,6] From large, randomized, and controlled clinical trials, it has been established that anti-VEGF drugs are able to cease the progression of CNV. However, despite the suppression of mCNV, we are witnessing the decline of VA, which seems to be related to the development and progression of macular atrophy, not avoided by these agents. Uemoto *et al*,[17] analysed 27 eyes with mCNV after treatment with bevacizumab. They exposed that despite there was regression of CNV, the posterior development of chorioretinal atrophy surrounding the regressed CNV, leads to severe visual impairment. On the other hand, Parravano *et al*,[18] described fewer amount of eyes developing an increase of chorioretinal atrophy size, in patients treated with ranibizumab, compared with PDT in a 24 months *follow-up*.

The clinical benefit of ranibizumab at 12 month *follow-up*, depending on disease activity, in patients with mCNV was confirmed in the RADIANCE trial,[19] a phase III randomized controlled trial. Similarly Vadalà *et al*,[20] reported the efficacy of ranibizumab in an on demand regimen, in a population of 40 eyes during 13 months of *follow-up*. Similar results were disclosed by Franqueira *et al*,[21] at a 3-year *follow-up* study. More recently, Ruiz-Moreno *et al*,[16] reported the effectiveness of both bevacizumab and ranibizumab at 6 years of *follow-up*, in eyes with mCNV. They stated similar visual outcomes, with VA gain until the third year of *follow-up*, albeit without significant improvements at years 4, 5, and 6.

In our study, we assessed the long-term progression of macular atrophy and functional outcomes in patients with pathological myopia, submitted to PRN treatment of IVR injections.

As we did not notice any statistically significant correlations between progression of the macular atrophy and age, degree of myopia, axial length, refractive error or number of IVR injections, our results are in contrast to what several reports emphasize concerning that refractive error, lesion dimension and age can influence treatment response.[5] This could be due to our small sample size and longer *follow-up*.

In the end of *follow-up*, and in spite of treatment, atrophy progression affected 92.3% of the eyes, with 69.2% of the eyes with atrophy area exceeding 1 mm^2, which suggests that atrophic changes seem to be part of the natural history of high myopia and not merely related to the treatment of mCNV. These outcomes were slightly higher to the rate of 70% described by Farinha *et al*,[22] in eyes treated only with ranibizumab, with a mean *follow-up* of 43.9±4.7 months. The same authors described a 100% rate of prevalence of macular atrophy in a group of eyes treated with PDT and IVR, with a mean *follow-up* time of 85.7±21.1 months.[22] Our results corroborates Oishi *et al*[23] data. They investigate the visual prognosis and progression of chorioretinal atrophy in a *follow-up* period of more than 48 months, in 22 eyes with mCNV, treated with IV injections of bevacizumab. They noted that enlargement of atrophy occurred in 41 % of eyes in 1 year, reaching 73 % of cases at the final visit, affecting visual improvement.

There was an increase in VA up to the third year of *follow-up*, probably due to mCNV regression, as it has already been suggested.[2,24] The decline in VA from there seems to be attributable to the development of macular atrophy, around the regressed mCNV, which in turn appears to be unresponsive to treatment with ranibizumab. Merely the

presence of central macular atrophy resulting from subfoveal CNV, and not properly its progression, appears to be responsible for the decline of VA, thus explaining the lack of a significant correlation between the atrophy progression and BCVA. We can also question whether injections of ranibizumab in an on demand treatment regimen, could aggravate atrophy progression, as suggested by the CATT Research Group.[25]

Finally, although not statistically significant, there was a slight increase in central macular thickness, a result which is contrary to what would be expected in view of the progression of macular atrophy. It may be caused to, on one hand, the small sample size and on the other hand, due to the fact that the SD-OCT images at baseline were made with either Spectralis or Cirrus, whereas at the end of *follow-up*, all SD-OCT were Cirrus.

The present study has numerous limitations, such as its retrospective nature, a small sample size, the lack of a control group and the inclusion of eyes previously treated with PDT. Oppositely, this investigation has the advantage of an extended *follow-up* of more than 7 years, and provides a long-term analysis on the functional and morphologic prognosis of ranibizumab treated eyes in pathological myopia.

Summarizing, we showed that treatment with ranibizumab did not prevent macular atrophy, and is associated with visual acuity stabilization at seven years. Thus, due to the macular atrophy development and progression after repeated anti-VEGF treatments, an individualized and cautious treatment regimen may be the best option. Strategies to manage atrophy should be the next step in achieving better visual outcome.

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