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Choroidal neovascularisation complicating geographic atrophy in age-related macular degeneration

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ABSTRACT

Objective To investigate the morphological and functional outcomes after intravitreal ranibizumab injections for choroidal neovascularisation (CNV) complicating geographic atrophy (GA).

Design Retrospective, interventional, consecutive case series.

Methods We reviewed the charts of all consecutive patients with GA due to age-related macular degeneration (AMD), who received intravitreal ranibizumab injections for the development of CNV at least 24 months earlier.

Results 21 treatment-naive eyes of 21 consecutive patients (4 men, 17 women, mean age 86.9±1.6 years) were included. In 95.2% of eyes a type 2 CNV was present, extrafoveal in 42.8% of cases. After a mean of 5.0±0.87 (range 1–20) intravitreal ranibizumab injections, best-corrected visual acuity (BCVA) significantly worsened at the 24-month follow-up visit (0.73±0.05 vs 0.88±0.08 logMAR, respectively; p=0.01). A significant reduction of intraretinal cystic lesions, subretinal fluid and pigment epithelium detachment (p<0.001) and a significant increase of GA area (p=0.003) were present at last visit.

Conclusions Ranibizumab treatment of GA-associated CNVs provides no BCVA improvement at 24 months follow-up despite an anatomic response of CNV. Low effectiveness of ranibizumab in these cases is likely due to GA progression.

INTRODUCTION

Age-related macular degeneration (AMD) is the leading cause of blindness and visual disability in patients over the age of 55 years in developed countries.[1] It has been subdivided into three categories[2]: (1) early AMD, characterised by multiple small drusen (<63 μm) or intermediate drusen (≥63 μm and <125 μm) with no evidence of advanced AMD; (2) intermediate AMD characterised by extensive intermediate drusen or large drusen (≥125 μm) with no evidence of advanced AMD; and (3) advanced AMD, characterised by the presence of one or other of geographic atrophy (GA) or exudative AMD.

GA is characterised by the presence of a discrete area of retinal depigmentation at least 175 μm in diameter with a sharp border and visible choroidal vessels; it is generally slowly progressive.[2] Exudative AMD is characterised by a choroidal neovascularisation (CNV) developing under the retina, responsible for serous or haemorrhagic detachment of either the retinal pigment epithelium (RPE) or sensory retina, and presence of subretinal fibrous tissue[2]; onset of vision loss is generally acute.

The prevalence of GA is 3.5% in subjects older than 75 years, and accounts for approximately half the prevalence of exudative AMD. GA accounts for approximately 25% of cases with severe central vision loss. Exudative AMD accounts for approximately 75% of cases with severe central vision loss, if untreated. However, in some eyes with GA, a CNV may develop, thus affecting the natural history and causing further vision loss.

Ranibizumab (Lucentis, Genentech, South San Francisco, California, USA), is a recombinant, humanised, monoclonal antibody antigen-binding fragment (Fab) that neutralises all biologically active forms of vascular endothelial growth factor A (VEGF).[3] Intravitreal ranibizumab was the first therapy for exudative AMD that showed, in two phase III clinical studies, prevention in vision loss, and improvement in mean visual acuity, in a remarkable proportion of patients.[4 5] These benefits persisted through 24 months of follow-up. However, these results regard eyes diagnosed exclusively with exudative AMD. To date, there are no data regarding the effects of intravitreal ranibizumab in eyes with GA that develop CNV in the progression of the disease.

In this study we investigated the morphological and functional outcomes after intravitreal ranibizumab injections for CNV complicating GA due to AMD.

METHODS

We reviewed the charts of all consecutive patients with GA that developed a CNV and received intravitreal injections of ranibizumab at the University Eye Clinic of Creteil at least 24 months before. A written informed consent according to the tenets of the Declaration of Helsinki was obtained from each patient enrolled. French Society of Ophthalmology Ethics Committee approval was obtained for the retrospective review of data. Criteria for inclusion were: (1) age ≥50 years; (2) diagnosis of GA due to AMD, defined as a discrete area of retinal depigmentation at least 360 μm in diameter with a sharp border and visible choroidal vessels; (3) best-corrected visual acuity (BCVA) better than 20/400 (20 letters) as evaluated by Early Treatment Diabetic Retinopathy Study (ETDRS) charts; and (4) presence of newly diagnosed active CNV as evaluated with fundus biomicroscopy and fluorescein angiography (FA) at least

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24 months earlier. Patients with previous treatment for neovascular AMD in the study eye, refractive error of more than −6 dioptres, CNV attributable to other causes than AMD, active intraocular inflammation or any other retinopathy (such as diabetic retinopathy, retinal venous occlusion or epiretinal membrane) in the study eye, were excluded.

At baseline, each patient underwent a detailed medical and ocular history, a complete ophthalmologic examination (standard assessment in our clinic) which included slit-lamp biomicroscopy, intraocular pressure (IOP) assessment, measurement of BCVA using standard ETDRS charts, fundus biomicroscopy, fundus autofluorescence (FAF), FA and spectral-domain optical coherence tomography (Spectralis HRA+OCT, Heidelberg Engineering, Heidelberg, Germany).

Initial treatment consisted in one single intravitreal injection of 0.5 mg/0.05 ml ranibizumab performed by a retinal specialist according to the usual technique.[6] After the initial treatment, each patient underwent, monthly, a detailed medical and ocular history, assessment of BCVA using ETDRS charts and ophthalmic examination, which included slit-lamp biomicroscopy, IOP assessment, fundus biomicroscopy and OCT examination (standard assessment in our clinic).

The patients received further intravitreal injections if any of the following conditions applied: BCVA loss of at least five letters associated with recurrence of fluid within a previously dry macula as evaluated by OCT; persistence of intra/subretinal fluid (SRF) as evaluated by OCT; new-onset macular haemorrhages. In case of doubtful findings, FA was performed during follow-up, and persistence or recurrence of leakage from the lesions was considered as a retreatment criterion.

Main outcome measures were changes in mean BCVA (expressed as a logarithm of the minimum angle of resolution (logMAR)), and in morphological features associated with GA progression and CNV activity (two graders, GQ and NM), at 24 months from first treatment.

As qualitative parameters of GA progression, the foveal sparing on FAF and SD-OCT images, and the IS/OS layer status (present or disrupted/absent) at the fovea on SD-OCT scans were evaluated at the 24-month follow-up visits, and compared with baseline. SD-OCT was used in combination with FAF to distinguish whether a hypoautofluorescence was due to the blocking effect by xanthophylls or to atrophy (loss of outer retina on SD-OCT scans). Moreover, the development of an atrophic scar at the CNV (loss of outer retina on SD-OCT scans) site was evaluated at the 24-month follow-up visits. As qualitative parameters of CNV response to treatment, presence of intraretinal cystic lesions, SRF, pigment epithelium detachment (PED), and fibroglial scar at the fovea (ie. hyperreflective subretinal lesion), were evaluated on SD-OCT scans at the 24-month follow-up visits, and compared with baseline.

As a quantitative parameter of GA progression, the GA areas were measured on FAF frames at the 24-month follow-up visits, and compared with baseline measurements. The atrophic areas were outlined (boundaries drawn on FAF images, and sizes calculation) using the Heidelberg software (Spectralis Acquisition and Viewing Modules; V.3.2, Heidelberg Engineering). As a quantitative parameter of CNV response to treatment, the greatest linear dimensions (GLDs) on late phase FA frames, and the retinal thickness at the CNV site (defined by the distance between the inner retinal surface and the inner aspect of the hyper-reflective layer represented by the Bruch's membrane/choriocapillaris complex), and the retinal thickness of the 1-mm central retina (central macular thickness (CMT) measured using a 19-horizontal lines protocol) on SD-OCT were measured at the 24-month follow-up visits, and compared with baseline measurements.

As part of this study, in order to evaluate GA progression before starting treatment with intravitreal ranibizumab injections, changes in the GA areas over time were measured on FAF frames in selected eyes (when previous FAF before the advent of CNV were available). Enlargement rate was calculated based on two visits (baseline visit and last follow- up visit). The change in lesion size between these two visits (last follow-up and baseline) was divided by the time of follow-up (in years). Enlargement rate was calculated for lesion size, both on the original area scale and after transforming the measurements to the square-root scale.

Statistical calculations were performed using SPSS V.17.0. Comparisons of mean BCVA, and quantitative parameter of GA progression and CNV activity between baseline and 24-month follow-up were performed using the paired t test. The χ^2 test was used to assess changes of qualitative parameters of GA progression and CNV activity from baseline to last visit. Regression analysis was used to correlate BCVA with morphological features at baseline and 24-month follow-up. Analysis of covariance was used to correlate BCVA and site of neovascularisation, and to correlate BCVA and IS/OS layer status (present or disrupted/absent) at the fovea and at the CNV site. To quantify inter-grader concordance concerning the width of area of foveal sparing as measured with FAF and SD-OCT and the measurement of GA area, Cohen k coefficients for the reliability of nominal data,[7], the k′ coefficient for pooled classification proportions[8] and the k″ coefficient adjusted for prevalence according to Byrt *et al*[9] were computed. The chosen level of statistical significance was $p<0.05$.

RESULTS

Demographics and clinical data of the study population

Twenty-one treatment-naive eyes of 21 consecutive patients (4 men, 17 women, mean age 86.9±1.6 years) with CNV complicating GA due to AMD met the inclusion criteria and were included in the analysis. Most fellow eyes also presented GA without CNV (17 out of 21); four fellow eyes presented active or fibrovascular CNV. Clinical data are summarised in tables 1 and 2.

All eyes presented a type 2 CNV (sub-neurosensory, well delineated, classic or visible on FA) (figures 1 and 2), except 1/21 eyes that showed a type 1 CNV (sub-RPE, indistinct or occult on FA) (figures 3 and 4). In 12/21 eyes, the CNV was located in the sub/juxtafoveal area (figures 1 and 2), while in 9/21 eyes it was extrafoveal (figures 1 and 2). Patients received a mean of 5.0±0.87 (range 1–20) intravitreal ranibizumab injections during 24 months. No injection-related complications such as

Table 1 Clinical data at baseline and 24-month follow-up visit of 21 eyes with CNV complicating GA due to age-related macular degeneration

	Baseline	Month 24	p Value
BCVA (logMAR)	0.73±0.05	0.88±0.08	0.01
GA area ($\mu m^{2)}$	5613.6±896.9	8956.1±1268	0.003
CNV GLD (μm)	844.8±169.0	531.2±168.6	0.02
Retinal thickness at CNV (μm)	252.2±13.0	187.5±14.1	<0.001
CMT (μm)	307.3±20.5	256.1±13.1	0.01

BCVA, best-corrected visual acuity; CMT, central macular thickness; CNV, choroidal neovascularisation; GA, geographic atrophy; GLD, greatest linear dimension; logMAR, logarithm of the minimum angle of resolution.

Table 2 Demographics and response to intravitreal ranibizumab injections in 21 patients with choroidal neovascularisation complicating GA due to age-related macular degeneration

Case	Age (years)	Gender	BCVA, baseline (ETDRS letters)	BCVA, 24 months (ETDRS letters)	FAF GA area, baseline (μm^2)	FAF GA area, 24 months (μm^2)
#1	86	F	48	42	4500	8916
#2	87	F	47	43	5322	10020
#3	88	F	47	45	5898	9920
#4	89	F	49	43	4908	9550
#5	85	F	49	40	6131	9210
#6	85	F	50	40	5622	9710
#7	87	F	43	58	5610	8380
#8	85	M	46	41	6360	9595
#9	88	F	51	34	5980	7665
#10	86	F	48	37	6162	10832
#11	87	F	44	42	5829	9230
#12	85	M	50	32	3232	5820
#13	87	F	47	39	5426	7280
#14	90	F	45	38	4532	8190
#15	86	F	48	42	6702	9490
#16	85	F	49	41	6415	10650
#17	85	M	47	41	7504	9632
#18	89	M	50	39	5813	8910
#19	89	F	47	40	5040	7710
#20	88	F	51	41	5700	10200
#21	89	F	51	40	5192	7170

BCVA, best-corrected visual acuity; ETDRS, early treatment diabetic retinopathy study; FAF, fundus autofluorescence, GA, geographic atrophy.

cataract, retinal detachment, or endophthalmitis were observed during the study period.

Baseline BCVA (0.73±0.05 logMAR (47.9±2.2 ETDRS letters)) improved but not significantly at the 3-month follow-up (0.66±1.2 logMAR (52±3.2 ETDRS letters); p>0.05), but worsened at the 24-month follow-up visit (0.88±0.08 logMAR (41.0±1.8 ETDRS letters); p=0.01). Correlation between baseline and 24-month follow-up BCVA was statistically significant (R=0.7, p<0.001), correlation of 24-month BCVA with patient's age was R=0.1, p=0.5, while correlation between number of injections and 24-month BCVA was R=0.4, p=0.02. BCVA reduction at 24 months was significantly correlated with both subfoveal CNV and extrafoveal CNV (p<0.001).

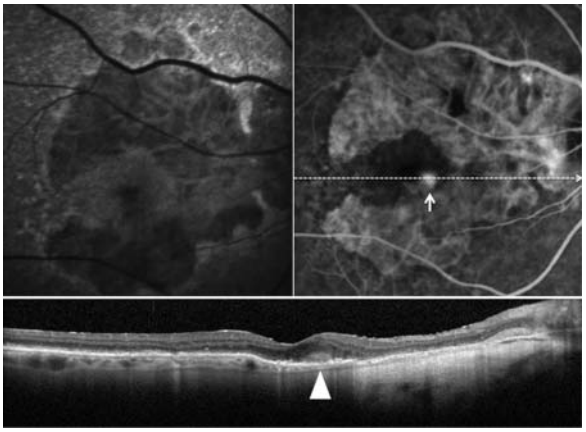

Figure 1 Fundus autofluorescence (FAF), fluorescein angiography (FA) and spectral-domain optical coherence tomography (SD-OCT) of case #7 at baseline. Right eye FAF shows a large area of foveal sparing geographic atrophy due to age-related macular degeneration (top left panel). FA shows late leakage from the juxtafoveal type 2 (visible) choroidal neovascularisation (CNV) (top right panel, arrow). SD-OCT shows exudative retinal changes and retinal thickening associated with the CNV (bottom panel, arrowhead).

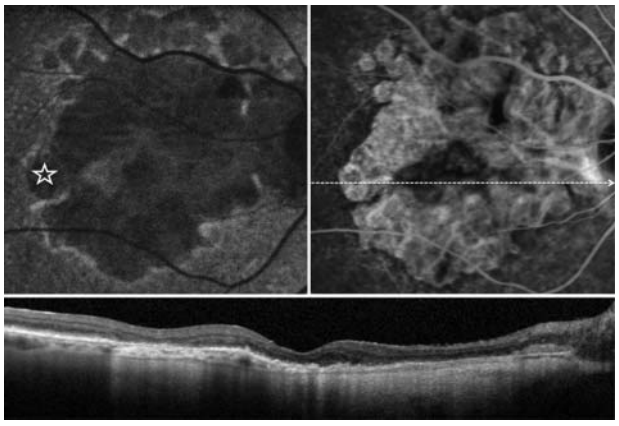

Figure 2 Fundus autofluorescence (FAF), fluorescein angiography (FA) and spectral-domain optical coherence tomography (SD-OCT) of case #7 at 24 months from baseline examination, after three intravitreal injections of ranibizumab. Right eye FAF shows enlargement, in the extrafoveal region, of geographic atrophy due to age-related macular degeneration (top left panel, asterisk). FA shows absence of leakage from the site where the choroidal neovascularisation (CNV) developed 24 months before (top right panel). SD-OCT shows the absence of exudative retinal changes and complete regression of the CNV (bottom panel).

Analysis of qualitative and quantitative parameters of GA progression

Overall, on the basis of combined FAF and SD-OCT images, 17/21 eyes (80.9%) and 15/21 eyes (71.4%) presented a foveal

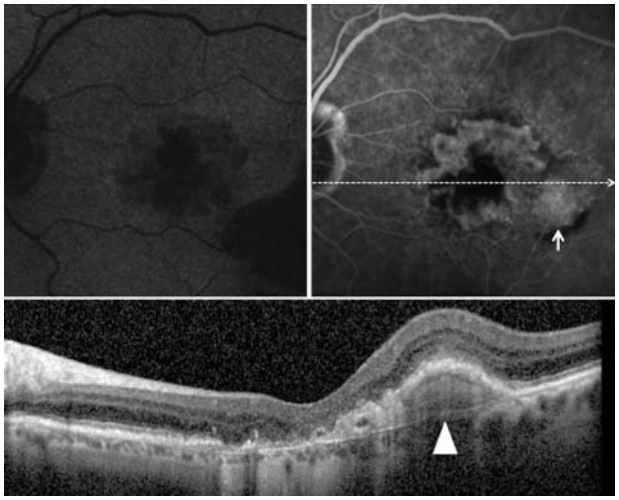

Figure 3 Fundus autofluorescence (FAF), fluorescein angiography (FA) and spectral-domain optical coherence tomography (SD-OCT) of case #3 at baseline. Left eye FAF shows a geographic atrophy due to age-related macular degeneration within the macula (top left panel). FA shows an extrafoveal type 1 (occult) choroidal neovascularisation (CNV) (top right panel, arrow). SD-OCT shows pigment epithelium detachment and retinal thickening associated with the CNV (bottom panel, arrowhead).

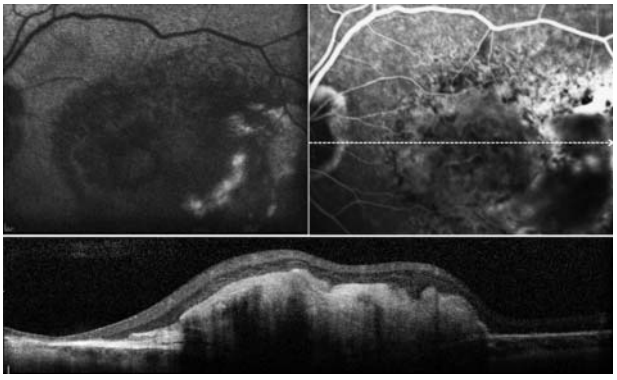

Figure 4 Fundus autofluorescence (FAF), fluorescein angiography (FA) and spectral-domain optical coherence tomography (SD-OCT) of case #3 at 24 months from baseline examination, after 20 intravitreal injections of ranibizumab. Left eye FAF (top left panel), FA (top right panel) and SD-OCT (bottom panel) show a large fibroglial scar involving the fovea and the temporal macula (the site where the CNV developed 24 months earlier).

sparing GA at baseline and at 24 months, respectively (p=0.005). Both eyes developing foveal involvement at 24 months, had subfoveal CNV at baseline (suggesting that it was due to scar of CNV). Inter-individual agreement between graders for foveal sparing as measured with FAF and SD-OCT, with consistent gradings, was significant (k=k′=0.8, p=0.001, k″=0.7). The IS/OS layer, as evaluated by SD-OCT at the fovea, was present in 4/21 eyes at baseline; in all of them, the IS/OS layer became disrupted/absent at 24 months. Correlation between IS/OS layer status (present or disrupted/absent) at the fovea and BCVA at baseline and at 24-month visit was significant (p<0.001). Eleven of 21 eyes (52.4%) developed an atrophic scar at the CNV site scans at the 24-month follow-up visits. The mean GA area, as evaluated on FAF frames, significantly increased from 5613±896 μm^2 at baseline to 8956 ±1268 μm^2 at 24 months (p=0.003). Inter-individual agreement between graders for GA area, with consistent gradings, was significant (k=k′=0.9, p=0.001, k″=0.7).

In 8/21 eyes GA progression was present on consecutive FAF frames before treatment, with a mean enlargement rate of 0.9 mm^2/year (range 0.05–1.8 mm^2/year). After treatment with ranibizumab an increased enlargement rate was noticed, although not significant (1.1 mm^2/year; range 0.07–2.1 mm^2/year, p=0.1).

Analysis of qualitative and quantitative parameters of CNV response to treatment

Overall, on SD-OCT scans passing throughout the fovea, intraretinal cystic lesions were present in 5/21 eyes (23.8%) at baseline and in 2/21 eyes (9.5%) at month 24 (p<0.001), SRF was present in 4/21 eyes (19.0%) at baseline and in 1/21 eyes (4.7%) at month 24 (p<0.001), and PED was present in 1/21 eyes (4.7%) at baseline and in 0/21 eyes at month 24 (p<0.001). Three of 21 eyes (14.3%) and 11/21 eyes (52.4%) developed a fibroglial scar at the fovea and the CNV site scans at 24 months, respectively. No significant correlation was found between IS/OS layer status (present or disrupted/absent) at the CNV site and BCVA at baseline and 24 months (p>0.05). Mean GLD, as evaluated on late phase FA frames, and retinal thickness at the CNV site and CMT, as evaluated on SD-OCT, changed from 844.8±169.0 μm, 252.2±13.0 μm and 307.3 ±20.5 μm at baseline to 531.2±168.6 μm (p=0.02), 187.5 ±14.1 μm (p<0.001) and 256.1±13.1 μm (p=0.01) at the 24-month visit.

DISCUSSION

In this study we retrospectively investigated the effects of intravitreal ranibizumab injections in eyes with GA complicated by CNV. Overall, 21 eyes with GA due to AMD and newly diagnosed active CNV, were analysed with respect to morphological and functional changes over 24 months. Despite a significant reduction of CNV activity, a reduction of BCVA was present at the 24-month visit (p=0.01). To the best of our knowledge, there are no published data on the management of patients showing the coexistence of the two forms of advanced AMD in the same eye.

In the MARINA trial,[4] and the ANCHOR trial,[5] the final mean BCVA at 24 months improved by 7.2 letters, and 10.7 letters, respectively, after monthly intravitreal injections of ranibizumab. In the current study, using a variable-dosing regimen, mean BCVA at 24 months decreased by eight letters, suggesting less favourable functional outcomes in the treatment of AMD eyes with CNV complicating GA by intravitreal ranibizumab injections. Similarly, less favourable functional outcomes appeared in the current study, compared with the MARINA trial, as regards clinically significant improvement in BCVA, defined as a gain of 15 or more letters (4.76% of eyes, and 34% of eyes, respectively), and decrease of 15 or less letters (47.6% of eyes, and 91% of eyes, respectively). Our functional outcomes also look less favourable when compared with the PrONTO study,[10] in which the final mean BCVA at 24 months improved by 11.1 letters, after a variable-dosing regimen of intravitreal ranibizumab, compared with the six letters' decrease of the current study. Moreover in the PrONTO study, 97.5% of eyes avoided a 15-letter BCVA decrease (47.6% of eyes in the current study), and 43% of eyes gained at least 15 letters of BCVA (4.76% of eyes in the current study). Interestingly, in the current series, patients received fewer intravitreal ranibizumab injections compared with the PrONTO study (5.0 and 9.9, respectively).

In the study of Rothenbuehler *et al*,[11] similarly to the current series, patients received one injection of ranibizumab followed by a pro-re-nata regimen. In their prospective analysis, the authors found that after 24 months and a mean of 9.9 intravitreal ranibizumab injections, 30% of eyes gained >15 letters, and 55% of eyes lost or gained <15 letters. Therefore, our functional outcomes appear less favourable than those of Rothenbuehler *et al*.[11]

Nonetheless, in our study, we found an improvement in both qualitative and quantitative morphological parameters of CNV activity, from baseline to 24 months. A significant reduction of intraretinal cystic lesions, SRF and PED was present at the 24-month visit. GLD, CMT and CNV thickness also significantly reduced at the 24-month visit. Therefore, the less favourable functional outcomes of our study (despite overall good morphological outcomes), compared with previous studies of intravitreal ranibizumab injections for exudative AMD, might be due to the intervening atrophic changes secondary to GA. In fact, an overall disruption of the IS/OS layer at the fovea and a significant increase of the GA area were present at the 24-month visit. Moreover, a high correlation between baseline and the 24-month follow-up BCVA was found, possibly suggesting an important role of pre-existing atrophy in the BCVA response.

The significant increase in GA area at month 24 in our series may simply represent natural disease progression. However,

based on the data from selected eyes (when previous FAF before the advent of CNV were available), GA progression rate seems increased after anti-VEGF treatment. These data, together with recently published findings from the Comparison of Age-related Macular Degeneration Treatments Trials CATT study,[12] suggest that progression of GA may be somehow related to the anti-VEGF treatment.

In the current series, improvement in qualitative and quantitative parameters of CNV activity were achieved by means of far less intravitreal injections of ranibizumab over 24 months compared with previous studies.[10 11] This might be due to a reduced expression of VEGF in the retina, responsible for less CNV activity.[13] In GA, a possible mechanism suggested for CNV development is the over-production of VEGF by the RPE following the choriocapillaries degeneration that triggers choroidal neovascularisation and wet AMD. However, the overall production of VEGF would be limited by RPE cells loss associated with GA. Consequently, fewer intravitreal injections of ranibizumab would succeed in determining regression of CNV and associated exudative changes.

Our study has several limitations, mainly due the retrospective nature of the analysis, and the small number of studied eyes. Moreover, the absence of a control group does not allow evaluation of the possible effects of anti-VEGF treatment on GA progression. Further investigations are needed to improve our knowledge regarding the efficacy and safety of intravitreal ranibizumab in the management of CNV complicating GA.

In conclusion, intravitreal ranibizumab injections may represent a valuable therapeutic option for CNV complicating GA. Good morphological outcomes are achieved with less treatments compared with exudative AMD. Functional outcomes might be limited by the intervening atrophic changes secondary to GA.

Contributors GQ, EHS: design and conduct of the study; GQ, NM, FC, RF: collection, management, analysis; GQ, EHS: interpretation of the data; GQ, RF, EHS: preparation; GQ, EHS: review, or approval of the manuscript.

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Competing interests None.

Patient consent Obtained.

Ethics approval French Society of Ophthalmology Ethics Committee approval was obtained for the retrospective review of data.

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