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Intravitreal anti-VEGF therapy for extrafoveal macular neovascularisation secondary to age-related macular degeneration: five-year results in a tertiary centre

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OBJECTIVES: To assess the long-term efficacy of intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapy on best-corrected visual acuity (BCVA) and foveal morphology in patients with extrafoveal macular neovascularisation (MNV) secondary to age-related macular degeneration (AMD) over five years.

METHODS: A total of 104 eyes with treatment-naïve extrafoveal MNV treated with intravitreal anti-VEGF injections were analysed retrospectively. BCVA was assessed at baseline and annually for five years. Central foveal thickness (CFT), intraretinal fluid (IRF), subretinal fluid (SRF), pigment epithelial detachments (PED), subretinal hyperreflective material (SHRM), and foveal atrophy (incomplete/complete retinal pigment epithelium and outer retinal atrophy (iRORA/cRORA))—were documented.

RESULTS: After five years, 46% of the eyes had unchanged or improved vision by one or more lines, whereas mean BCVA declined from 0.28 ± 0.20 logMAR at baseline to 0.50 ± 0.49 logMAR after five years ($p = 0.016$). CFT, and the prevalence of IRF and SRF decreased significantly ($p < 0.001$), while iRORA ($p = 0.041$), and cRORA ($p < 0.001$) increased by year five. Presence of cRORA was associated with worse five-year BCVA ($p < 0.001$).

CONCLUSION: Anti-VEGF therapy for extrafoveal MNV secondary to AMD stabilised or improved BCVA in approximately half of the patients; however, mean BCVA declined after five years. Long-term functional benefits were limited due to morphological changes in the macula, such as subfoveal atrophy.

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INTRODUCTION

Neovascular age-related macular degeneration (nAMD) is the leading cause of vision impairment in elderly individuals in industrialised countries, particularly when macular neovascularisation (MNV) involves the fovea [1–3]. MNV can result in exudation, subretinal haemorrhages, fibrosis, and macular atrophy resulting in progressive and irreversible vision loss at advanced stages.

Trials on photodynamic therapy (PDT) with verteporfin and intravitreal anti-vascular endothelial growth factor (VEGF) therapy demonstrated efficacy in managing subfoveal nAMD. However, no randomised controlled clinical trial has focused on extrafoveal MNV [4–12]. The Macular Photocoagulation Study (MPS) group conducted the only prospective randomised trial investigating the treatment effects of laser photocoagulation on extrafoveal MNVs during the 1980s and 1990s [13, 14]. These studies provide valuable insights but may now be outdated given the availability of anti-VEGF agents for intravitreal therapy.

Subfoveal and juxtafoveal MNV pose a significant threat to visual function due to their direct impact on foveal morphology. In contrast, eyes with extrafoveal MNV in nAMD, accounting for about 5–8% of all MNVs in nAMD, usually present with better

visual acuity and may have a more favourable prognosis, provided the fovea remains unaffected or only minimally involved [15–18]. Despite anti-VEGF therapy now being the standard of care for MNV secondary to nAMD, PDT and laser photocoagulation remain rarely used alternatives for extrafoveal lesions [19–23]. However, robust data regarding the long-term effects of anti-VEGF therapy in extrafoveal MNV are scarce, leaving a significant gap in the current literature [24, 25]. This study aims to report the functional and morphological outcomes of intravitreal anti-VEGF therapy for extrafoveal MNV secondary to nAMD in a tertiary centre over a five-year period.

METHODS

Study design and patient selection

This large retrospective study analysed data from treatment-naïve eyes with newly diagnosed, extrafoveal MNV secondary to nAMD [13, 26]. Patients were treated at the Department of Ophthalmology, University of Tübingen, Germany, between May 2009 and October 2019. Fluorescein angiography (FA) images from over 3500 consecutive patients with AMD were retrospectively reviewed to identify cases with extrafoveal MNV. A senior retina specialist (FG) assessed the type and localisation of the MNV in respect to the inclusion criteria. The inclusion criteria were: 1—age ≥ 50

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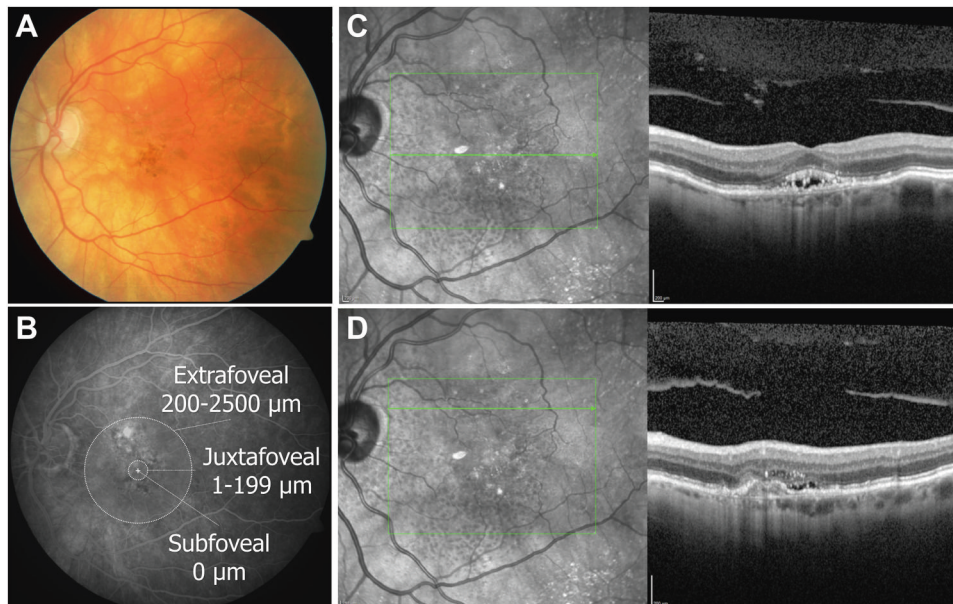


Fig. 1 Multimodal imaging of extrafoveal MNV. **A** Colour fundus photograph showing alterations in the retinal pigment epithelium and small haemorrhages. **B** Midphase of the fluorescein angiography delineates the extrafoveal localisation of the MNV superonasal to the fovea. **C** Horizontal OCT scan through the fovea shows subretinal fluid and intraretinal hyperreflective foci. **D** Horizontal OCT scan through the MNV lesion shows retinal thickening, RPE detachment, intra- and subretinal fluid, intra- and subretinal hyperreflective foci. MNV macular neovascularisation, RPE retinal pigment epithelium, FA fluorescein angiography, OCT optical coherence tomography.

years; 2—diagnosis of nAMD confirmed by clinical examination and ancillary imaging [26]; 3—extrafoveal MNV confirmed by FA; 4—follow-up of at five years; 5—available optical coherence tomography (OCT) at baseline and all follow-up examinations.

Exclusion criteria were: 1—subfoveal, juxtafoveal or juxtapapillary MNV; 2—previous treatment of nAMD; 3—high myopia (≥ -6 dpt); 4—MNV secondary to conditions other than nAMD (e.g. high myopia, trauma, angioid streaks, central serous chorioretinopathy); 5—ocular comorbidities affecting the macular morphology (e.g., diabetic maculopathy, retinal vein occlusion, vitreomacular interface diseases); 6—polypoidal choroidal vasculopathy (PCV); 7—amblyopia; 8—previous retinal surgery.

All patients underwent comprehensive routine ophthalmological evaluations, including BCVA, slit-lamp biomicroscopy, dilated funduscopy, and multimodal imaging (Fig. 1) using FA (digital fundus camera, Carl Zeiss Meditec AG, Jena, Germany), and OCT (SD-OCT; Spectralis, Heidelberg Engineering, Germany) imaging of the macula.

Extrafoveal MNV was defined as MNV with its border on the foveal side located between 200 μm and 2500 μm from the centre of the foveal avascular zone [13]. The distance of the foveal border of the MNV from the centre of the fovea was measured using FA imaging and corroborated with OCT data (Fig. 1). MNV subtypes (types 1, 2, or 3) were classified based on FA and OCT imaging.

BCVA was obtained as Snellen equivalent and converted to the logarithm of minimum angle of resolution (logMAR) for statistical analysis. Morphological characteristics assessed were central foveal thickness (CFT), intraretinal fluid (IRF), subretinal fluid (SRF), pigment epithelium detachment (PED), subretinal hyperreflective material (SHRM), and atrophy of the retinal pigment epithelium and outer retinal layer atrophy (RORA) within the central 400 μm subfield of the macula. Morphological criteria definitions of the Consensus Nomenclature for Reporting Neovascular Age-Related Macular Degeneration Data Study group were used [26]. Subfoveal atrophy was categorised as incomplete (iRORA) or complete (cRORA) based on specific OCT features [27, 28].

All patients received three monthly doses of intravitreal anti-VEGF therapy initially, followed by pro re nata (PRN) or treat and extend (TAE) strategy. The choice of anti-VEGF agent (ranibizumab 0.5 mg (Lucentis[®], Novartis, Basel, Switzerland), aflibercept 2 mg (Eylea[®], Bayer, Leverkusen, Germany), bevacizumab 1.25 mg (Avastin[®], Roche, Basel, Switzerland)) and the therapy regimen after the upload phase (PRN or TAE) was at the discretion of the treating physician. This reflects real-world clinical practice and enhances the generalisability of the findings. A switch to an alternative anti-VEGF agent was performed in cases of suboptimal

therapeutic response, as evidenced by persistent intraretinal and/or subretinal fluid on OCT. The number of intravitreal injections received by each patient over the five-year period was recorded.

Statistical analysis

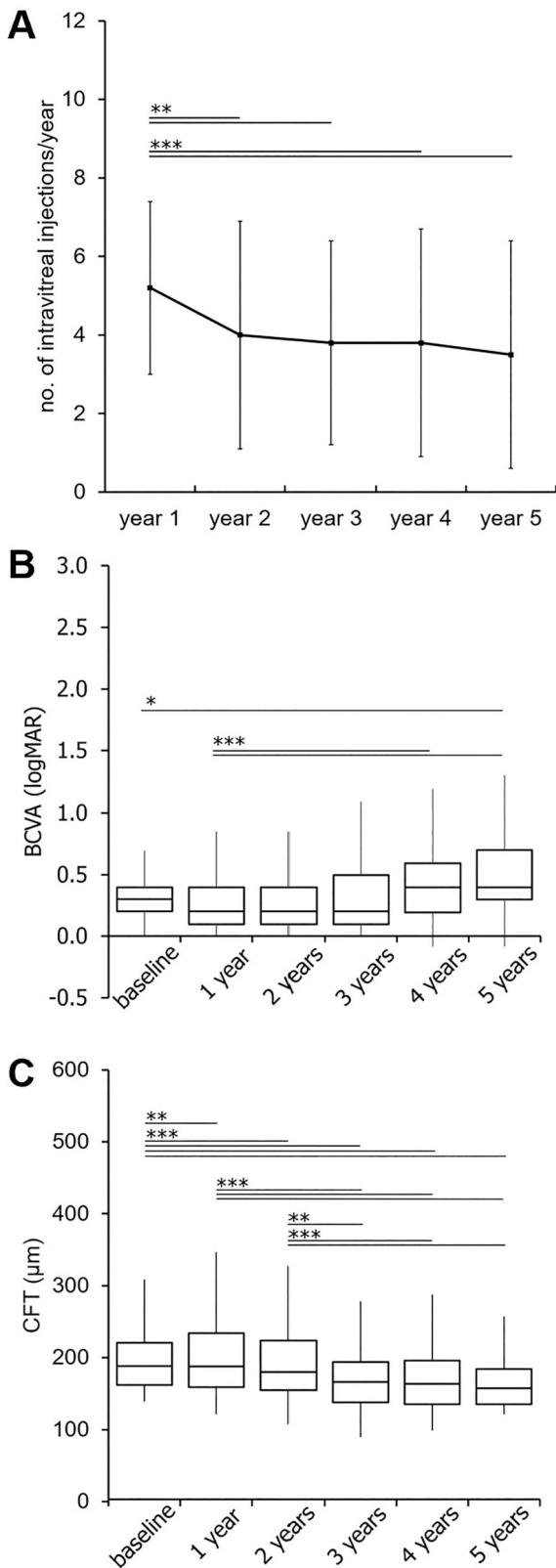
Statistical analyses were conducted using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp, Armonk, NY). Normality of continuous variables was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Categorical variables were expressed as frequency (n) and percentages (%), while continuous variables were expressed as mean (\pm standard deviation), median, and range (minimum-maximum). Chi Square, Cochran's Q, and McNemar tests were used to detect changes in morphological features across the five years and between baseline and five years, respectively. The Kruskal-Wallis test was used to compare the number of injections from year to year. The Friedman test was employed to evaluate changes in BCVA and CFT over time. Post-hoc pairwise comparisons were adjusted using Bonferroni correction to control for multiple comparisons. Multiple linear regression models were applied to identify factors influencing BCVA at baseline and year five. Predictor variables included age, gender, baseline BCVA, CFT, and morphological features such as IRF, SRF, PED, SHRM, and iRORA/cRORA. The distance between the MNV's posterior edge and the centre of the foveal avascular zone was also considered. A p -value of $p \leq 0.05$ was considered statistically significant for all tests.

Ethics approval

This study adhered to the tenets of the Declaration of Helsinki. Ethical approval was obtained from the institutional ethics committee of the University Hospital Tübingen before the analysis (project number: 626/2024BO2).

RESULTS

A total of 104 eyes of 93 treatment-naïve patients with extrafoveal MNV secondary to nAMD were included in this study. The mean \pm SD age of the patients was 76.9 ± 6.6 years. The majority of patients (59.1%) were female. Among the included eyes, 52 (50.0%) were right eyes. A total of 82 patients (88.2%) presented with unilateral and 11 patients (11.8%) with bilateral extrafoveal MNV.



At baseline, 69 eyes (66.3%) were phakic and 35 eyes (33.7%) pseudophakic, with the number of pseudophakic eyes increasing to 63 (60.6%) after five years. The mean distance of the foveal border of MNV from the centre of the foveal avascular zone was $787.4 \pm 273.9 \mu\text{m}$. Type 1 was the most common MNV subtype (62

Fig. 2 Treatment intensity, BCVA and CFT over the 5-year study period. **A** Mean number of intravitreal injections per year. Injection frequency peaked in year 1 and declined significantly thereafter, stabilising at approximately four injections per year. **B** Best-corrected visual acuity (BCVA, logMAR). A significant decline in BCVA was observed between baseline and five-year follow-up. **C** Central foveal thickness (CFT, μm). CFT significantly decreased within the first three years and remained stable thereafter. Values are presented as **(A)** mean \pm standard deviation, and as **(B, C)** box-and-whisker plots, showing minimum, lower quartile, median, upper quartile, and maximum). Asterisks denote statistical significance: * $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$.

eyes (59.6%)) followed by type 3 MNV (24 eyes (23.1%)) and type 2 MNV (18 eyes (17.3%)). Patients received a mean of 20.3 ± 10.5 (range: 3–57) anti-VEGF injections per eye over the five-year follow-up period. Bevacizumab was used in 57 eyes (54.8%) in the upload phase, ranibizumab in 39 eyes (37.5%) and aflibercept in 8 eyes (7.7%). The mean number of injections administered per year decreased significantly in the years following the first year of treatment (year one: 5.2 ± 2.2 injections; year two: 4.0 ± 2.9 injections ($p = 0.006$); year three: 3.8 ± 2.6 injections ($p = 0.002$); year four: 3.8 ± 2.9 injections ($p < 0.001$); year five: 3.5 ± 2.9 injections ($p < 0.001$)) (Fig. 2).

Mean baseline BCVA at baseline was 0.28 ± 0.20 logMAR (20/40 Snellen) and 0.50 (20/63 Snellen) ($p = 0.016$) after five years (Fig. 2). Compared to baseline, no significant change in mean BCVA was observed for the first four years. After five years 29 eyes (27.9%) had improved BCVA by one or more lines, 56 eyes (53.8%) experienced a decline, and 19 eyes (18.3%) maintained stable vision. Among the 56 eyes with a BCVA decline, 19.6% lost one line, 30.4 two lines, and 50.0% three or more lines.

Seventy-five eyes (72.1%) had a relatively good baseline BCVA of 0.3 logMAR ($\geq 20/40$ Snellen)—an important threshold for a good BCVA with legal and functional implications (in many countries minimum BCVA required to drive, required by several occupations, clinical benchmark to assess moderate visual impairment). Forty-six eyes (41.8%) had a baseline BCVA of ≤ 0.2 logMAR ($\geq 20/32$ Snellen) and 25 eyes (24.0%) had a BCVA of 0.1 or 0.0 . After five years only 36 eyes had a BCVA of ≤ 0.3 .

A sub-analysis of BCVA in respect to the MNV subtypes revealed significantly worse mean baseline BCVA (0.39 ± 0.22 logMAR) for type 3 compared to type 1 (0.25 ± 0.20 logMAR, $p = 0.020$) and type 2 (0.23 ± 0.14 logMAR, $p = 0.043$). However, the mean BCVA at five years did not show significant differences between the MNV subtypes ($p = 0.123$) (Table 1). In MNV type 1, 30 eyes (48.4%) had stable or improved BCVA after five years, while 32 eyes (51.6%) decreased in BCVA. Type 2 was associated with a higher portion of eyes with BCVA decline than other MNV subtypes (BCVA stable/improved: 6 eyes (33.3%), BCVA decline: 12 eyes (66.6%)). Half of the patients (12 eyes (50.0%)) with type 3 MNV showed BCVA deterioration.

Mean CFT decreased significantly from $255.5 \pm 91.2 \mu\text{m}$ at baseline to $213.6 \pm 104.2 \mu\text{m}$ ($p = 0.003$) after the first year and to $165.7 \pm 84.5 \mu\text{m}$ after five years ($p < 0.001$) (Fig. 2). Yearly data for BCVA and morphological parameters are provided in Supplemental Table 1.

Over the five-year follow-up period, the prevalence IRF decreased notably, from 27.9% at baseline to 12.5% by year five ($p = 0.006$), and likewise SRF showed a significant reduction, from 50.0% at baseline to 11.5% at year five ($p < 0.001$). The presence of PED remained stable over time, with no significant change observed across the five years ($p = 0.267$). Also, the prevalence of SHRMs increased, but not significantly, from 19.2% at baseline to 26.9% at year five ($p = 1.000$). In contrast, subfoveal atrophy in terms of iRORA/cRORA was found at baseline in 5.8%/1.9% of the

Table 1. Baseline and 5-year clinical and morphological characteristics of eyes with MNV types 1, 2, and 3. Data included BCVA, CFT, and prevalence of IRF, SRF, PED, SHRM, and atrophy (iRORA, cRORA).

MNV subtype	MNV type 1		MNV type 2		MNV type 3		Differences between MNV-types		Total	
	baseline	5 yrs	p	baseline	5 yrs	p	baseline	5 yrs	baseline	5 yrs
No. of eyes, n (%)	62 (59.6%)			18 (17.3)			24 (23.1)		104 (100)	
visit	baseline	5 yrs	p	baseline	5 yrs	p	baseline	5 yrs	baseline	5 yrs
BCVA (logMAR, mean ± SD)	0.25 ± 0.20	0.44 ± 0.48	0.001^a	0.23 ± 0.14	0.57 ± 0.49	0.007^a	0.39 ± 0.22	0.61 ± 0.52	0.28 ± 0.20	0.50 ± 0.49
									0.013^b / 0.123 ^b	0.016^a
CFT (µm, mean ± SD)	244 ± 88	173 ± 87	<0.001^a	255 ± 86	160 ± 45	0.001^a	287 ± 101	151 ± 100	255 ± 91	165 ± 85
									0.174 ^b / 0.063 ^b	<0.001^a
IRF (n (%))	8 (12.9)	5 (8.1)	0.549 ^c	2 (11.1)	2 (11.1)	1.000 ^c	19 (79.2)	6 (25.0)	29 (27.9)	13 (12.5)
									0.002^c	0.006^c
									<0.001^d / 0.101 ^d	
SRF (n (%))	32 (51.6)	8 (12.9)	<0.001^c	12 (66.7)	4 (22.2)	0.021^c	8 (33.3)	0 (0)	52 (50.0)	12 (11.5)
									0.094 ^d / 0.072 ^d	<0.001^c
PED, (n (%))	7 (11.3)	6 (9.7)	1.000 ^c	0 (0)	0 (0)	-	5 (20.8)	1 (4.2)	12 (11.5)	7 (6.7)
									0.112 ^d / 0.300 ^d	0.383 ^c
SHRM, (n (%))	12 (19.4)	15 (24.2)	0.607 ^c	6 (33.3)	6 (33.3)	1.000 ^c	2 (8.3)	7 (29.2)	20 (19.2)	28 (26.9)
									0.126 ^d / 0.715 ^d	1.000 ^c
iRORA (n (%))	3 (4.8)	8 (12.9)	0.182 ^c	2 (11.1)	3 (16.7)	1.000 ^c	1 (4.2)	5 (20.8)	6 (5.8)	16 (15.4)
									0.510 ^e / 0.646 ^e	0.041^c
cRORA (n (%))	2 (3.2)	13 (21.0)	<0.003^c	0 (0)	6 (33.3)	0.031^c	0 (0)	13 (30.8)	2 (1.9)	32 (30.8)
									1.000^e / 0.014^e	<0.001^c

P-values represent within-group comparisons over time, and between-group comparisons across MNV types.

Significant p-values are shown in bold.

MNV macular neovascularisation, BCVA best-corrected visual acuity, CFT central foveal thickness, IRF intraretinal fluid, SRF subretinal fluid, PED pigment epithelium detachment, SHRM subretinal hyperreflective material, iRORA/cRORA incomplete/complete retinal pigment epithelium and outer retinal atrophy.

^aWilcoxon Signed Rank-Test.

^bKruskal-Wallis-Test.

^cMcNemar-test.

^dChi-squared test comparing differences in the prevalence of morphological characteristics between MNV subtypes at baseline (p^{baseline}) or five year-examination (p^{5yrs}).

^eFisher-Freeman-Halton Exact Test.

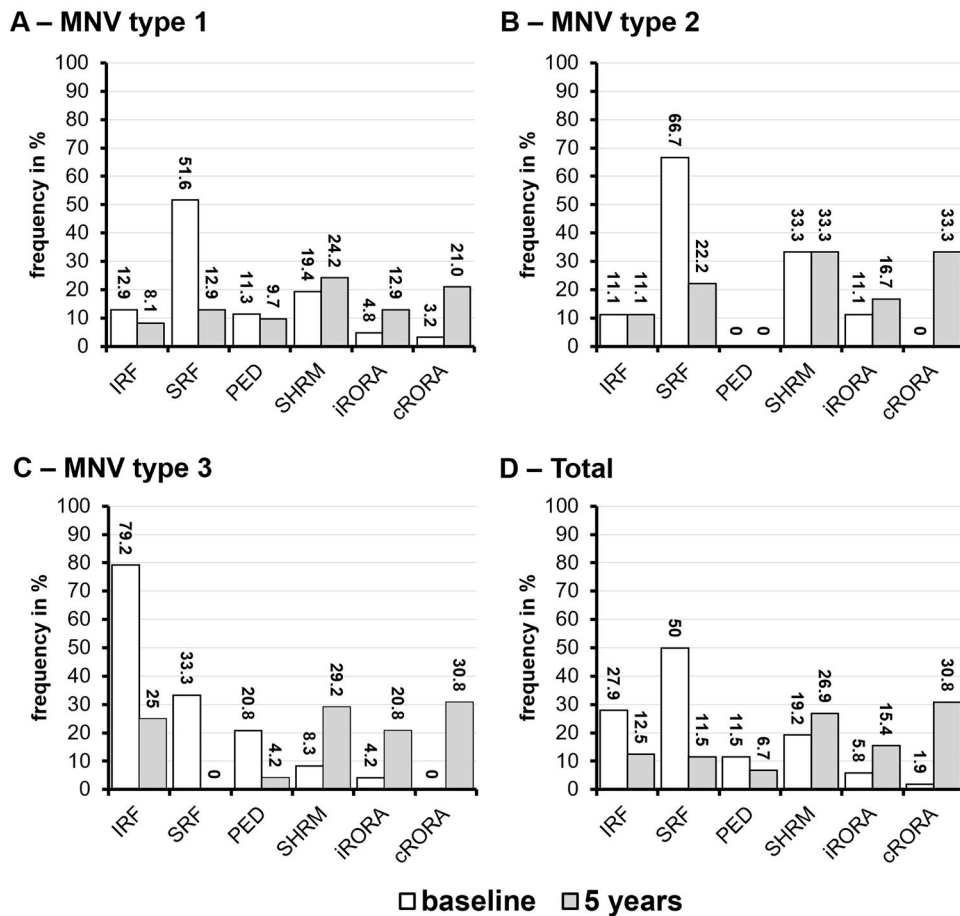


Fig. 3 Morphological parameters at baseline (white bars) and after 5 years (grey bars) stratified by MNV subtype. A MNV type 1, **B** type 2, **C** type 3, and **D** all types combined. Assessed features include IRF, SRF, PED, SHRM, iRORA, and cRORA. MNV macular neovascularisation, IRF intraretinal fluid, SRF subretinal fluid, PED pigment epithelium detachment, SHRM subretinal hyperreflective material, iRORA/cRORA incomplete/complete retinal pigment epithelium and outer retinal atrophy.

eyes and 15.4%/30.8% at the five-year follow-up ($p = 0.041/ p < 0.001$) (Fig. 3).

Factors significantly associated with worse baseline BCVA included higher CFT ($p = 0.013$), presence of IRF ($p = 0.037$), SHRM ($p = 0.030$), and cRORA ($p = 0.001$). SRF, PED, iRORA and the distance of the MNV to the fovea did not have a significant impact on baseline BCVA.

Five-year mean BCVA was significantly associated with cRORA ($p < 0.001$), but not with iRORA ($p = 0.612$). SHRM was not significantly correlated with five-year BCVA ($p = 0.215$). None of the other morphological parameters showed a significant association with the mean BCVA at five-year (Fig. 4).

DISCUSSION

This study showed stabilisation or improvement of the BCVA in half of the patients with extrafoveal MNV secondary to AMD under anti-VEGF therapy after five years. However, the observed decline in mean BCVA in the whole cohort underlined the chronic, progressive nature of AMD despite ongoing treatment. The presented results align with prior studies, confirming the efficacy of anti-VEGF agents in managing exudation and delaying visual deterioration, but ultimately treatment cannot completely halt the progression of nAMD in the majority of patients [10, 25, 29–31].

Before the introduction of anti-VEGF therapies, thermal laser photocoagulation and PDT were the primary treatment alternatives for extrafoveal MNV. The Macular Photocoagulation Study

(MPS) demonstrated that thermal laser photocoagulation reduces the risk of moderate and severe vision loss in patients with extrafoveal and juxtafoveal MNV by ablating lesions [14]. However, central scotomas caused by laser-induced retinal damage, and the high recurrence rate of MNV frequently led to subfoveal progression and limited the beneficial effect of this treatment [14, 32]. While PDT was initially promising in slowing MNV progression and stabilising vision, its long-term outcomes remained suboptimal [7, 21, 33]. PDT was unable to prevent significant functional decline and MNV recurrence in many patients [34]. Comparative studies confirmed that PDT was less effective than anti-VEGF therapy in preserving vision [7, 35, 36].

The introduction of anti-VEGF therapies revolutionised the management of nAMD. By inhibiting VEGF, these agents effectively reduce exudation and control disease activity without causing collateral damage to retinal structures, which was noted in thermal photocoagulation or PDT. Pivotal studies showed efficacy of anti-VEGF therapy in maintaining or improving vision in nAMD patients [7, 8, 11, 29, 37]. But, extrafoveal MNVs were not specifically addressed in these studies.

To our knowledge, there is only a single study that compared thermal laser photocoagulation of extrafoveal MNV with intravitreal anti-VEGF injections showing good efficacy of ranibizumab while laser photocoagulation was associated with visual acuity deterioration and high recurrence rates [38]. This case series included only 13 eyes in the subgroup treated with thermal laser photocoagulation and 11 eyes treated with intravitreal ranibizumab with a limited follow-up of 23.6 ± 2.26

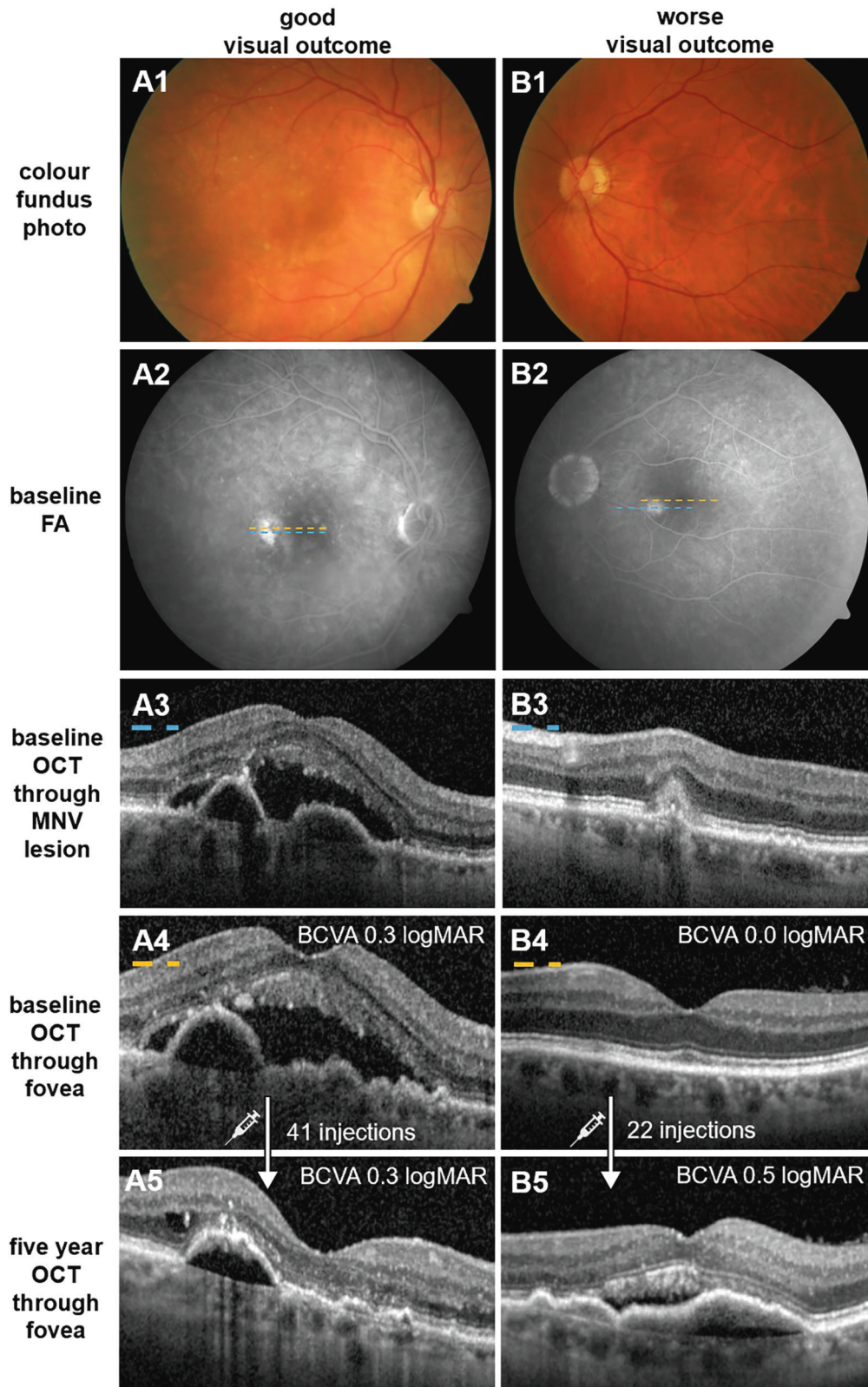


Fig. 4 Representative cases of extrafoveal MNV treated with intravitreal anti-VEGF therapy. Good visual outcome (**A**): An 86-year-old female with MNV located temporal-inferior to the fovea in the right eye. The lesion's central border was 751 μm from the foveal centre. Baseline BCVA of 0.3 logMAR (20/40 Snellen) was maintained over five years with 41 intravitreal anti-VEGF injections. Worse visual outcome (**B**): A 70-year-old male with MNV located nasal-inferior to the fovea in the left eye. The lesion's central border was 775 μm from the foveal centre. Although initial BCVA was 0.0 logMAR (20/20 Snellen), it declined to 0.5 logMAR (20/63 Snellen) after five years despite 22 intravitreal injections. Panels show: A1/B1—colour fundus photography at baseline; A2/B2—FA at baseline; A3/B3—baseline OCT through the MNV lesion (blue dashed line in FA); A4/B4—baseline OCT through the fovea (yellow dashed line in FA); A5/B5—OCT through the fovea after five years of treatment. MNV macular neovascularisation, BCVA best-corrected visual acuity, FA fluorescein angiography, OCT optical coherence tomography.

and 19.1 ± 9.74 months, respectively. Other case series with smaller cohorts and shorter observation periods have reported the efficacy of anti-VEGF therapy in extrafoveal MNV, yielding results that align with our findings [24, 39]. Our data revealed preserved or improved vision after five years in a significant subset of eyes. However, mean BCVA decreased slowly in half of the patients under ongoing anti-VEGF therapy over the five-year period. These results reflect the heterogenous outcomes in our cohort.²⁻⁴

As expected, patients in our study had better baseline BCVA than those reported in studies that included subfoveal MNV [39, 40]. Therefore, the decline we observed may not only reflect poor treatment efficacy, but also the limited potential for improvement in patients who already start with higher baseline BCVA [41]. In fact, many eyes in our cohort showed relatively good baseline BCVA ((72.1% with BCVA of ≤ 0.3 logMAR ($\geq 20/40$ Snellen); 41.8% with ≤ 0.2 logMAR ($\geq 20/32$ Snellen); 24.0% with 0.1 logMAR (20/25 Snellen) or better)). Because of this “ceiling effect”, their capacity for further visual improvement was restricted. As a result, even modest disease progression or treatment limitations could lead to a proportionally larger decline in mean BCVA. In contrast, patients with poorer baseline BCVA often already have more advanced retinal damage or central involvement at therapy initiation, which limits the extent of further decline. In such cases, the modest functional gains from anti-VEGF treatment may counterbalance potential losses, resulting in relatively stable or slightly improved mean BCVA. These differences in baseline BCVA contribute to the variability in outcomes observed in our study.

The type of MNV was not found to affect the outcome after five years. Although MNV type 3 had worse baseline BCVA, the five-year BCVA did not differ between MNV subtypes. However, the percentage of eyes with a decline in BCVA differed between MNV types [42]. Subfoveal atrophy (cRORA) increased in all MNV subtypes making it the only morphological parameter that is associated with the 5-year BCVA outcome. A high increase in cRORA was seen in type 3 MNV from 0 eyes (0.0%) to 13 eyes (30.8%). Interpretation of morphological changes is limited by the relatively small sample size of eyes with MNV types 2 and 3.

This study's strengths include a large cohort size and the extended follow-up duration, making it the most extensive study to date on the long-term outcomes of anti-VEGF therapy for treatment-naïve extrafoveal MNV in nAMD. However, the lack of standardised treatment protocols is a notable limitation. ICGA was performed on physician discretion in cases with suspected PCV or suboptimal response to therapy. Therefore, the presence of undetected PCV or pachychoroid neovascularisation in some eyes cannot be ruled out with certainty. Furthermore, the absence of a control group, while ethically understandable, limits comparison with alternative treatment modalities. Change of the lens status over the treatment period could also impact BCVA outcomes. However, our statistical analysis showed no significant differences in BCVA between phakic and pseudophakic patients at baseline or final follow-up. Prospective studies with standardised protocols would provide more definitive results, though the low prevalence of extrafoveal MNV presents challenges for patient recruitment. Moreover, morphological parameters were assessed on OCT scans. Autofluorescence imaging would improve the visibility of RPE-atrophy and enhance the analysis, which was not a standard procedure in this retrospective real-world study.

Our results emphasise the importance early detection and intervention for extrafoveal MNV, since baseline BCVA was a significant predictor of the long-term outcome. While anti-VEGF therapy effectively reduces the exudation and stabilises BCVA initially, its long-term functional benefits were limited for a number of patients, because of the morphological changes in the macula, such as atrophy. This highlights the need to optimise

current treatment approaches, and to explore alternatives aiming to preserve the morphological integrity of the macula.

SUMMARY

What was known before:

- Anti-VEGF therapy is effective for subfoveal MNV in AMD.

What this study adds:

- This study reports the largest long-term real-world evaluation of anti-VEGF therapy for extrafoveal MNV secondary to AMD from a tertiary centre.
- Although best-corrected visual acuity (BCVA) remained stable or improved in one half of the eyes, the overall mean BCVA declined within five years. Morphologically, reduction in CFT and foveal fluid accumulation was seen, but subretinal hyperreflective material and atrophy increased.
- While anti-VEGF is beneficial, it cannot entirely halt the progression of visual loss in extrafoveal MNV secondary to AMD.

DATA AVAILABILITY

The datasets generated and analysed during the current study are available from the corresponding author on reasonable request.

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AUTHOR CONTRIBUTIONS

Concept and design: FG, NK, DAW; Acquisition of data: FG, NK, CJG, KAD, DAW; Analysis of data and drafting of manuscript: FG, NK, CJG, KAD, DAW; Interpretation of data and critical revision of the manuscript for important intellectual content: FG, NK, CJG, KAD, DAW.

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COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL

Ethical guidelines were followed, obtaining approval from the Institutional Review Board (IRB) or Ethics Committee (project number: 626/2024B02). Patient confidentiality and data anonymisation were strictly maintained.

ADDITIONAL INFORMATION

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