Five-Year Real-World Outcomes of Occult and Classic Choroidal Neovascularization: Data From the Fight Retinal Blindness! Project

ALESSANDRO INVERNIZZI, VUONG NGUYEN, KELVIN TEO, DANIEL BARTHELMES, ADRIAN FUNG, ANDREA VINCENT, AND MARK GILLIES

• PURPOSE: To compare 5-year real-world outcomes of eyes with classic and occult choroidal neovascularization (CNV) treated with anti–vascular endothelial growth factor (anti-VEGF) injections.

• DESIGN: Retrospective analysis from a prospectively designed observational database.

• METHODS: Treatment-naïve eyes diagnosed with occult or minimally or predominantly classic CNV that commenced anti-VEGF treatment between January 2007 and December 2012 were identified from a registry of neovascular age-related macular degeneration (nAMD) treatment outcomes. Baseline characteristics, visual acuity (VA) at 5 years, change in VA, time to first inactivation, number of injections, and proportion of visits graded with active nAMD over the 5 years were compared between the 3 groups.

• RESULTS: A total of 1929 eyes from 1730 subjects (1196 occult, 289 minimally classic, and 444 predominantly classic CNV) were analyzed. Baseline VA (mean [standard deviation]) was higher in occult CNVs (56.9 [17.4] letters) than in minimally (52.9 [19.7] letters) and predominantly (49.1 [19.9] letters) classic CNVs ($P = .003$ and $P < .0001$, respectively). VA change was similar across the groups. At 5 years eyes with occult CNVs still had better VA than other CNVs. Age, lesion size, and baseline VA, but not CNV type, significantly affected final VA in the multivariate model. Predominantly classic CNVs became inactive sooner and were overall less active than other CNV types. The number of injections received was similar across the groups.

• CONCLUSIONS: Eyes with occult CNVs had overall a better VA than other CNVs. The difference in final VA was not significant after adjusting for baseline VA. Five-year outcomes and treatment patterns were not affected by the lesion type. (Am J Ophthalmol 2019;204:105–112. © 2019 Elsevier Inc. All rights reserved.)

THE DEVELOPMENT OF CHOROIDAL NEOVASCULARIzation (CNV) has a dramatic impact on the management and the prognosis of patients with age-related macular degeneration. In the 1980s and 1990s, CNV was classified according to fundus fluorescein angiographic (FFA) findings according to criteria of the Macula Photocoagulation Study Group. "Classic" CNV was characterized by an area of choroidal hyperfluorescence with well-demarcated boundaries discernible early in the fluorescein angiogram. "Occult" CNV comprised 2 forms: fibrovascular pigment epithelial detachment (PED) and late-phase leakage of undetermined source. Both forms of "occult" CNV were less discrete and leaked later during the angiogram than "classic" CNV.[1] The angiographic appearance was correlated to the location of the neovascular complex when histologic studies on excised membranes found the new vessels to be located between the Bruch membrane and the retinal pigment epithelium (RPE) in occult lesions and between the neural retina and the RPE in classic lesions.[2,3]

The advent of optical coherence tomography (OCT) over the last decade has allowed in vivo cross-sectional imaging of CNVs that has confirmed the different locations of the different neovascular complex patterns seen on angiography. Consequently, a new classification has been adopted based on anatomic location of the neovascular tissue. Type 1, 2, and 3 neovascularizations have been named to describe neovascularization underneath the RPE, underneath the retina, and within the retina, respectively.[4] Although not precise, most type 1 neovascularization correlates with "occult" CNV and most type 2 neovascularization with "classic" CNV.[5]

The classification of the CNVs has traditionally been considered important clinically, since the natural history

Accepted for publication Mar 1, 2019.

From the Eye Clinic, Department of Biomedical and Clinical Science "Luigi Sacco," Luigi Sacco Hospital, University of Milan, Milan, Italy (A.I.); The University of Sydney, Save Sight Institute, Discipline of Ophthalmology, Sydney Medical School, Sydney, New South Wales, Australia (A.I., V.N., K.T., D.B., A.F., M.G.); Singapore Eye Research Institute, Singapore National Eye Centre, Singapore (K.T.); University Hospital Zurich and University of Zurich, Zurich, Switzerland (D.B.); Westmead Hospital, Sydney, New South Wales, Australia (A.F.); Faculty of Medicine and Health Sciences, Macquarie University, Sydney, New South Wales, Australia (A.F.); and Department of Ophthalmology, New Zealand National Eye Centre, Faculty of Medical and Health Science, University of Auckland, Auckland, New Zealand (A.V.).

Inquiries to Alessandro Invernizzi, Eye Clinic, Department of Biomedical and Clinical Science "Luigi Sacco," Luigi Sacco Hospital, University of Milan, Via G. B. Grassi 74, 20157 Milano, Italy; e-mail: alessandro.invernizzi@gmail.com

0002-9394/$36.00
https://doi.org/10.1016/j.ajo.2019.03.001

of the disease and its response to certain treatments varied between the CNV types.[6,7] This was particularly true when first-line treatment of CNV was by macular photocoagulation or photodynamic therapy (PDT) with verteporfin.[8–10] The pivotal phase 3 studies of ranibizumab, an antibody against vascular endothelial growth factor (VEGF), for neovascular age-related macular degeneration (nAMD), were split into the ANCHOR study for predominantly classic CNV(classic component >50% of the lesion size),[10] which included PDT for eyes randomized to control therapy, and the MARINA study of occult lesions, which included sham-treated controls, since PDT was ineffective for these lesions.[11,12]

The significance of CNV classification has declined as anti-VEGF agents were found to be effective in treating nAMD patients regardless of the lesion type.[11–13] A recent analysis on large cohorts of patients treated with anti-VEGF agents in a randomized controlled trial (RCT), however, reported that classic CNV may have worse long-term outcomes.[14] New RCTs to test antiangiogenic drugs also list the presence of specific CNV types among their eligibility criteria.[15,16]

The current clinical relevance of classifying CNVs in nAMD eyes is uncertain. The aim of this study was to assess the real-world outcomes of eyes with nAMD according to their physician-reported FFA-based classification of CNV type in order to determine whether there are differences in visual outcomes, number of injections required, and percentage of visits at which the CNV lesion was graded as active over 5 years.

METHODS

THIS STUDY FOLLOWED THE STROBE (STRENGHTENING THE Reporting of Observational studies in Epidemiology) checklist items for reporting observational study data.[17]

• **DESIGN AND SETTING:** Data were obtained from the Fight Retinal Blindness! (FRB!) database, which prospectively tracks real-world outcomes of treatments for ocular conditions, predominantly nAMD, during routine clinical practice. The FRB! database has been endorsed by the International Consortium for Health Outcomes Measurement to track its minimum set of standardized outcome measures for macular degeneration.[18,19] Details of the FRB! database have been described previously.[18]

Institutional ethics approval was obtained from the Human Research Ethics Committees of the University of Sydney; the Royal Victorian Eye and Ear Hospital; the Royal Australian and New Zealand College of Ophthalmologists; the University Hospital, Zurich; and the Singhealth, Singapore. Ethics committees in Australia and New Zealand approved the use of "opt out" patient consent. The study adhered to the tenets of the Declaration of Helsinki. This study included patients and practices from Australia, New Zealand, Switzerland, and Singapore.

• **DATA SOURCES/MEASUREMENTS:** Demographic and clinical features were recorded at the baseline visit, including age, sex, overall lesion size measured as the greatest linear dimension (GLD), and FFA-based CNV lesion type (occult, minimally classic, predominantly classic, retinal angiomatous proliferations, polypoidal choroidal vasculopathy) as reported by the treating physician. Minimally classic CNV were defined as CNV having a classic component >0% but <50% of the lesion size. The lesion was graded as predominantly classic when the classic component was greater than 50% of its total area.[20] The number of letters read on a logarithm of the minimum angle of resolution (logMAR) visual acuity (VA) chart (best of uncorrected, corrected, or pinhole); treatment given, if any; lesion activity; and ocular adverse events were recorded in subsequent follow-up visits.[18] CNV activity was judged by the treating physician. Generally a CNV is defined as active when leakage on FFA, blood at funduscopic examination, or intraretinal/subretinal fluid or mid-reflective material is detected on OCT. The FRB! registry tracks real-world treatment outcomes. Thus, treatment decisions, such as the choice of drug and frequency and timing of treatment, were entirely at the discretion of the treating practitioners according to their experience and drug availability in their countries. From previous experience and publications, most FRB! users currently employ a treat-and-extend regimen.[21] However, it is likely that many patients were on other regimens such as pro re nata for a substantial period, since the analysis includes data from 2007, when treat-and-extend may not have been so widely used.[18]

• **PARTICIPANTS:** Treatment-naïve eyes commencing treatment with anti-VEGF for nAMD between January 1, 2007 and December 31, 2012 were considered for the analysis. Only eyes that were recorded as being affected by occult, minimally classic, or predominantly classic CNV and had received at least 3 injections in the first year of treatment were included in the study.

• **OUTCOMES:** The primary outcome was the difference in VA 5 years after starting treatment between occult, minimally classic, and predominantly classic CNVs. Secondary outcomes included baseline VA, VA change, number of injections, and the proportion of visits graded with active CNV over 5 years across the different CNV groups.

• **STATISTICAL ANALYSES:** Descriptive statistics included the mean, standard deviation, median, quartiles (Q1 and Q3), and percentages, where appropriate.

Comparison of baseline characteristics between occult, minimally classic, and predominantly classic were conducted using analysis of variance (ANOVA) followed by

pairwise comparisons. Within each group, change in VA was analyzed using paired *t* tests. Unadjusted VA at 5 years was compared across the 3 groups using ANOVA with pairwise comparisons. Adjusted VA at 5 years was compared across lesion types using multivariate mixed-effects regression models adjusted for age, baseline VA, and lesion size (fixed-effects), and clustering by patient and practice (random-effects). Five-year VA outcomes over time were visualized using locally weighted scatterplot smoothing curves for observed data and predicted values from longitudinal generalized additive models adjusted for baseline vision using all visit data, including noncompleters. Mixed-effects logistic regression models adjusted for age, baseline VA, and lesion size (fixed-effects), and clustering by patient and practice (random-effects), were used to compare the overall proportion of visits in which the lesion was graded as active. Time to first inactivation (first visit after baseline when the lesion was graded as inactive) was compared between cases and controls using a Kaplan-Meier survival analysis. Analyses of VA included the last observation carried forward of all noncompleters unless otherwise specified.

P values were adjusted for pairwise comparisons using the Holm-Bonferroni correction. All statistical analyses were conducted using R V.3.4.2 with the lme4 (V 1.1-14) package for mixed-effects regression analysis and the survival (V 2.41-3) package for Kaplan-Meier survival analysis.[22–25]

RESULTS

A TOTAL OF 2207 TREATMENT-NAÏVE EYES DIAGNOSED WITH either occult, minimally classic, or predominantly classic CNV that were started on anti-VEGF treatment between January 1, 2007 and December 31, 2012 were identified from the FRB! registry. Of these, 278 eyes were excluded because they did not receive at least 3 injections. The remaining 1929 eyes from 1730 subjects fulfilled the inclusion criteria and were enrolled into the study. Of these, 1196 (62%) were graded as having occult CNV, 289 (15%) minimally classic, and 444 (23%) predominantly classic. Five years of treatment were completed by 517 (43.2%) eyes with occult CNV, 129 (44.6%) eyes with minimally classic CNV, and 165 (37.1%) with predominantly classic CNV.

• **DEMOGRAPHIC CHARACTERISTICS:** Baseline demographic characteristics are presented in Table 1. Visual acuity at baseline was significantly different across the 3 CNV types. Occult CNVs had significantly better VA than minimally and predominantly classic CNVs ($P = .003$, and $P < .0001$, respectively). The difference in VA between minimally and predominantly classic was also significant ($P = .02$). The GLD was significantly different across the groups (all $P < .001$), with minimally classic eyes having the largest lesions, followed by occult and predominantly classic. There were more women than men in all the groups, but there were significantly more male patients in the predominantly classic compared to occult and minimally classic CNV groups. There was no difference in terms of age across the groups.

• **VISUAL OUTCOMES AT 5 YEARS:** Five-year outcomes are presented in Table 2. Mean VA increased during the first year of treatment, then slowly declined in all groups. After 5 years of treatment, the change in VA compared to baseline was not significant in any of the 3 groups (all $P > .27$). Eyes with occult CNVs had better VA at 5 years than eyes with minimally classic CNVs ($P = .06$) and predominantly classic CNVs ($P < .0001$; Figure 1). This difference was not significant after adjusting for baseline VA ($P = .36$; Figure 2). In the multivariate model, subject age, baseline GLD, and baseline VA (all $P < .0001$), but not CNV type, had a significant effect on the 5-year VA.

• **LESION ACTIVITY AND INJECTION FREQUENCY:** The time (median [Q1-Q3]) to the first grading of the CNV lesion as inactive was shortest in predominantly classic CNVs (106 [63-239] days), followed by occult (119 [64-287]) and then minimally classic (141 [84-304]) CNVs and was significantly different between CNV types ($P = .05$, Figure 3). Predominantly classic lesions were overall less active than occult (49% vs 56% of visits, $P = .009$) and minimally classic lesions (49% vs 54% of visits, $P = .006$) over the 5 years of follow-up. During the first 12 months of treatment, the proportion of visits with "active" lesions was 68% in the minimally classic group, followed by 65% in the occult and 60% in the predominantly classic group. During the second year, the group with the highest proportion of visits with "active" lesions had become occult CNVs (54%), followed by minimally classic (51%) and predominantly classic (43%). This ranking remained consistent during the following years (Figure 4A).

Injection frequency over 5 years was analyzed only for eyes completing 5 years of follow-up. The number of injections (median [Q1-Q3]) received in 5 years of treatment was 30 [22-40] in the occult group, 29 [22-37] in the minimally classic group, and 29 [23-38] in the predominantly classic group. All eyes, regardless of the lesion type, received a higher number of injections during the first year of treatment (8 [7-10] in the occult group, 8 [6-10] in the minimally classic group, and 9 [7-10] in the predominantly classic group). The number of treatments dropped to a median of 5-6 during the following years in all groups (Figure 4B).

DISCUSSION

IN THIS STUDY, WE HAVE ANALYZED THE LONG-TERM, REAL-world outcomes of nAMD eyes treated with intravitreal injections of VEGF inhibitors according to their angiographic CNV lesion type. We found that occult CNVs

TABLE 1. Baseline Features of the 3 Choroidal Neovascularization Types

	Occult	Minimally Classic	Predominantly Classic	O vs MC P Value[a]	O vs PC P Value[a]	MC vs PC P Value[a]
Eyes, n	1196	289	444			
Patients, n	1035	276	419			
Age, mean years (SD, range)	79.6 (7.9, 52-101)	79.5 (7.3, 58-98)	79.8 (7.7, 53-101)	.98	.84	.85
Sex, % male	32.9	34.6	43.7	.85	.0002*	.03*
Baseline VA, mean letters (SD)	56.9 (17.5)	52.9 (19.7)	49.2 (19.9)	.003*	<.0001*	.02*
VA ≤35 letters, %	11.3	16.3	25.5			
VA ≥70 letters, %	27.5	22.5	19.1			
Lesion size, mean μm (SD)	2551.1 (1614.9)	2984.7 (1861.9)	2165.5 (1345.6)	.0001*	.0001*	<.0001*

MC = minimally classic; O = occult; PC = predominantly classic; VA = visual acuity.
P values designated by asterisk (*) indicates statistical significance.
[a]Pairwise comparisons were adjusted for using Tukey's honestly significant difference correction.

TABLE 2. Five-Year Outcomes of the 3 Choroidal Neovascularization Types

	Occult	Minimally Classic	Predominantly Classic	O vs MC *P* Value[b]	O vs PC *P* Value[b]	MC vs PC *P* Value[b]
Median (Q1, Q3) days follow-up	1637 (908, 2267)	1635 (896, 2240)	1379 (657, 2056)			
VA, mean letters (SD)	56.7 (22.2)	53.2 (22.9)	50.4 (24.9)	.06	<.0001*	.25
VA change from baseline, mean (95% CI)	-0.24 (-0.92 to 1.39)	0.01 (-2.62 to 2.60)	1.19 (-3.31 to 0.93)	.98	.44	.74
VA ≤35 letters, %	18.2	23.1	27.0			
VA ≥70 letters, %	35.2	31.8	27.4			
5 years completers, n (%)	517 (43.2)	129 (44.6)	165 (37.1)			
Injections, median (Q1-Q3)[a]	30 (22-40)	29 (22-37)	29 (23-38)			
Overall proportion of visits with active lesion, %	56	54	49	.32	.009*	.004*

P values designated by asterisk (*) indicates statistical significance.
MC = minimally classic; O = occult; PC = predominantly classic; Q1 = 25% quartile; Q3 = 75% quartile.
[a]Values calculated on 5-year completers only.
[b]Pairwise comparisons were adjusted for using Tukey's honestly significant difference correction.

had better baseline and final VA compared to other lesions, but treatment requirements and efficacy were similar for all CNV types, with no difference in VA at 5 years found between occult, minimally classic, and predominantly classic CNVs after adjusting for baseline VA. This suggests that prompt detection of nAMD and initiation of treatment is crucial to obtain better outcomes and that knowledge of the CNV type does not affect clinical management or outcome when adequate treatment is administered.

We did not attempt to match the 3 groups with different lesion types at baseline in this analysis. This allowed us to compare the baseline features of eyes affected by different CNV types. As previously reported, the mean age of patients was similar across the 3 groups and about two thirds of all patients were women.[3] Interestingly, the proportion of male patients was significantly higher in the predominantly classic group compared to the other groups. A similar trend, although not statistically significant, was found in an analysis comparing the VIP and TAP trials of PDT with verteporfin.[26] We have no definite explanation for this finding, but sex-related variations in the composition and anatomy of the Bruch membrane, angiogenic cytokine distribution, and antigen distribution in and around the Bruch membrane may occur.[27]

Baseline lesion size varied significantly among the 3 groups, with the minimally classic CNVs having the largest GLD, followed by occult and predominantly classic CNVs. This result has been previously reported[26] and can be explained by the different patterns of growth of the different types of CNV. Briefly, occult CNVs originate with multiple sites of ingrowth from the choriocapillaris through the Bruch membrane and expand following the

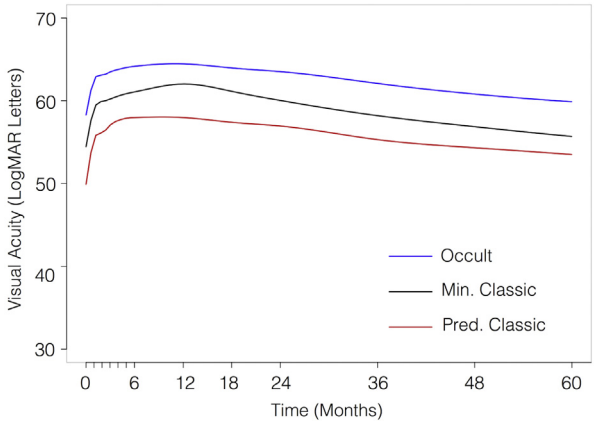

FIGURE 1. Locally weighted scatterplot smoothing curve, using last observation carried forward for noncompleters, describing visual acuity changes over 5 years of follow-up in the 3 types of choroidal neovascularizations. Min. = minimally; Pred. = predominantly.

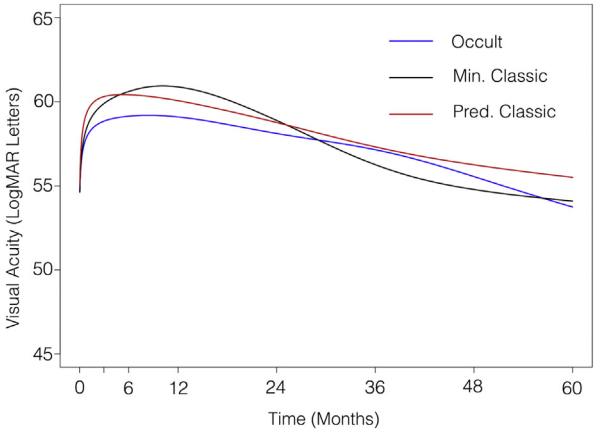

FIGURE 2. Predicted visual acuity (VA) from longitudinal generalized additive models over 5 years of follow-up in eyes with the 3 types of choroidal neovascularizations after adjusting for baseline VA. Min. = minimally; Pred. = predominantly.

natural cleavage plane between the Bruch membrane and the RPE; thus they may become quite large before they cause visual symptoms. By contrast, classic CNVs break into the subretinal space through a focal defect in the RPE and quickly damage the overlaying retina directly.[27] Minimally classic CNVs occur when a classic lesion generates from a preexisting occult CNV, with the combination of the 2 accounting for the largest size.

Mean baseline VA was significantly higher at baseline and throughout 5 years in the occult CNV group than in the minimally and predominantly classic groups. It is known that the lesion location in relation to the fovea does not vary in the 3 CNV types[5]; however, lower VA in eyes with classic CNV has been previously reported.[26]

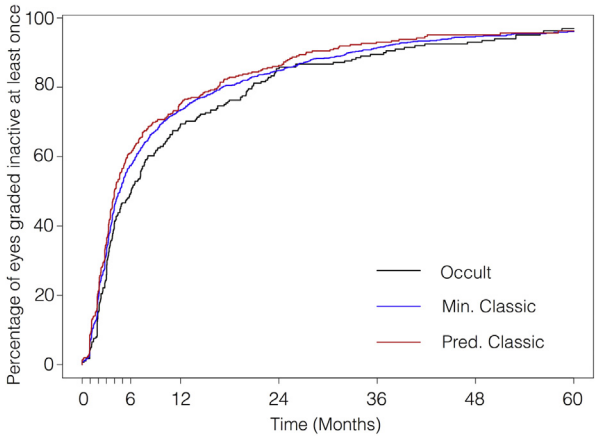

FIGURE 3. Kaplan-Meier analysis of time to first grading of lesion as "inactive." Min. = minimally; Pred. = predominantly.

Similar to the GLD, this can be explained by the different location of the new vessels and their relationship with the overlying retina. While the fine network of new vessels growing between the Bruch membrane and the RPE seen in occult CNVs could nutritionally support the RPE and outer retina, when the neovascular complex sprouts into the subretinal space it invariably alters the photoreceptors' function and consequently affects vision.[27]

Visual acuity change followed the same pattern through the years regardless of the lesion type in the present study (Figure 1). After the initiation of treatment, VA improved during the first 12 to 24 months and then slowly decreased. After 5 years, there was no significant difference in mean VA from baseline in any of the groups. This is similar to previous reports of long-term outcomes of nAMD treated with anti-VEGF in real-life settings.[28,29] Since occult CNVs started with significantly better mean VA and the VA change was similar in all the groups, occult CNV had better vision than the other groups at the end of the study, but final VA was the same for all groups after adjusting for baseline VA. Subject age, lesion size, baseline VA, and CNV type have all been widely reported to influence visual outcomes in nAMD.[30–33] Our analysis, by contrast, found that the CNV type affects long-term outcomes only indirectly by affecting baseline VA. Only the age of the subject, the size of the lesion, and the baseline VA in fact had a significant independent effect on the VA at 5 years in the multivariate analysis of the present study. This result again highlights that early detection and prompt treatment are crucial to obtain better visual outcomes long term in eyes with nAMD irrespective of the lesion type.

The time to the first visit graded as inactive, based on the treating physician evaluation, was significantly different across the 3 groups. Predominantly classic lesions tended to respond faster to anti-VEGF treatment than occult

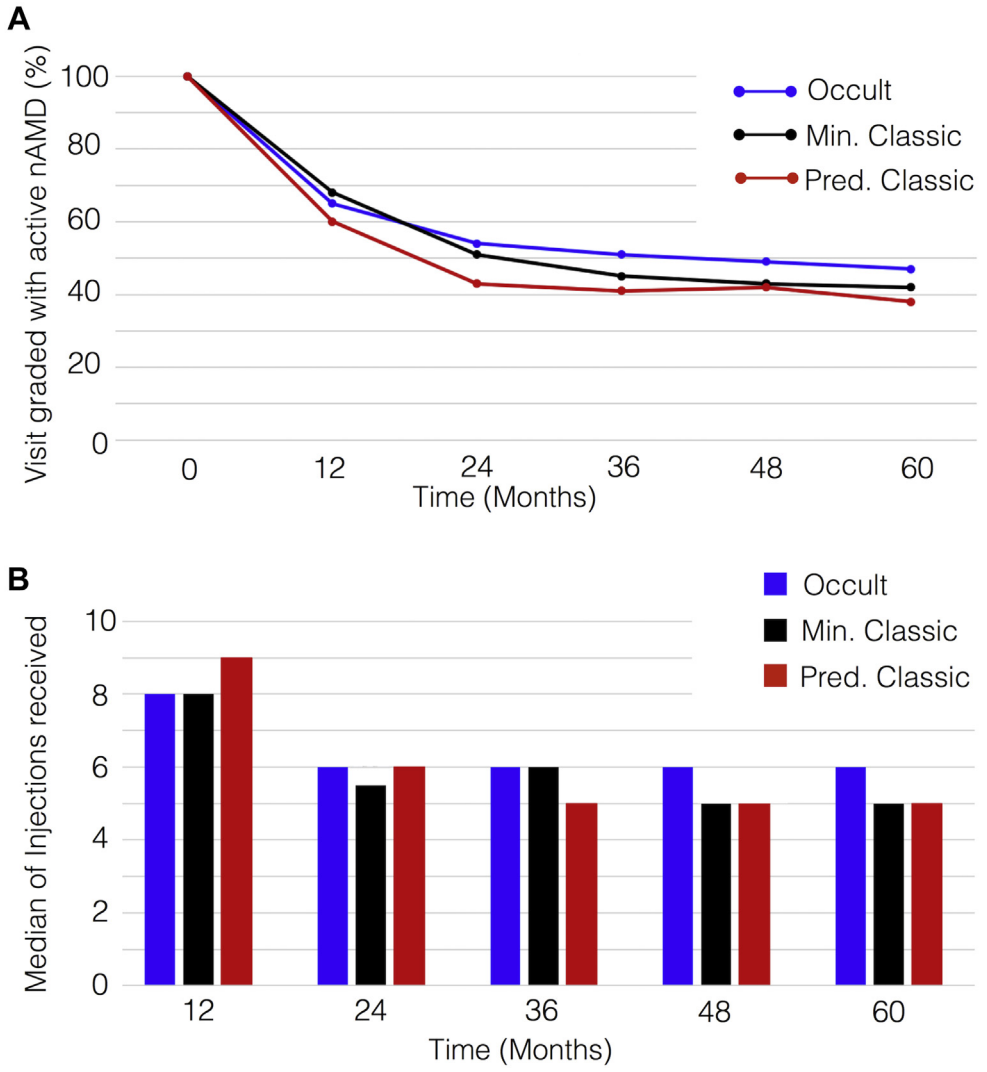

FIGURE 4. Lesion activity (A) and number of treatments received (B) over the 5 years of follow-up in the 3 different types of choroidal neovascularizations. Min. = minimally; nAMD = neovascular age-related macular degeneration; Pred. = predominantly.

and minimally classic lesions. This difference had been previously reported by our group[34] and is likely related to the lesion size and the location of the neovascular complex in relation to the RPE and the consequent exposure to the drug delivered into the vitreous cavity. The intact RPE over occult CNV is the likely reason for these lesions to remain somewhat more active through the years of follow-up than classic CNVs. Despite these differences, the median number of injections was similar among the 3 groups. This also suggests that anti-VEGF drugs have similar efficacy in nAMD for all lesion types.[11–13]

Our study has some limitations. First, according to the FRB! registry procedures, the classification of the lesions was based on physicians' judgment without a standardized imaging protocol and a centralized reading center.[18] This may have resulted in the mistaken inclusion of some type 3 lesions in the analysis. The registry categories for types of neovascularization are based on the angiographic classification, but clinicians now also routinely perform OCT scans when they diagnose the condition, which would reduce the risk of misclassification of type 3 lesions.[5] Second, our analysis did not include atypical nAMD such as type 3 neovascularization and polypoidal choroidal vasculopathy because of the relatively small number of eyes diagnosed with such lesions that have been followed for 5 years in the FRB! database. The drop-out rates at 5 years were high, as is usually the case for observational studies, and unevenly distributed, with the predominantly classic group losing the highest proportion of patients over 5 years. This may be because eyes with classic lesions started with lower baseline VA and had inferior outcomes as a result. Since tracking of subretinal fibrosis and atrophy was only added to the FRB! registry in April 2016, we cannot say when these events started, or whether they were even present at

baseline, in eyes that started treatment before then. Their development could be unevenly distributed in the different CNV types, which might explain why classic CNVs had worse vision. Finally, the eyes included in our study could have received bevacizumab, ranibizumab, or aflibercept according to the treating physician's choice. The uneven proportion of eyes treated with the 3 agents, the relatively more recent availability of aflibercept than the other drugs, and the high percentage of subjects treated with more than 1 anti-VEGF agent through the years of follow-up (switching) prevented us from analyzing the long-term effect of different drugs on specific CNV types.

To conclude, eyes with occult CNV lesions overall had a better VA at 5 years than other CNV types, mainly because of the better starting VA, but the VA change was similar across the different lesion types. Five-year outcomes were only affected by the subject age, lesion size, and baseline VA, not by the lesion type. Lesion activity was slightly higher in occult CNVs, but the number of treatments received was not affected by the lesion type. While the identification of atypical neovascular lesions such as type 3 neovascularization or polypoidal choroidal vasculopathy may still be relevant in the anti-VEGF era,[35,36] the traditional classification of CNV lesions into occult, minimally classic, or predominantly classic appears irrelevant to patient management and long-term outcomes in subjects with nAMD treated with anti-VEGF injections in a real-world setting.

FINANCIAL SUPPORT: THE FIGHT RETINAL BLINDNESS! PROJECT IS SUPPORTED BY A GRANT FROM THE MACULAR DISEASE Foundation Australia and unrestricted educational grants from Bayer and Novartis. Financial Disclosures: Daniel Barthelmes and Mark Gillies are inventors of the software used to collect the data for this analysis. The following authors have no financial disclosures: Alessandro Invernizzi, Vuong Nguyen, Kelvin Teo, Adrian Fung, and Andrea Vincent. All authors attest that they meet the current ICMJE criteria for authorship.

The Fight Retinal Blindness! Investigators: Auckland District Health Board, New Zealand (Dr D. Squirrell); Cairns Eye Surgery, Queensland (Dr A. Field); Canberra Hospital, Australian Capital Territory (Dr C. Dayajeewa, Dr J. Wells, Dr R. Essex); Central Coast Eye Specialist, New South Wales (Dr S. Young); Centre for Eye Research Australia, Victoria (Professor R. Guymer); Coastwide Eye Surgery, New South Wales (Dr R. Ferrier); Crest Eye Associates, New Zealand (Dr J. Ah-Chan); Doncaster Eye Center, Victoria (Dr L. Chow); Dr Nadia Wittles Practice, South Australia (Dr N. Wittles); Eye Associates, New South Wales (Dr M. Gillies, Dr A. Hunt); Eye Surgeons Miranda, New South Wales (Dr A. Hunt); Eyemedics (Wayville), South Australia (Dr K. Billing, Dr J. Chen, Dr J. Landers, Dr S. Lake, Dr M. Perks, Dr R. Phillips, Dr N. Saha); Gladesville Eye Specialists, New South Wales (Dr S. Young); Hornsby Eye Specialists, New South Wales (Dr S. Lal); Les Manning Practice, Queensland (Dr L. Manning); Lions Eye Institute, Western Australia (Professor I. McAllister); Marsden Eye Specialists, New South Wales (Dr J. Arnold); Mona Vale Eye Centre, New South Wales (Dr C. Lim); Nepean Valley Eye Surgeons, New South Wales (Dr G. Banerjee); Retina Associates, New South Wales (Associate Professor S. Fraser-Bell, Associate Professor A. Fung, Professor A. Hunyor, Dr C. Younan); Retina Specialists, New Zealand (Dr R. Barnes, Dr A. Vincent); Specialist Eye Group, Victoria (Dr L. Chow); Sydney Eye Hospital, New South Wales; University Hospital Zurich, Switzerland (Dr D. Barthelmes); Victoria Parade Eye Consultants, Victoria (Dr M. Daniell, Professor R. Guymer, Dr A. Harper, Dr L. Lim, Dr J. O'Day).

REFERENCES

1. Subfoveal neovascular lesions in age-related macular degeneration. Guidelines for evaluation and treatment in the macular photocoagulation study. Macular Photocoagulation Study Group. *Arch Ophthalmol* 1991;109(9):1242–1257.
2. Grossniklaus HE, Gass JD. Clinicopathologic correlations of surgically excised type 1 and type 2 submacular choroidal neovascular membranes. *Am J Ophthalmol* 1998;126(1):59–69.
3. Bressler NM, Bressler SB, Fine SL. Age-related macular degeneration. *Surv Ophthalmol* 1988;32(6):375–413.
4. Freund KB, Zweifel SA, Engelbert M. Do we need a new classification for choroidal neovascularization in age-related macular degeneration? *Retina* 2010;30(9):1333–1349.
5. Jung JJ, Chen CY, Mrejen S, et al. The incidence of neovascular subtypes in newly diagnosed neovascular age-related macular degeneration. *Am J Ophthalmol* 2014;158(4):769–779.e762.
6. Stevens TS, Bressler NM, Maguire MG, et al. Occult choroidal neovascularization in age-related macular degeneration. A natural history study. *Arch Ophthalmol* 1997;115(3):345–350.
7. Occult choroidal neovascularization. Influence on visual outcome in patients with age-related macular degeneration. Macular Photocoagulation Study Group. *Arch Ophthalmol* 1996;114(4):400–412.
8. Laser photocoagulation of subfoveal recurrent neovascular lesions in age-related macular degeneration. Results of a randomized clinical trial. Macular Photocoagulation Study Group. *Arch Ophthalmol* 1991;109(9):1232–1241.
9. Laser photocoagulation of subfoveal neovascular lesions in age-related macular degeneration. Results of a randomized clinical trial. Macular Photocoagulation Study Group. *Arch Ophthalmol* 1991;109(9):1220–1231.
10. Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: one-year results of 2 randomized clinical trials–TAP report. Treatment of age-related macular degeneration with photodynamic therapy (TAP) Study Group. *Arch Ophthalmol* 1999;117(10):1329–1345.
11. Brown DM, Kaiser PK, Michels M, et al. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. *N Engl J Med* 2006;355(14):1432–1444.
12. Chang TS, Bressler NM, Fine JT, Dolan CM, Ward J, Klesert TR. Improved vision-related function after ranibizumab treatment of neovascular age-related macular degeneration: results of a randomized clinical trial. *Arch Ophthalmol* 2007;125(11):1460–1469.
13. Heier JS, Brown DM, Chong V, et al. Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration. *Ophthalmology* 2012;119(12):2537–2548.
14. Daniel E, Pan W, Ying GS, et al. Development and course of scars in the Comparison of Age-related Macular

Degeneration Treatments Trials. *Ophthalmology* 2018;125(7):1037–1046.
15. Danis R, McLaughlin MM, Tolentino M, et al. Pazopanib eye drops: a randomised trial in neovascular age-related macular degeneration. *Br J Ophthalmol* 2014;98(2):172–178.
16. Jaffe GJ, Ciulla TA, Ciardella AP, et al. Dual antagonism of PDGF and VEGF in neovascular age-related macular degeneration: a phase IIb, multicenter, randomized controlled trial. *Ophthalmology* 2017;124(2):224–234.
17. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Prev Med* 2007;45(4):247–251.
18. Gillies MC, Walton R, Liong J, et al. Efficient capture of high-quality data on outcomes of treatment for macular diseases: the fight retinal blindness! Project. *Retina* 2014;34(1):188–195.
19. Rodrigues IA, Sprinkhuizen SM, Barthelmes D, et al. Defining a minimum set of standardized patient-centered outcome measures for macular degeneration. *Am J Ophthalmol* 2016;168:1–12.
20. Bressler NM. Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: two-year results of 2 randomized clinical trials-TAP report 2. *Arch Ophthalmol* 2001;119(2):198–207.
21. Arnold JJ, Campain A, Barthelmes D, et al. Two-year outcomes of "treat and extend" intravitreal therapy for neovascular age-related macular degeneration. *Ophthalmology* 2015;122(6):1212–1219.
22. Therneau TM. A Package for Survival Analysis in S. Available at: https://CRAN.R-project.org/package=survival. Published 2015. Accessed February 7, 2018.
23. R: A Language and Environment for Statistical Computing Vienna, Austria: R Foundation for Statistical Computing; 2016.
24. Muggeo VM. Segmented: an R package to fit regression models with broken-line relationships. *R News* 2008;8(1):20–25.
25. Bates DM, Maechler M, Bolker B, Walker S. Fitting linear mixed-effects models using lme4. *J Stat Softw* 2015;67(1):1–48.
26. Blinder KJ, Bradley S, Bressler NM, et al. Effect of lesion size, visual acuity, and lesion composition on visual acuity change with and without verteporfin therapy for choroidal neovascularization secondary to age-related macular degeneration: TAP and VIP report no. 1. *Am J Ophthalmol* 2003;136(3):407–418.
27. Grossniklaus HE, Green WR. Choroidal neovascularization. *Am J Ophthalmol* 2004;137(3):496–503.
28. Arevalo JF, Lasave AF, Wu L, et al. Intravitreal bevacizumab for choroidal neovascularization in age-related macular degeneration: 5-year results of the Pan-American Collaborative Retina Study Group. *Retina* 2016;36(5):859–867.
29. Maguire MG, Martin DF, Ying GS, et al. Five-year outcomes with anti-vascular endothelial growth factor treatment of neovascular age-related macular degeneration: the Comparison of Age-Related Macular Degeneration Treatments Trials. *Ophthalmology* 2016;123(8):1751–1761.
30. Ying GS, Huang J, Maguire MG, et al. Baseline predictors for one-year visual outcomes with ranibizumab or bevacizumab for neovascular age-related macular degeneration. *Ophthalmology* 2013;120(1):122–129.
31. Chae B, Jung JJ, Mrejen S, et al. Baseline predictors for good versus poor visual outcomes in the treatment of neovascular age-related macular degeneration with intravitreal anti-VEGF therapy. *Invest Ophthalmol Vis Sci* 2015;56(9):5040–5047.
32. Ying GS, Maguire MG, Daniel E, et al. Association of baseline characteristics and early vision response with 2-year vision outcomes in the Comparison of AMD Treatments Trials (CATT). *Ophthalmology* 2015;122(12):2523–2531.e2521.
33. Tsilimbaris MK, Lopez-Galvez MI, Gallego-Pinazo R, Margaron P, Lambrou GN. Epidemiological and clinical baseline characteristics as predictive biomarkers of response to anti-VEGF treatment in patients with neovascular AMD. *J Ophthalmol* 2016;2016:4367631.
34. Gillies MC, Campain A, Walton R, et al. Time to initial clinician-reported inactivation of neovascular age-related macular degeneration treated primarily with ranibizumab. *Ophthalmology* 2015;122(3):589–594.e581.
35. Daniel E, Shaffer J, Ying GS, et al. Outcomes in eyes with retinal angiomatous proliferation in the Comparison of Age-Related Macular Degeneration Treatments Trials (CATT). *Ophthalmology* 2016;123(3):609–616.
36. Cheung CMG, Lai TYY, Ruamviboonsuk P, et al. Polypoidal choroidal vasculopathy: definition, pathogenesis, diagnosis, and management. *Ophthalmology* 2018;125(5):708–724.