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ORIGINAL RESEARCH

Real-World Outcomes in Pre-Existing Neovascular Age-Related Macular Degeneration Subjects Undergoing Avacincaptad Therapy for Geographic Atrophy

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Purpose: To evaluate real-world outcomes in subjects with pre-existing neovascular age-related macular degeneration (AMD) undergoing intravitreal avacincaptad pegol (IVA) treatment for geographic atrophy (GA).

Methods: This study was undertaken as a retrospective, case-controlled assessment of patients undergoing IVA treatment for GA from 2 community-based retina practices. Patients were separated into 1) a Study Group consisting of subjects with pre-existing neovascular AMD prior to initiation of IVA for GA, and 2) a Control Group consisting of AMD subjects without neovascularization prior to initiation of IVA for GA. Study and Control Group subjects had a baseline visual acuity of ≥ 20/200, a total GA lesion area of ≥ 1 mm^2 and ≤ 17.5 mm^2, and follow-up of 12-months following IVA commencement.

Results: A total of 64 patients were analyzed. No significant differences in baseline characteristics were found between cohorts. The Study Group had a greater decrease in visual acuity [−0.2 (−0.24 to −0.16) logMAR versus −0.04 (−0.06 to 0.02) logMAR; p<0.0001], a greater increase in GA lesion growth [1.36 (1.09–1.63) mm^2 versus 0.52 (0.34–0.70) mm^2; p<0.0001], and a higher incidence of exudation (p=0.0002) compared to the Control Group during the study period.

Conclusion: This study suggests that patients undergoing IVA therapy for GA with pre-existing neovascular AMD have worse visual and anatomic outcomes at 12-months compared to a matched control group without pre-existing neovascularization; such patients therefore should be carefully counseled prior to initiation of IVA for the management of GA.

Keywords: geographic atrophy, avacincaptad pegol, pre-existing neovascular age-related macular degeneration, complement inhibition, Izervay

Introduction

The Food and Drug Administration (FDA) approved Avacincaptad Pegol (Izervay; Iveric Bio, USA) (2 mg/0.1 mL) for the management of geographic atrophy (GA) secondary to age-related macular degeneration (AMD) following a favorable review of the GATHER pivotal Phase III clinical trials.[1,2] Although intravitreal avacincaptad pegol (IVA) was reported to reduce total GA lesion growth compared to sham, it is notable that the GATHER trials excluded all subjects with pre-existing neovascular age-related macular degeneration (nAMD) in the study eye. Interestingly, the FDA opted to label IVA broadly, stating that it is indicated for use for the treatment of GA secondary to AMD unqualified.[3]

One of the most noteworthy adverse events reported with the use of IVA has been the development of choroidal neovascularization (CNV), which may be considered a conversion into nAMD in subjects without prior exudation. In the GATHER 1 trial, CNV developed in approximately 12% of patients injected monthly at 18 months (only 3.6% in the sham).[1] However, retina specialists commonly encounter nAMD patients who also have concomitant GA which is either

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threatening central vision loss or has become the main reason for the patient's vision loss. Oftentimes these patients have had their CNV stabilized following a course of anti-vascular endothelial growth factor (VEGF) therapy and only require maintenance injections at infrequent intervals such as every 3 or 4 months; in some cases, these patients even have their anti-VEGF therapy discontinued secondary to disease inactivity.[4] Since this subgroup of patients were deliberately excluded from the GATHER trials as discussed above, there currently exists no data on these patients with pre-existing nAMD undergoing IVA treatment for GA. The authors report in this study real-world outcomes at 12-months in pre-existing nAMD patients undergoing IVA treatment for GA.

Methods

This study was undertaken as a retrospective, case-controlled assessment of AMD patients who were initiated on IVA therapy for GA at 2 community-based retina practices in Texas and Florida between August and September of 2023. The assessments were in compliance with the principles of the Declaration of Helsinki and the Health Insurance Portability and Accountability Act of 1996. The conduct of this study was authorized by the Panhandle Eye Group Institutional Review Board (IORG0009239; IRB00011013-16). Informed consent was waived because all data was retrospectively gathered and identifying patient information was omitted.

A medical records search produced a list of potential subjects who were initiated on IVA treatment for GA secondary to AMD in the time frame above. Potential subjects were allocated into 1) a Study Group column if they had a diagnosis of nAMD and had received anti-VEGF injections prior to initiation of IVA treatment for GA, or into 2) a Control Group column if they had a diagnosis of "dry" AMD without a history of CNV or exudation prior to initiation of IVA treatment for GA. The study's inclusion/exclusion criteria relevant to both cohorts are presented in Table 1. In addition to the criteria listed in Table 1, subjects in the Study Group had to have either "stable" or "inactive" CNV to be included. For the purpose of this study, stable CNV was considered when the subject was receiving maintenance anti-VEGF injections at an interval of ≥ 8 weeks and was without evidence of exudation (eg subretinal fluid, intraretinal fluid, cystoid macular edema, or macular hemorrhage) prior to IVA treatment initiation. Inactive CNV was considered when the subject had been discontinued from anti-VEGF therapy secondary to disease inactivity, was without evidence of exudation during the baseline examination, and had not received an anti-VEGF treatment in ≥ 6 months prior to IVA therapy commencement. Once all Study Group patients meeting the criteria for inclusion were finalized for analysis, the number of patients in the Control Group was further reduced to equally match the number of patients in the Study Group. This was accomplished by assigning all potential Control Group patients a number, and a random number-generating program was utilized to

Table 1 The Inclusion and Exclusion Criteria at Baseline for Both Cohorts

Inclusion	Exclusion
The subject's age was ≥ 60 years	The clarity of the ocular media, pupillary dilation, or the subject's fixation was inadequate to allow the collection of high-quality images
The study eye had a Snellen visual acuity of ≥ 20/200	The GA was secondary to a condition other than AMD (eg myopic degeneration, macular dystrophy, etc.)
The study eye had GA secondary to AMD and was treatment-naïve to GA treatment	An ocular disease was present in the study eye that in the opinion of the researcher could compromise the patient's visual function (eg glaucoma, diabetic retinopathy, etc.)
The total area of GA in the study eye was ≥ 1.0 mm^2 and ≤ 17.5 mm^2, and the total area of GA was completely visualized on the macula-centered image and was not adjoining with any areas of peripapillary atrophy.	The study eye had a history of intraocular surgery (ie cataract surgery) within 3 months prior to commencement of IVA treatment for GA
The subject had 12 months (48–56 weeks) of follow-up following commencement of IVA treatment for GA	

Abbreviations: GA, Geographic atrophy; AMD, age-related macular degeneration; IVA, intravitreal avacincaptad pegol.

select patients to the final Control Group, thereby producing cohorts equal in total number for analysis. When both eyes of the same patient met the criteria for analysis, the eye with the better visual acuity was chosen.

GA was diagnosed by the presence of an area of well-demarcated atrophy of the outer retinal layers secondary to the loss of photoreceptors, retinal pigment epithelium, and the underlying choriocapillaris as observed with multi-modal imaging, which includes optical coherence tomography (OCT), fluorescein angiography (FA), fundus autofluorescence (FAF), and indocyanine green angiography (ICGA).[5] The terminology employed in this study for GA classification is based on OCT findings according to recent consensus definitions that have been adopted.[6] The Heidelberg Spectralis system (Heidelberg Engineering) acquired the OCT, FA, ICGA, and FAF images. The OCT images were obtained with 97-line volume scan (20° × 20°, high-resolution mode, ART = 9) and 73-line volume scan (20° × 15°, high-resolution mode, ART = 9) protocols. Masked fellowship-trained retina specialists (RBR and RMR) tabulated the GA independently, and RegionFinder software (Heidelberg Engineering, version 2.6.4.0) calculated the total area of GA on FAF according to previously published techniques.[7] Concordance between masked image graders was considered when there was < 10% difference in the total measured GA area. When the total area of GA was not concordant between graders, the case was arbitrated by a third researcher (SWR).

The baseline examination of this study was the documented patient encounter in which commencement of IVA therapy for GA was decided. Patients in both cohorts variably received their intravitreal injection(s) either on the same day or within one week of the examination in which treatment was decided. The intended IVA treatment schedule for all patients in both cohorts was within a 29–35 day interval. The anti-VEGF treatment strategy employed for the Study Group was a "treat-and-extend" schedule, and if new-onset CNV exudation occurred in the Control Group, the anti-VEGF treatment strategy was also a "treat-and-extend" schedule. In brief, the "treat-and-extend" protocol consisted of monthly anti-VEGF injections until the macula on OCT was absent from intraretinal and/or subretinal edema and the macula was without hemorrhage on biomicroscopy. The treatment interval was extended by two-week increments until a maximum inter-visit interval was achieved. If intraretinal and/or subretinal edema recurred on OCT, macular hemorrhage developed, or the Snellen visual acuity dropped by 2 or more lines, the treatment interval was reduced by 1–2 weeks. The decision as to whether or not discontinue IVA therapy in favor of anti-VEGF monotherapy versus continuing on with IVA therapy in addition to anti-VEGF therapy varied according to the preferences of the managing specialist and the individual patient. Patients undergoing both IVA and anti-VEGF therapy received treatments either on the same day or within one week apart depending on to the preferences of the managing specialist and the individual patient.

Study Outcomes

Change in visual acuity between cohorts at the end of the 12-month (48–56 weeks) study period was the primary outcome. The secondary outcome was change in GA total surface area between cohorts at the end of the 12-month (48–56 weeks) study period.

Statistical Analyses

Snellen visual acuity with pinhole approximation was converted into logMAR units for the purpose of analysis. For quantitative data, the nonparametric Wilcoxon rank sum test or Wilcoxon signed-rank test (for paired data) was used to compare the 2 distributions. The JMP 11 (SAS Institute, USA) statistical software package was employed. Nominal outcome variables were assessed via contingency analysis with likelihood ratios, whereas one-way analysis of the variance assessed numerical outcomes.

Results

A total of 64 patients (32 in the Study Group and 32 in the Control Group) were analyzed. All subjects (100%) in both cohorts used an AREDS II (Age-related Eye Disease Studies II) vitamin throughout the entire study period. Concordance in image grading between the two masked reviewers was 89.1% (57/64).

The Study and Control Group baseline characteristics are displayed in Table 2. No significant differences at baseline were observed between cohorts. The Study Group had undergone a mean of 21.4 (±11.1) anti-VEGF treatments over a mean period of 41.2 (±4.8) months prior to initiation of IVA therapy for GA. The type of anti-VEGF medication

Table 2 Study and Control Group Baseline Characteristics. Means with (95% Confidence Intervals)

Variable	Study Group N=32	Control Group N=32	*P* value
Age (years)	80.9 (78.3–83.5)	78.9 (76.3–81.4)	0.26
Gender	Male = 16 (50.0%)	Male = 17 (53.1%)	0.70
	Female = 16 (50.0%)	Female = 15 (46.9%)	
Status of Lens	Phakic = 6 (18.8%)	Phakic = 7 (21.9%)	0.85
	Pseudophakic = 26 (81.2%)	Pseudophakic = 25 (78.1%)	
Status of Fellow Eye	GA = 14 (43.8%)	GA = 12 (37.5%)	0.89
	nAMD = 14 (43.8%)	nAMD = 15 (46.9%)	
	Intermediate DAMD = 4 (12.5%)	Intermediate DAMD = 5 (15.6%)	
Smoking History	Current = 5 (15.6%)	Current = 4 (12.5%)	0.86
	Former = 8 (25.0%)	Former = 11 (34.4%)	
	Never = 19 (59.4%)	Never = 17 (53.1%)	
Visual Acuity (logMAR)	0.37 (0.26–0.49)	0.40 (0.28–0.51)	0.74
Central Macular Thickness on OCT (microns)	250.7 (242.2–259.3)	263.7 (255.1–272.3)	0.22
Total Area of GA (mm^2)	5.48 (4.22–6.63)	5.70 (4.54–6.85)	0.66
Size of Total GA lesion <7.5 mm^2	Yes = 24 (75.0%)	Yes = 23 (71.9%)	0.81
	No = 8 (25.0%)	No = 9 (28.1%)	
Unifocal GA lesion	Yes = 14 (43.8%)	Yes = 16 (50.%)	0.70
	No = 18 (56.2%)	No = 16 (50.0%)	
GA lesion with subfoveal involvement	Yes = 6 (18.8%)	Yes = 8 (25.0%)	0.54
	No = 26 (81.2%)	No = 24 (75.0%)	
Classification of GA lesion according to OCT findings	i-ORA = 0 (0.0%)	i-ORA = 1 (3.1%)	0.83
	c-ORA = 2 (6.2%)	c-ORA = 3 (9.4%)	
	i-ORORA = 6 (18.8%)	i-ORORA = 6 (18.8%)	
	c-ORORA = 24 (75.0%)	c-ORORA = 22 (75.0%)	

Abbreviations: GA, Geographic atrophy; nAMD, neovascular age-related macular degeneration; DAMD, dry age-related macular degeneration; OCT, optical coherence tomography; i-ORA, incomplete outer retinal atrophy; c-ORA, complete outer retinal atrophy; i-ORORA, incomplete RPE and outer retinal atrophy; c-ORORA, complete RPE and outer retinal atrophy.

previously used in the Study Group was bevacizumab (Avastin; Genentech, Inc)(1.25 mg/0.05mL) in 8 subjects (25.0%), aflibercept (VEGF-Trap Eye/Eylea; Regeneron, Tarrytown, NY) (2 mg/0.05mL) in 4 subjects (12.5%), and a combination of 2 or more anti-VEGF medications in 20 subjects (62.5%). Regarding CNV features in the Study Group at the time of initial diagnosis of nAMD, 25.0% (8/32) were classified as Type 1, 50.0% (16/32) were classified as Type 2, and 25.0% (8/32) were classified as Type 3 lesions. The FA leaking patterns at the time of initial diagnosis of nAMD in the Study Group were as follows: 68.8% (22/32) occult, 9.4% (3/32) minimally-classic, and 21.9% (7/32) classic. The CNV total lesion size on ICGA at the time of initial diagnosis of nAMD in the Study Group was 1.72 (±1.3) mm^2, and the CNV total lesion size on ICGA had decreased to 1.41 (±1.2) mm^2 following anti-VEGF therapy at the time of our study's

Table 3 Study and Control Group Outcomes at 12 Months. Means with (95% Confidence Intervals)

Variable	Study Group N=32	Control Group N=32	*P* value
Number of IVA injections administered	9.1 (8.5–9.7)	10.1 (9.5–10.7)	0.19
Visual Acuity (logMAR)	0.57 (0.46–0.68)	0.44 (0.33–0.56)	0.16
Change in Visual Acuity from baseline to 12 months after IVA treatment initiation (logMAR)	−0.2 (−0.24 to −0.16)	−0.04 (−0.06 to 0.02)	<0.0001
Total Area of GA (mm^2)	6.84 (5.65–8.03)	6.22 (5.03–7.40)	0.46
Change in Size of GA lesion from baseline to 12 months after IVA treatment initiation (mm^2)	1.36 (1.09–1.63)	0.52 (0.34–0.70)	<0.0001
Central Macular Thickness on OCT (microns)	252.5 (243.6–261.4)	246.0 (237.1–254.9)	0.84

Abbreviations: GA, Geographic atrophy; OCT, optical coherence tomography; IVA, intravitreal avacincaptad pegol.

baseline examination prior to initiation of IVA therapy for GA. According to the definitions in the Methods, the CNV was "inactive" in 8 subjects (25.0%) and "stable" in 24 subjects (75.0%) at baseline.

The 12-month outcomes after commencement of IVA therapy for GA for both cohorts are presented in Table 3. Both primary and secondary outcomes were in favor of the Control Cohort. In regards to the Study Group, a mean of 4.7 (±1.1) anti-VEGF injections were administered during the 12-month study period. There were only 4 subjects (12.5%) in the Study Group who did not receive at least one anti-VEGF treatment during the study period, and all 4 of these subjects had been classified as having "inactive" CNV at baseline. The type of anti-VEGF medication used in the Study Group during the study period were as follows: 39.3% (11/28) bevacizumab, 25.0% (7/28) aflibercept, and 35.7% (10/28) Faricimab (Vabysmo; Roche/Genentech; Basel, Switzerland)(6mg/0.05mL). Recurrent exudation in the Study Group during the 12-month study period occurred in 50.0% (16/32) of subjects, and 6.3% (3/32) of subjects opted to discontinue IVA therapy in favor of anti-VEGF monotherapy following recurrent exudation. At the end of the 12-month study period, 15.6% (5/32) of subjects in the Study Group were observed to still have evidence of persistent exudation (ie subretinal fluid, intraretinal fluid, and/or macular hemorrhage) on examination. In regards to the Control Group, 9.4% (3/32) of subjects experienced CNV development and exudation during the 12-month study period versus 50.0% (16/32) in the Study Group (p=0.0002). Regarding the CNV features in the three subjects of the Control Group who experienced exudation, two were classified as having a Type 1 lesion and one had a Type 2 lesion. The FA leaking pattern at the time of exudation in the Control Group was occult in two of the subjects and classic in one of the subjects. Of the 3 subjects in the Control Group who developed CNV during the study period, one opted to discontinue IVA therapy in favor of anti-VEGF monotherapy, whereas the other two opted to undergo both IVA therapy and anti-VEGF treatment. Two of the Control Group subjects who developed CNV during the study period underwent 5 bevacizumab injections whereas one of the subjects underwent 4 aflibercept injections during the 12-month study period. There were no cases of vitritis, retinal vasculitis, or endophthalmitis in either cohort during the 12-month study period. Figures1–3 provide a case example of the course of a Study Group patient included in the analysis.

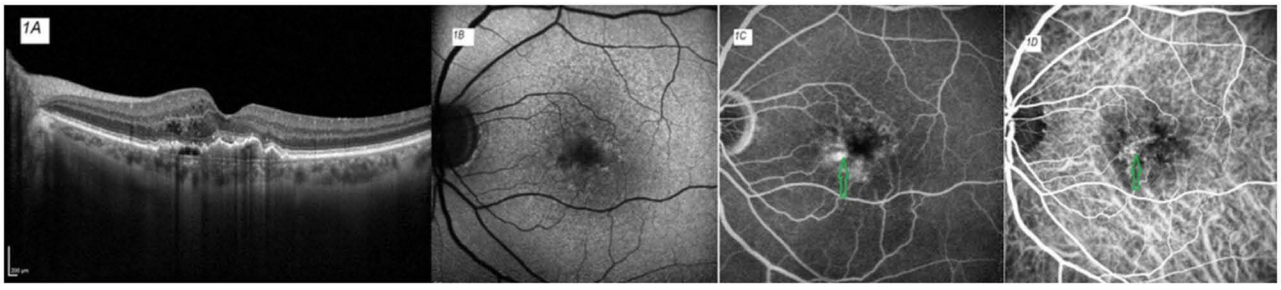

Figure 1 The optical coherence tomography image (**A**), fundus autofluorescence image (**B**), the fluorescein angiography image (**C**), and the indocyanine green angiography image (**D**) demonstrate new-onset choroidal neovascularization in an 83-year old female with age-related macular degeneration. Optical coherence tomography displays intraretinal edema, and both fluorescein angiography and indocyanine green angiography exhibit a "hot spot" (green arrow) consistent with Type III choroidal neovascularization. Fundus autofluorescence does not reveal any geographic atrophy. The patient's visual acuity was 20/70, and she was started on intravitreal bevacizumab therapy.

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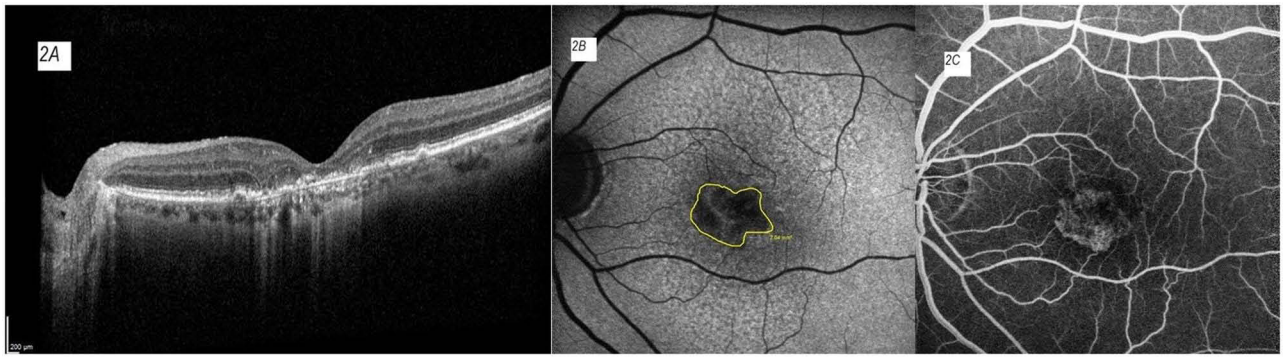

Figure 2 The optical coherence tomography image (**A**), fundus autofluorescence image (**B**), and the fluorescein angiography image (**C**) are from the same patient in Figure 1. After receiving 14 bevacizumab injections over about 2.5 years, fundus autofluorescence revealed unifocal geographic atrophy measuring 2.04 mm^2 (encircled in yellow) adjacent to the center of the macula. At the time of these images, the patient was receiving intravitreal bevacizumab injections at a maintenance interval of every 8–10 weeks. Optical coherence tomography was free from exudation and fluorescein angiography did not reveal any areas of active leakage. The patient's visual acuity was 20/50. Monthly avacincaptad pegol therapy was initiated.

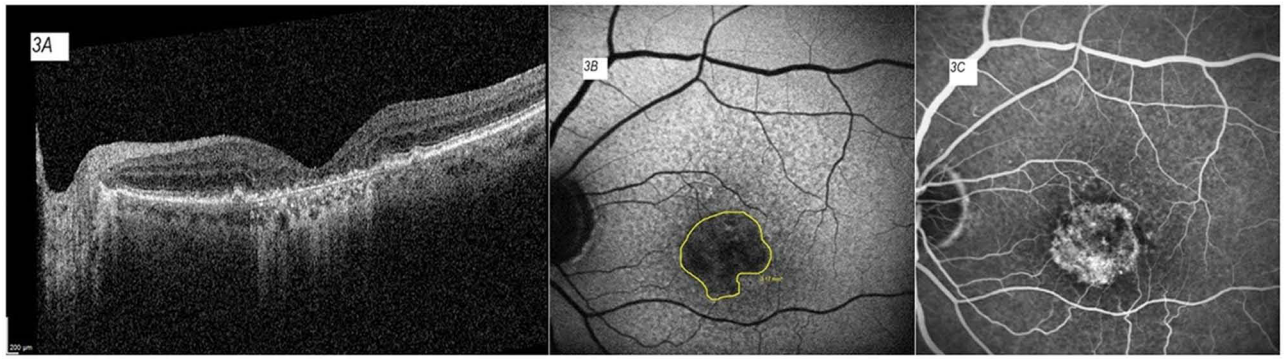

Figure 3 The optical coherence tomography image (**A**), fundus autofluorescence image (**B**), and the fluorescein angiography image (**C**) are from the same subject as the one in Figures 1 and 2 captured 12-months after commencement with avacincaptad pegol therapy. Since the time of Figure 2, the subject had undergone 5 bevacizumab injections and 10 avacincaptad pegol injections. Optical coherence tomography remained free from exudation and fluorescein angiography did not expose any areas of active leakage. However, the total geographic atrophy surface area on fundus autofluorescence grew to 3.17 mm^2 (yellow encirclement) and was now involving most of the center of the macula. The patient's visual acuity was now reduced to 20/80.

Discussion

It has been recognized that complement inhibition therapy for GA increases the incidence of CNV compared to sham.[1,2,8,9] Although the exact mechanism for this higher incidence remains unidentified, researchers have put forth the following explanations: 1) healthier VEGF A-producing cells are preserved secondary to the clinical efficacy of CI treatment,[10] 2) blocking C3a and C5a production results in a change from pro-inflammatory M1 macrophages to pro-angiogenic M2 macrophages,[11] 3) decreasing C3 and C5 in a laser-induced CNV animal model resulted in more CNV compared to controls,[12] 4) activation of inflammasomes in macrophages and microglial cells whose cytokines are needed to preserve homeostasis of the choroidal vasculature is decreased by CI treatment,[13] and 5) CNV may have a protective effect in reducing the onslaught of GA.[14] It is also acknowledged that a majority of nAMD patients treated with anti-VEGF therapy eventually develop macular atrophy with ensuing vision involvement.[15–18] Furthermore, the published literature suggests that CNV and GA may be overlapping signs of a shared immunologic disease process in AMD.[19–21] Since community retina specialists commonly encounter nAMD patients who have been stabilized on anti-VEGF therapy but who are then in danger of losing their central vision from progressive GA growth, this study provides specialists caring for this important subgroup of patients guidance for management decisions in a "real-world" setting.

The Study Group with pre-existing nAMD had worse visual and functional outcomes compared to the Control Group during our study's 12-month period. However, the incidence of recurrent exudation was significantly greater in the Study Group than the incidence of new-onset exudation in the Control Group, suggesting that IVA therapy may

disproportionately effect subjects with pre-existing nAMD in regards to activating the CNV disease process (and destabilizing a formerly "stable" or "inactive" group of nAMD subjects) compared to subjects without pre-existing nAMD. Since half of the Study Group subjects who were previously either "stable" or "inactive" on anti-VEGF therapy at baseline experienced recurrent exudation during the 12-month study period (and 15% still had persistent exudation at study's end), this helps explain why the Study Group had worse final visual acuity compared to the Control Group who had a new-onset exudation rate of only about 9%. Of particular note, nearly all of the subjects in both the Study and Control Groups continued receiving IVA injections in addition to anti-VEGF therapy once recurrent or new-onset exudation occurred, and the mean number of IVA injections during the study period did not differ significantly between cohorts. Therefore, a difference in mean IVA injection numbers between cohorts does not explain why the Study Group had significantly greater growth in GA size compared to the Control Group. The authors believe the higher incidence of exudation in the Study Group compared to the Control Group (16 vs 3 subjects, respectively) provides the best explanation for why the GA growth was significantly greater in the Study Group, although there are reports that a higher number of anti-VEGF injections may be a cause for GA to progress.[22] Further research is warranted to elucidate the link between CNV exudation, anti-VEGF injection numbers, and GA progression.

The strengths of this study include its case-controlled design, the newness of the reported data in a "real-world" environment, and its application of user-friendly and validated software for measuring GA. The weaknesses of this study include its limited number of patients involved in the investigation, its application of Snellen visual acuity with pinhole approximation rather than ETDRS letter scoring, and its retrospective design. Nevertheless, this study provides meaningful data for specialists to counsel their nAMD patients when considering IVA therapy for GA. In conclusion, patients with pre-existing nAMD lose more vision, have greater GA lesion growth, and have a greater likelihood of exudation compared to patients without pre-existing nAMD at 12-months following initiation of IVA treatment for GA. In light of this, careful patient counseling should be undertaken prior to initiating IVA therapy in patients with pre-existing nAMD, and further research on this topic is warranted to further clarify the relationship of CNV exudation and complement inhibition as well as effects of anti-VEGF therapy in this patient population.

Abbreviations

nAMD, neovascular age-related macular degeneration; VEGF, vascular endothelial growth factor; CMT, central macular thickness; OCT, optical coherence tomography; VA, visual acuity; IVA, intravitreal avacincaptad pegol.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

The study was approved by the Panhandle Eye Group Institutional Review Board (IORG0009239; IRB00011013-16) in accordance with the Ethical Standards laid down in the Declaration of Helsinki. Informed consent from study participants was waived because this was a retrospective study with no identifying patient information presented.

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Disclosure

The authors report no conflicts of interest in this work.

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