Baseline Visual Acuity at Wet AMD Diagnosis Predicts Long-Term Vision Outcomes: An Analysis of the IRIS Registry

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BACKGROUND AND OBJECTIVE: Clinical trials in neovascular age-related macular degeneration (nAMD) demonstrate that high visual acuity (VA) can be maintained, and low VA can be improved with anti-vascular endothelial growth factor (VEGF) treatment. Few real-world data investigating the relationship between baseline VA and long-term outcomes exist. This study compares VA at diagnosis and after treatment using data from a large patient registry.

PATIENTS AND METHODS: Retrospective study of IRIS Registry patients diagnosed with nAMD in one or both eyes between January 2013 and June 2017. Patients received at least two anti-VEGF injections in the study eye(s) less than 45 days apart during the study period. Primary outcomes were the percentage of eyes with 20/40 VA or better at diagnosis and association of VA at diagnosis with longer-term visual outcomes.

RESULTS: The study included 162,902 eyes. Among all included eyes, 34.3% presented with 20/40 VA or better at diagnosis. Patients with 20/40 vision or better at baseline maintained a mean VA of 20/40 or better for 2 years after treatment initiation.

CONCLUSIONS: Baseline VA at nAMD diagnosis predicts long-term VA outcomes. Early diagnosis before VA is adversely affected is a key factor in preserving vision in patients with nAMD.

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INTRODUCTION

Significant vision loss typically occurs in a subset of patients who convert from intermediate (dry) to neovascular (wet) age-related macular degeneration (nAMD). Those patients who do progress frequently experience a rapid loss of visual acuity (VA) at the onset of neovascular exudation, with the potential to lose multiple lines of vision prior

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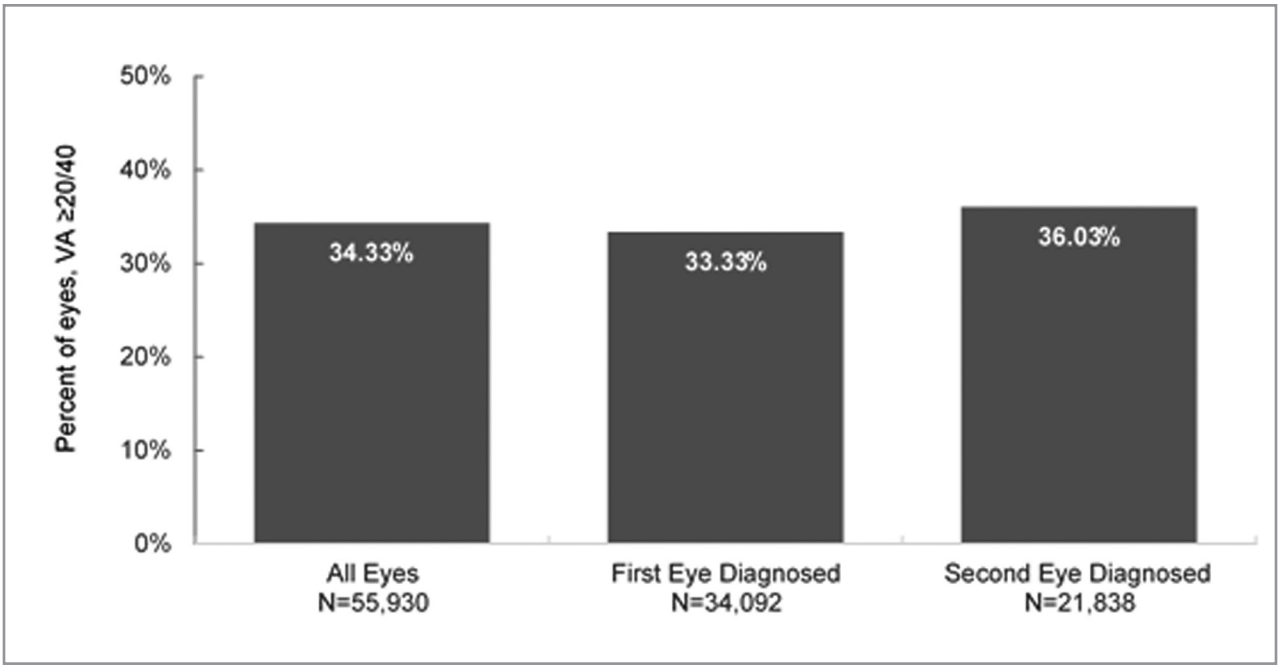

Figure 1. Visual acuity at the time of neovascular age-related macular degeneration diagnosis.

to detection and treatment initiation.[1-3] It is now well accepted that baseline VA is one of the strongest predictors of long-term vision outcomes after treatment with anti-vascular endothelial growth factor (VEGF) agents.[4-6]

Data from controlled, pivotal studies of intravitreal (IVT) anti-VEGF injection therapy have shown that more than 95% of patients can maintain vision within 3 lines of baseline VA, and 41% can improve vision by 3 or more lines; unfortunately, many patients never return to functional vision of 20/40 or better.[7-9] VA remains significantly better over time in patients who have better VA at diagnosis and treatment initiation.[2] Despite study results that consistently indicate that starting with a better VA at baseline will result in better long-term VA, data from real-world community-based studies show that at the time of diagnosis of nAMD, the mean VA is 20/80 or worse and that only between 13% and 21% of patients have a VA of 20/40 or better,[10-13] indicating that early diagnosis prior to significant vision loss remains a substantial challenge in real-world clinical practice.

The American Academy of Ophthalmology's Intelligent Research in Sight (IRIS) Registry is one of the largest clinical specialty registries worldwide.[14] We used this database to quantify baseline VA in patients at time of initial diagnosis of nAMD and to determine how baseline vision relates to long-term visual outcomes in real-world clinical settings, post-IVT anti-VEGF treatment.

PATIENTS AND METHODS

This is a non-interventional, retrospective cohort study of a population of patients diagnosed with nAMD between January 1, 2013, and June 30, 2017, who were entered in the IRIS Registry. Eyes were included if they received an nAMD diagnosis during the study period (as defined by the date of first anti-VEGF treatment with a diagnosis of Exudative Macular Degeneration [ICD 9 362.52, ICD 10 H35.32]), had a baseline VA measured 14 days or fewer prior to the first anti-VEGF injection, and if they received at least two intravitreal (IVT) anti-VEGF injections in the study eye(s) less than 45 days apart during the study period. Data were excluded for patients who received anti-VEGF therapy prior to the diagnosis of nAMD (to mitigate the inclusion of other retinal diseases) and eyes with VA worse than counting fingers due to the high potential for retinal pathology other than choroidal neovascularization (CNV). Receiving an IVT anti-VEGF injection on the same day as the diagnosis was not an exclusion criterion. Uncorrected VA readings were excluded, and VA readings without a specified type of testing distance were assumed to be distance VA. Data were analyzed across all eyes, and for first and second eyes that met inclusion criteria.

The primary objective was to evaluate the percentage of eyes that had 20/40 VA or better at the time of nAMD diagnosis. Secondary objectives were to evaluate the association of VA at diagnosis with longer-term treatment outcomes (VA at Year 1 and Year 2). The entirety of the

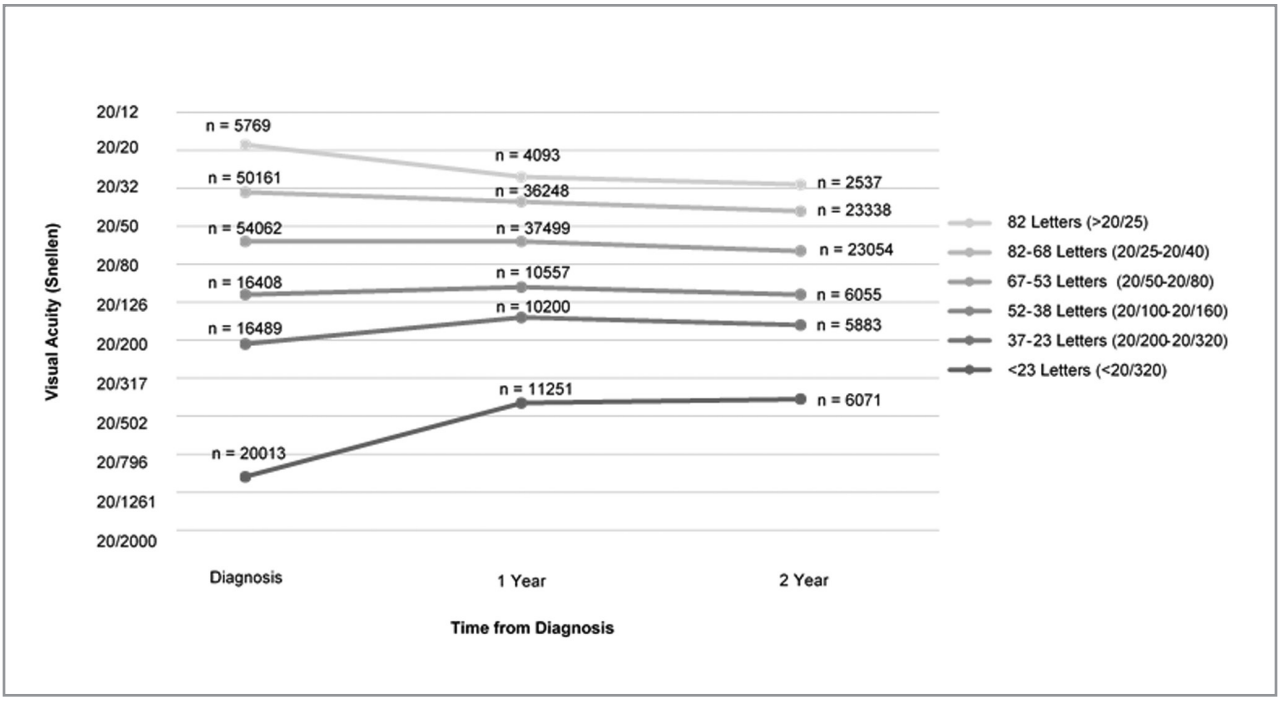

Figure 2. Baseline, 1-year, and 2-year visual acuity after neovascular age-related macular degeneration diagnosis.

data in this study was collected from the IRIS Registry with methods of data extraction previously described.[14]

Statistical Analysis

In this study, the terms index, baseline, and date of diagnosis were considered synonymous with the date of first anti-VEGF injection. In each of the analyses, when the date of diagnosis and the date of first injection occurred on different dates, the date of injection was used in the analysis. Additionally, instances where an analysis included readings for 1 year and 2 years post-diagnosis, the range of capture for each of these timepoints encompassed ± 90 days of that date respectively. Further, if an individual had multiple visits within the timeframe, the visit closest to the 1- or 2-year post-diagnosis date was used in the analysis.

Descriptive statistics were provided using means (standard deviations [SD]) or medians (interquartile range [IQR]) for continuous variables and counts (percentages) for categorical variables. VA measurements were converted from Snellen fractions to the logarithm of the minimum angle of resolution (logMAR) VA units for analysis.[15]

RESULTS

There were 236,843 eyes (n = 220,434 patients) identified with nAMD during the study period, as determined by first anti-VEGF agent IVT injection, with a total of 162,902 eyes (n = 153,141 patients) that met the inclusion criteria.

Table 1 shows demographic data. A higher percentage of patients were female (62.5%), white (97.5%), and non-Hispanic or unknown (97.4%). The average age was 80.5 years. Eyes were categorized into six groups based on VA at the time of the first anti-VEGF injection (baseline VA) for the secondary analyses: greater than 82 letters (Snellen VA > 20/25); 82 to 68 letters (20/25 to 20/40); 67 to 53 letters (20/50 to 20/80); 52 to 38 letters (20/100 to 20/160); 37 to 23 letters (20/200 to 20/320); and less than 23 letters (< 20/320).

Figure 1 shows the VA at the time of nAMD diagnosis with vision of 20/40 or better between all eyes and between first and second eye diagnosis (the latter comparison was statistically significant; $P < .001$). The mean VA at diagnosis was 0.62 ± 0.52 (mean ± standard deviation) logMAR (20/83) for all eyes, 0.63 ± 0.53 (20/85) for first eyes, and 0.60 ± 0.50 (20/79), for second eyes (Table 2).

In all groups, eyes with better VA at baseline retained better VA at both Years 1 and 2 (Figure 3). Only groups of eyes with a mean VA of 20/40 or better at baseline maintained 20/40 or better vision 2 years after treatment initiation. Across all VA groups and all eyes, mean VA was similar at baseline, Year 1, and Year 2 (Baseline: 0.62 ± 0.52 logMAR (20/83); Year 1: 0.55 ± 0.50 logMAR (20/80); Year 2: 0.57 ± 0.52 logMAR (20/80).

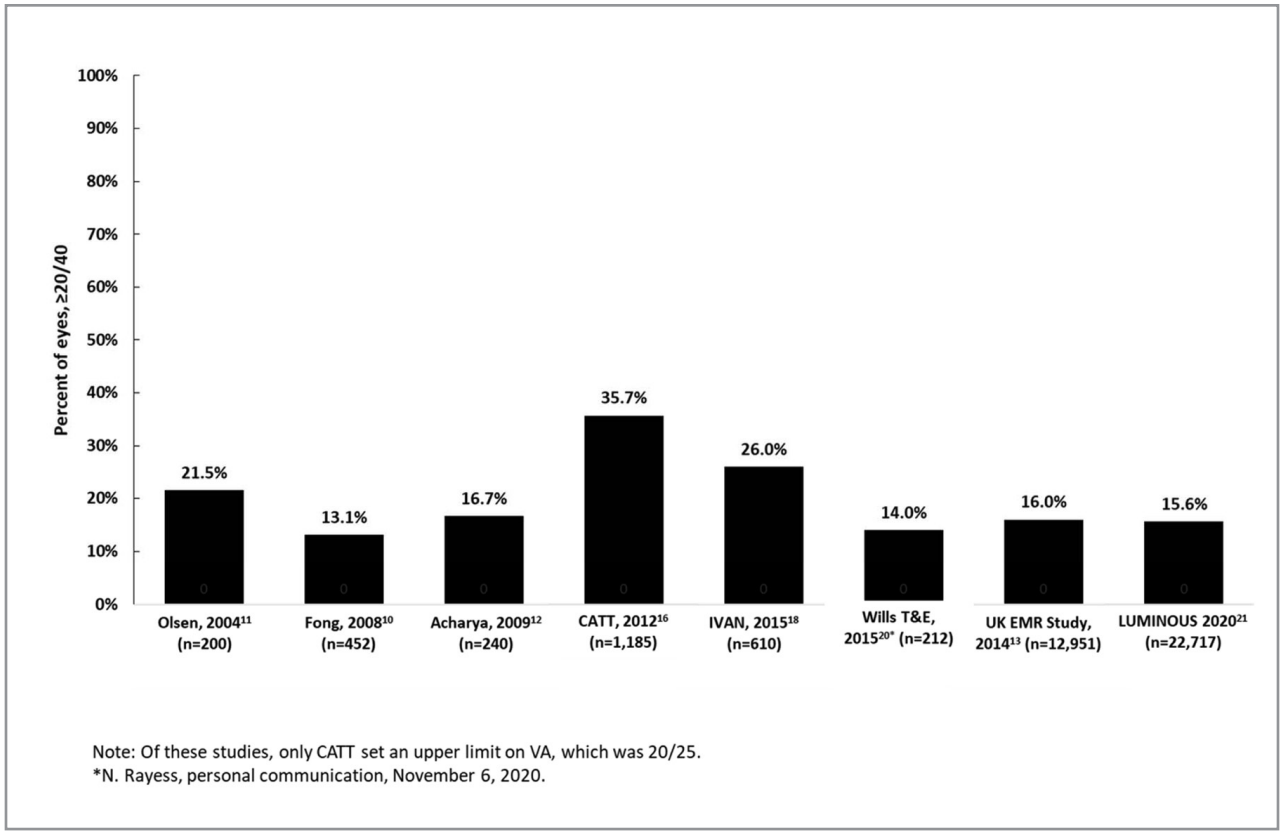

Figure 3. Percent of patients with visual acuity better than 20/40 when initiating anti-vascular endothelial growth factor therapy in clinical trials.

Although better VA at time of nAMD diagnosis was associated with a greater likelihood of maintaining at least 20/40 VA over time, Figure 2 shows that eyes with worse VA at baseline were associated with larger VA gains from baseline. Eyes with baseline VA of 37 to 23 letters (20/200-20/320) showed the greatest gain in VA at Year 1, improving to 0.37 ± 0.64 logMAR (20/160), and to 0.38 ± 0.68 logMAR (20/160) at Year 2. In contrast, mean VA declined slightly in the those with greater than 82 letters at baseline, from 0.03 ± 0.08 logMAR (> 20/25) to 0.14 ± 0.25 logMAR (20/32) at Year 1 and 0.18 ± 0.31 logMAR at Year 2 (20/32). For those with baseline vision of 82 to 68 letters, vision remained consistent, from 0.22 ± 0.08 logMAR (20/40) at baseline to 0.27 ± 0.25 logMAR (20/40) at Year 1 and 0.32 ± 0.31 logMAR (20/40) at Year 2.

DISCUSSION

In this large, real-world population of patients from the IRIS Registry with newly diagnosed nAMD, VA outcomes of 20/40 or better after Year 1 and Year 2 were observed for eyes treated with IVT anti-VEGF therapy when baseline VA was 20/40 or better. These data confirm the benefits suggested in CATT,[4,16] which also found initiating IVT anti-VEGF therapy when baseline VA is relatively good results in significantly better long-term VA outcomes in Year 1 and Year 2.

In this analysis, eyes with poor VA (20/200-20/320) at baseline achieved the greatest magnitude of visual improvement (to 20/160 at 2 years), although these outcomes still fell short of good functional vision. Our results agree with other published data that show delaying treatment is a predictor of worse VA outcomes;[17] Ying et al. demonstrated that patients with a delay in treatment of 21 weeks or more compared to a delay of 7 weeks or less had an odds ratio of 2.62 for worsening vision post-treatment.[4]

This analysis is consistent with data from published studies from the past two decades that suggest that typically fewer than 35% of eyes have a VA of 20/40 or better at the time of nAMD diagnosis (Figure 3).[10-13,18-21] Of particular note in our study, of the 21,838 patients who received a diagnosis on nAMD in the second eye, the second eye diagnosed fared only slightly better than the first: 36.0% of

second eyes had a VA of 20/40 or greater at diagnosis compared with 33.3% of first eyes, even when patients were presumably already under the watchful care of a treating physician.

When patients in the baseline VA group of 20/40 or better were diagnosed and treated with IVT anti-VEGF injections, this group of patients maintained at least 20/40 VA through 2 years of follow-up (Figure 2). With the exception of CATT, where eyes were enrolled with baseline vision of 20/25 or worse, the published studies used as comparators had no upper limit on visual acuity (Figure 3).[10-13,16,18,20-21] In our analysis, eyes with better than 20/40 at time of diagnosis maintained a mean VA of 20/40 or better after 2 years of follow-up, although these eyes did lose some degree of vision. Only eyes with 20/200 or less at baseline exhibited a gain in mean VA following treatment, yet these groups were only able to reach the still significantly limited VA of 20/160 after 2 years of treatment. Although it is beyond the scope of this report to discuss the merits of alternative anti-VEGF management strategies, monthly fixed dosing, as needed treatment, and treat-and-extend regimens all show outcomes consistent with the BCVA results reported here.[5,7-9,16,18,20-22] This study further supports the growing belief that identifying and treating nAMD patients early in their disease diagnosis can result in better functional vision over the long term.

This study is not without limitations, including those inherent to analyses that rely on retrospective, real-world data registries. These data are subject to the accuracy and completeness of the staff entering the information, which may not be uniform across clinical sites. Further, our 2-year data included only 54% of those included at baseline, which may seem as though there was a high "drop out" rate. As with any

TABLE 1

Demographics by Baseline VA Group

Baseline VA (Letters)	**> 82**	**82-68**	**67-53**	**52-38**	**37-23**	**< 23**	**All VAs**
Baseline VA (Snellen)	**< 20/25**	**20/25-20/40**	**20/50-20/80**	**20/100-20/160**	**20/200-20/320**	**< 20/320**	**n/a**
Gender and Age[a,b]							
Male	2199 (43.43%)	16,594 (38.06)	17,671 (37.14%)	5,356 (36.93%)	5,466 (37.58%)	6370 (36.23%)	53,656 (37.55%)
Female	2864 (56.67%)	27,004 (61.94%)	29,914 (62.86%)	9,149 (63.07)	9,080 (62.42%)	11,211 (63.77%)	89,222 (62.45%)
Baseline age, mean (SD)	76.33 (10.06%)	79.00 (8.96%)	80.82 (8.82%)	81.69 (8.79%)	81.61 (8.83%)	82.31 (8.75%)	80.46 (9.01%)
Race[a,b]							
Non-white	107 (2.45%)	817 (2.19%)	927 (2.31%)	304 (2.49%)	376 (3.10%)	464 (3.27%)	2,995 (2.49%)
White	4264 (97.55%)	36,492 (97.81%)	39,276 (97.69%)	11,922 (97.51%)	11,754 (96.90%)	13,736 (96.73%)	117,444 (97.51%)
Ethnicity[a]							
Non-Hispanic Origin or Unknown	4,937 (97.42%)	42,705 (97.72%)	46,459 (97.45%)	14,104 (97.01%)	14,152 (97.16%)	17,009 (96.59%)	139,366 (97.35%)
Hispanic Origin	131 (2.58%)	996 (2.28%)	1,214 (2.55%)	435 (2.99%)	414 (2.84%)	601 (3.41%)	3,791 (2.65%)

[a] *Gender, race, and ethnicity were counted twice for patients who have two eyes that met the inclusion/exclusion criteria.*

[b] *Race and Gender information was missing for some patients and in those categories the numbers do not add up to 100% of patients.*

SD = standard deviation; VA = visual acuity

TABLE 2
Baseline VA by Group

	Cohort Count	Those With Baseline VA	Mean VA at Diagnosis
Patients	220,434	153,141	
All Eyes	236,843	162,902	20/83
First Eyes	150,208	102,284	20/85
Second Eyes	86,635	60,618	20/79

VA = visual acuity

real-world registry, it is impossible to completely track an individual patient, as he or she may have switched practices or stopped returning for treatment altogether and this data are not captured in the database. Although this may, in part, explain the lower number of patient records available for analysis at Year 2 compared to Year 1, our decrease is primarily due to the fact that many patients had not yet completed Year 2 follow-up within the data collection window. It should be noted that 97.5% of the evaluated population was white (which may not reflect the current racial makeup of the United States); the overwhelming percentage of white patients in this analysis suggests white patients may be more likely to seek diagnosis and treatment, or it may be reflective of socioeconomics and access to eye care in more racially diverse locations. Lastly, there is the possibility that clinical sites that treat larger numbers of non-whites are not participating in the IRIS Registry, although this seems unlikely.

In conclusion, this real-world analysis in the largest ophthalmology registry highlights an important unmet need to improve early nAMD diagnosis so that treatment may be initiated when visual prognosis is still good. We found a relatively small percentage of eyes (34%) have vision of 20/40 or better when initiating anti-VEGF therapy for nAMD. Those eyes with worse baseline vision resulted in better vision gains over 2 years than for those with better baseline vision, but still fell short of "good functional vision" (20/40). These results reinforce the importance of early detection methodologies to optimize VA for patients who convert to nAMD.

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