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Visual acuity outcomes after anti-VEGF treatment for neovascular age-related macular degeneration: AREDS2 Report Number 19

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Abstract

Purpose—To analyze best-corrected visual acuity (BCVA) outcomes after anti-vascular endothelial growth factor (VEGF) treatment for neovascular age-related macular degeneration (AMD).

Design—Prospective cohort study of participants enrolled in a clinical trial of oral supplements and receiving anti-VEGF therapy in routine clinical practice.

Participants—Age-Related Eye Disease Study 2 (AREDS2) participants (50–85 years) whose eyes met AREDS2 inclusion criteria at baseline (no late AMD; BCVA $\geq 20/100$; no previous anti-VEGF injections) but received at least one anti-VEGF injection for incident neovascular AMD during follow-up.

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Conflicts of Interest:

No conflicting relationship exists for these authors: Susan Vitale, Tiarnan Keenan, Elvira Agrón, Amitha Domalpally, Traci Clemons, Emily Chew

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Meeting presentation

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Methods—Participants underwent refracted BCVA testing, ophthalmoscopic examination, and stereoscopic color fundus photography at baseline and annual study visits over 5 years. Self-reports of anti-VEGF injections (numbers, dates, and names of drug) were collected at baseline and annual study visits, and at 6-monthly telephone calls.

Main outcome measures—The primary outcome measures were mean refracted BCVA and the proportions of eyes with BCVA 20/40 and 20/200. An exploratory outcome measure was the mean number of self-reported anti-VEGF injections.

Results—1105 eyes of 986 AREDS2 participants met the inclusion criteria; of these, 977 participants (99.1%) had at least one post-treatment visit. At the first and subsequent annual study visits after the first injection, mean refracted BCVAs were 68.0 letters (20/40), 66.1, 64.7, 63.2, and 61.5 (20/60). The proportions of eyes with BCVA 20/40 were 59.3%, 55.1%, 53.5%, 50.6%, and 49.7%, and those with BCVA 20/200 were 5.5%, 8.6%, 9.4%, 12.4%, and 14.4%. The mean annual numbers of self-reported anti-VEGF injections per eye were 2.9, 3.9, 3.3, 3.1, and 3.0.

Conclusions—Refracted BCVA data were obtained in a clinical trial environment but related to anti-VEGF treatment given in normal clinical practice. Visual outcomes declined slowly with increased follow-up time: mean BCVA decreased by approximately 1.5–2 letters per year. At five years, half of eyes achieved BCVA 20/40 but approximately one sixth were 20/200. These data may be useful in assessing the long-term effects of anti-VEGF therapy.

Précis

Refracted acuities of eyes with neovascular AMD were obtained in a trial environment but related to anti-VEGF given in the community. Mean acuity decreased by 1.5–2 letters per year. At five years, half achieved 20/40.

Introduction

Age-related macular degeneration (AMD) is a leading cause of visual loss. The condition is responsible for approximately 9% of global blindness.¹ However, it accounts for approximately half of blindness in developed countries. The proportion of blindness caused by AMD was estimated in 2013 at 50% in the UK²; the equivalent figure in the white population of the USA in 2000 was 54%.³ The two forms of late AMD are neovascular disease and atrophic disease, though these can coexist in the same eye. Neovascular AMD was previously responsible for the majority of severe visual loss in AMD.^{4–6} This is because untreated neovascular disease usually leads to extensive macular damage and irreversible visual loss to the level of legal blindness.

The advent of anti-vascular endothelial growth factor (VEGF) therapy led to substantial improvements in visual outcomes for people with neovascular AMD. For the first time, visual acuity (VA) was often improved or stabilized with initial treatment, as demonstrated in landmark randomized clinical trials (RCTs).^{7,8} For example, a recent meta-analysis of studies from Europe showed that the proportion of eyes with neovascular AMD that had visual impairment decreased significantly from 80% (before 2006) to 66% (2006 onwards).⁹ However, differences were subsequently observed between the visual outcomes reported in RCTs and those obtained in other settings, with lower mean VA gains often reported in

routine clinical care.^{10–12} Potential reasons for these differences have been explored,¹³ including lower frequencies of anti-VEGF injections and higher proportions of patients with comorbidities in routine clinical care settings. These ideas have led to increased interest in information obtained from ‘real-world’ studies, since data from these patients might be more representative and generalizable to populations of interest than RCT data alone.

VA measurements remain the primary outcome measure in RCTs of anti-VEGF therapy for neovascular AMD, with approval of the US Food and Drug Administration (FDA).^{14,15} Similarly, they are also the primary outcome measure in real-world reports of anti-VEGF therapy for neovascular AMD. Refracted best-corrected visual acuity (BCVA) measurements are usually obtained in RCTs, while corrected VA measurements without refraction are often used in real-world settings.^{13,16} The use of VA measurements without refraction is approved by the International Consortium for Health Outcomes Measurement (ICHOM) Macular Degeneration Standard Set¹⁶; however, this, along with potential differences in luminance levels and test distances between patients and between visits, may increase variability in real-world datasets.

The Age-Related Eye Disease Study 2 (AREDS2) was a multicenter phase III RCT designed to assess the effects of nutritional supplements on the course of AMD in people at moderate to high risk of progression to late AMD.¹⁷ The primary outcome of this clinical trial was the development of late AMD, defined as central geographic atrophy (GA) or neovascular AMD. All patients who developed neovascular AMD received standard of care treatment by their local ophthalmologists and continued to be followed up at the AREDS2 annual study visits. Detailed information was also collected on the course of the anti-VEGF therapy given by the local ophthalmologists, including refracted BCVA outcomes at multiple time-points, obtained as part of their AREDS2 study visits. The purpose of this current report was to examine the BCVA outcomes of the subset of AREDS2 participants who developed neovascular AMD and underwent anti-VEGF therapy.

Methods

The study design for AREDS2 has been described previously.¹⁷ In short, 4203 participants aged 50 to 85 years were recruited between 2006 and 2008 at 82 retinal specialty clinics in the USA. Inclusion criteria at enrollment were the presence of either bilateral large drusen or late AMD in one eye and large drusen in the fellow eye. Institutional review board approval was obtained at each clinical site and written informed consent for the research was obtained from all study participants. The research was conducted under the Declaration of Helsinki and complied with the Health Portability and Accessibility Act.

The AREDS2 participants were randomly assigned to placebo, lutein/zeaxanthin, docosahexaenoic acid (DHA) plus eicosapentaenoic acid (EPA), or the combination of lutein/zeaxanthin and DHA plus EPA. At baseline and annual study visits, comprehensive eye examinations were performed by certified study personnel using standardized protocols. The study visits included measurements of the BCVA, with refraction, using the electronic Early Treatment Diabetic Retinopathy Study (ETDRS) VA charts, and capture of digital stereoscopic color fundus photographs.

For the current report, the inclusion criteria were study eyes with a baseline (i.e. at the AREDS2 baseline study visit) AREDS2 severity level of 1 through 9 (i.e. no central GA and no neovascular AMD), baseline refracted BCVA ≥ 50 letters ($\geq 20/100$), no history of previous anti-VEGF injections, and the development of neovascular AMD with at least one anti-VEGF injection during AREDS2 follow-up.

VA data immediately preceding the first anti-VEGF injection were not available (as injections took place in local clinical care settings, and the first injection could have taken place at any time between annual study visits). BCVA data were available from the annual study visit preceding the first anti-VEGF injection (the 'pre-treatment visit'), though these were not considered comparable to VA data immediately before the first injection. Indeed, the pre-treatment visit BCVA could have been measured up to a maximum of one year before the first injection. The 'first post-treatment visit' was defined as the first annual study visit after the first anti-VEGF injection (Figure 1). Subsequent annual study visits were labeled 'second post-treatment visit', 'third post-treatment visit', etc. Refracted BCVA data for the pretreatment visit, the first post-treatment visit, and each subsequent annual post-treatment visit were recorded. VA outcomes at each time point included mean BCVA (ETDRS letters), proportion of eyes with BCVA $\geq 20/40$, proportion of eyes with BCVA $\geq 20/200$, and proportion of eyes that maintained BCVA $\geq 20/40$ (i.e. had BCVA $\geq 20/40$ at the pre-treatment visit and $\geq 20/40$ at the specified post-treatment visit). Follow-up was to a maximum of five years (since median follow-up in the AREDS2 was five years). Participants who developed neovascular AMD earlier during the AREDS2 time-line had longer follow-up, while those who developed neovascular AMD later had shorter follow-up. However, participant retention was very high, such that the number of eyes studied at different time-points reflect staggered start times during the AREDS2 time-line rather than cumulative losses to follow-up.

Questionnaires administered at the baseline and subsequent study visits collected medical and ophthalmologic history information. This comprised details of any treatment for late AMD since the last study visit, including data on anti-VEGF therapy in each eye (i.e. self-reported number of injections, dates of injections, and name of drug injected), as well as information on nutrition, medications, adverse events, and treatment compliance. In addition, at the mid-point between annual study visits, study coordinators contacted participants by telephone to update the medical and ophthalmologic history. Again, standardized information was obtained on the occurrence of any treatment for late AMD since the last study visit, including self-reported data on anti-VEGF therapy in each eye. The study form allowed documentation of up to eight injections per eye in the six-month interval preceding the study visit or telephone contact. Information on anti-VEGF injections was validated by the study coordinators, whenever possible, by verification with the clinical records of the local retinal specialist. For each annual in-person visit included in the analysis, the self-reported number of anti-VEGF injections per eye in the preceding year and cumulative number of anti-VEGF injections per eye were computed.

Statistical analyses were performed with Statistical Analysis System (SAS) 9.4. Descriptive statistics for each time point (categorical distributions, means, standard deviations, and

percentiles) were computed for all eyes (except for person-level characteristics of age and sex).

Results

A total of 1105 eyes of 986 AREDS2 participants met the inclusion criteria for this study (Table 1). At the AREDS2 baseline visit, the mean age of these participants was 74.8 years (range 50.5 to 86.0) and 59.6% were female. The pre-treatment visit occurred at the AREDS2 baseline visit or AREDS2 year 1, 2, 3, 4, and 5 study visits for 18.7%, 21.4%, 22.2%, 22.1%, 13.6% and 2.0% of eyes, respectively. The mean refracted BCVA at the pre-treatment visit was 74.9 letters (Snellen equivalent 20/32), range 0 to 95 letters; 76.4% had BCVA 20/40 and 0.9% had BCVA 20/200 (Table 1). At the pre-treatment visit, the most common AMD score (40.9% of eyes) was 7 (i.e. macular drusen and depigmentation area <0.5 disc areas, or drusen area 0.5 disc areas with any depigmentation), while 6.8% of eyes had a score of 1–5, 8.6% had a score of 9 (non-central GA), 4.1% had a score of 10 (central GA) and 7.5% had a score of 12 (neovascular AMD, i.e. had signs of neovascular AMD on color fundus photography at the AREDS2 visit, had not yet received an anti-VEGF injection, but were about to begin treatment over the subsequent year).

Of the 1105 eyes of 986 participants in this study, 1095 eyes (99.1%) of 977 participants (99.1%) had a first post-treatment visit, i.e. had at least one AREDS2 study visit after the first anti-VEGF injection (Table 1). At the first post-treatment visit, the mean refracted BCVA was 68.0 letters (20/40), range 0 to 93 letters. At this point, the majority of eyes (59.3%) had BCVA 20/40, while 5.5% of eyes had VA 20/200. Of the 829 eyes with BCVA 20/40 at the pre-treatment visit, the majority (71.4%) maintained BCVA 20/40 at the first post-treatment visit. The mean number of self-reported anti-VEGF injections per study eye in the year preceding the first post-treatment visit was 2.9, range 1 to 14.

Of the 1105 eyes of 986 participants in this study, 889 eyes (80.5%) of 802 (81.3%) participants had a second post-treatment visit, i.e. had at least two annual AREDS2 study visits after the first anti-VEGF injection. At the second post-treatment visit, the mean refracted BCVA was 66.1 letters (20/50), range 0 to 95 letters. At this point, the majority of eyes (55.1%) had VA 20/40, while 8.6% of eyes had VA 20/200. Of the 829 eyes with BCVA of 20/40 at the pre-treatment visit, the majority (66.0%) maintained BCVA 20/40 at the second post-treatment visit. The mean number of self-reported anti-VEGF injections in the year between the first and second post-treatment visits was 3.9, range 1 to 15; the mean cumulative number of self-reported injections from initiation of therapy was 6.8, range 1 to 25.

Equivalent data on subsequent post-treatment visits are shown in Table 1. The mean values of refracted BCVA at each study visit are shown in Figure 2. Mean BCVA was 68.0 letters (20/40) at the first post-treatment visit and decreased by approximately 1.5 letters per year to 61.5 (20/60) at the fifth post-treatment visit. The distributions of BCVA data at each study visit are shown in Figure 3. The proportion of study eyes with BCVA 20/40 decreased gradually with time from 59.3% at the first post-treatment visit to 49.7% at the

fifth post-treatment visit. Similarly, the proportion of eyes with BCVA 20/200 slowly increased from 5.5% to 14.4%, at the same time points.

The mean numbers of self-reported injections per study eye in the year preceding the first and subsequent post-treatment visits (i.e. representing full years of potential treatment) were 2.9, 3.9, 3.3, 3.1, and 3.0. The mean cumulative numbers of self-reported injections per study eye at the same time-points (Figure 4) were 2.9, 6.8, 9.9, 12.5, and 15.8. Under the assumption that the first anti-VEGF injection occurred at the mid-point between the pre-treatment visit and the first post-treatment visit, the mean number of self-reported injections per eye over the whole study period was 3.5 per year.

Discussion

The purpose of this study was to present VA outcomes from the subset of AREDS2 participants who underwent anti-VEGF therapy for incident neovascular AMD during AREDS2 follow-up. Mean BCVA decreased slowly over time, at approximately 1.5 letters per year. The proportion of eyes with excellent BCVA decreased gradually, while the proportion with poor vision increased; at the fifth post-treatment annual visit, approximately half of eyes had BCVA 20/40, while the proportion with BCVA 20/200 was 14%.

Although these data were obtained in the context of an RCT, the diagnosis of neovascular AMD and decision-making regarding anti-VEGF therapy initiation and ongoing treatment were made by local ophthalmologists in routine clinical care settings. As described above, differences have been observed between visual outcomes reported in RCTs of anti-VEGF therapy and those obtained in normal clinical care settings. Indeed, the extent to which RCT data are generalizable to populations has been an area of debate in ophthalmology^{11,13,18} and in other medical fields.^{19–22} These ideas have led to increased interest in real-world data, defined by the European Medicine Agency as ‘data collected outside randomized clinical trials usually during normal clinical care’.²³ Multiple real-world reports of visual outcomes following anti-VEGF therapy for neovascular AMD in routine clinical care settings have now been published, including data from meta-analyses, global registries, and electronic medical record (EMR) datasets.^{10,11,13,24–26}

The potential strengths and weaknesses of data from real-world studies and RCTs have been discussed.¹³ These include the fact that data from RCTs may often have higher internal validity but lower external validity (owing to, for example, narrower inclusion criteria, smaller participant numbers, and shorter follow-up times), whereas data from real-world studies may often have lower internal but higher external validity. In this way, the two sources of data should provide complementary evidence. By contrast, real-world observational studies may be useful in assessing to what extent results from interventional trials are generalizable to populations.

Real-world datasets for neovascular AMD are likely to become more standardized and comparable with one another, following recommendations by an ICHOM working group of experts in AMD outcomes.¹⁶ These include guidance that distance VA readings ideally be recorded using a LogMAR chart and that analyses should include not just change in mean

VA but also changes in the proportions of eyes with stable vision, good vision, and poor vision (e.g. as reported in the current study).

Comparison with literature

In the landmark RCT, MARINA, which employed fixed monthly injections of ranibizumab, mean baseline VA was 53.7 letters (20/80) and mean changes in VA at 1 year and 2 years were +7.2 and +6.6 letters, respectively.⁷ These are shown in Table 2, along with equivalent figures for other major RCTs, including ANCHOR (fixed monthly ranibizumab)⁸ and the Comparison of AMD Treatments Trial (CATT; monthly or *pro re nata* (PRN) ranibizumab or bevacizumab).²⁷

Compared with these results, reports from real-world datasets have sometimes demonstrated slightly lower mean VA gains. For example, as shown in Table 2, a study from the UK of 12,951 eyes treated with ranibizumab using predominantly a PRN approach reported baseline VA of 55 letters (20/80) and mean changes in VA at 1, 2, and 3 years of +2, +1, and -2 letters, respectively.¹⁰ However, one of the largest datasets of real-world outcomes of ranibizumab was created through meta-analysis of 42 observational studies; this consisted of over 24,000 eyes, with treatment performed using predominantly a PRN approach.¹¹ This study reported equivalent figures of 53.6 (20/80), +5.0, +3.4, and +1.1 letters, respectively.

Several studies have analyzed the long-term visual outcomes of eyes undergoing anti-VEGF treatment for neovascular AMD. The SEVEN-UP extension study of patients who had participated in MARINA or ANCHOR (followed by the HORIZON study²⁸) examined the visual outcomes of patients treated in routine clinical care after RCT completion: from a mean baseline VA of 54.3 letters, these patients demonstrated a mean change of -8.6 letters at 7 years.²⁹ Similarly, the results for patients who participated in the CATT for 2 years then entered normal clinical care showed a mean VA change of -3.3 letters at 5 years.³⁰ Data from the Fight Retinal Blindness! registry of routine clinical care (in Australia, New Zealand and Switzerland) demonstrated mean VA at baseline and mean change at 5 years and 7 years of 55.1 (20/80), -0.7, and -2.6 letters, respectively.³¹

Baseline VA in the AREDS2 dataset was not assessed at the time of diagnosis of the neovascular event so may not be compared directly with VA data in other studies. However, subsequent trajectories of visual loss can be compared more meaningfully. For example, in the CATT, the mean change in VA from 2 years to 5 years (during routine clinical care) was -10.8 letters (from 69.7 to 58.9).³⁰ In the current study, the mean change in VA for similar timepoints was -4.6 letters (from 66.1 to 61.5). Similarly, in the CATT, the proportion with good VA (20/40) at 2 years and 5 years decreased from 69% to 49%, while the proportion with poor VA (20/200) increased from 5% to 20%. In the current study, the proportion with good VA at the second and fifth post-treatment visits decreased from 55% to 50%, while the proportion with poor vision increased from 9% to 14%. Likely reasons for the less steep decline in VA in the current study include the following inter-related factors: (i) CATT inclusion of subfoveal neovascular AMD only, versus AREDS2 inclusion of neovascular disease in any location; (ii) AREDS2 inclusion of neovascular disease that followed GA, versus CATT exclusion of eyes with subfoveal GA; (iii) CATT requirement of baseline VA 20/320, versus AREDS2 requirement of 20/100 at AREDS2 baseline; (iv) CATT

inclusion of one study eye per patient, versus AREDS inclusion of bilateral neovascular AMD (12% of participants); (v) larger neovascular lesions observed in CATT than in AREDS2 [Maldonado RS, ARVO Abstract 2391, 2018]; (vi) method of data collection.

Data on injection frequency in previous studies are shown in Table 2. Data on injection frequency in the current study are highly limited, since they were obtained principally by patient self-report. In general, the number of injections in this study was very substantially lower than would be obtained by monthly dosing, and also appeared lower than the numbers observed in RCTs using PRN or Treat and Extend dosing. However, the figures were generally comparable (in the second and third years of treatment) to those observed in real-world studies, particularly those in the large meta-analysis of studies.¹¹ However, owing to the limitation of self-report, drawing conclusions from detailed comparison with other studies is not justified.

Strengths and limitations

The strengths of this study include its prospective observational nature, long follow-up period, and very high participant retention. The number of participants was large and all were treatment-naïve (with respect to neovascular AMD); almost 1,000 participants were included in this analysis, with nearly 60% having three year follow-up data. Another important strength is the use of standardized LogMAR BCVA measurement with refraction in all participants at multiple time-points.

One important limitation of this study is the lack of VA data immediately before the first anti-VEGF injection. Although we recorded VA data from the last AREDS2 visit prior to the first injection, we did not seek to present this as comparable with VA data obtained immediately before the first injection. For this reason, we have concentrated on analyzing subsequent trajectories of change in BCVA, rather than present VA outcomes with reference to pre-treatment VA. For similar reasons, follow-up intervals in this study are aligned with AREDS2 visits rather than time since first injection. However, the effect of this phenomenon has less importance at later time-points. In addition, the data on anti-VEGF injections are limited as they were acquired by patient self-report. Although they were collected from all participants every six months and, where possible, verified by the research coordinators with the treating physicians, this limitation means that detailed comparison with injection data from previous studies is not justified.

The results were collected within an RCT, but all anti-VEGF treatment decisions were made by local ophthalmologists during normal clinical care. Indeed, participants received a mixture of ranibizumab, bevacizumab, and (in fewer cases) aflibercept injections, and were treated according to a variety of dosing regimens (including PRN, Treat and Extend, and fixed interval). However, the results are not representative of real-world medicine either: (i) AREDS2 participants may not be representative of all real-world patients (e.g., in terms of comorbidities and adherence to appointments), (ii) ophthalmologists treating AREDS2 participants may not be representative of all real-world ophthalmologists, and (iii) RCT participation may alter management decisions. Hence, this clinical trial population does not represent real world experiences.

Conclusions

In conclusion, we have presented the refracted BCVA outcomes of AREDS2 participants who developed neovascular AMD and underwent anti-VEGF therapy in a routine clinical practice setting. In line with previous RCTs and real-world observational studies, visual outcomes declined slowly with increased follow-up time. These data are valuable in that they were obtained in the context of an RCT but pertain to anti-VEGF therapy given in routine clinical practice, in a well-characterized patient cohort. These data may be useful in assessing the long-term effects of anti-VEGF therapy.

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Abbreviations

AMD	age-related macular degeneration
AREDS2	Age-Related Eye Disease Study 2
BCVA	best-corrected visual acuity
CATT	Comparison of AMD Treatments Trial
DHA	docosahexaenoic acid
EMR	electronic medical record
EPA	eicosapentaenoic acid
ETDRS	Early Treatment Diabetic Retinopathy Study
FDA	Food and Drug Administration
GA	geographic atrophy
ICHOM	International Consortium for Health Outcomes Measurement
PRN	pro re nata
RCT	randomized controlled trial
SAS	Statistical Analysis System
VA	visual acuity
VEGF	vascular endothelial growth factor

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Figure 1.

Diagram showing the timeline and nomenclature of the Age-Related Eye Disease Study 2 (AREDS2) annual study visits in relation to the first anti-VEGF injection for each eye, i.e., demonstrating the ‘first post-treatment study visit’ and subsequent post-treatment study visits.

Figure 2.

Mean refracted best-corrected visual acuity (BCVA) of study eyes (Age-Related Eye Disease Study 2, AREDS2) over time, according to first and subsequent post-treatment study visits. Alongside the mean BCVA for eyes in this study (diamonds) are shown equivalent BCVA data for the Comparison of AMD Treatments Trial (CATT; circles); these are shown half-way between AREDS2 annual study visits because the CATT data were captured at yearly intervals after the first anti-VEGF injection, whereas the AREDS2 data were captured at variable periods of 0–11.9 months after first anti-VEGF injection (and yearly thereafter).

Figure 3.

Proportions of study eyes with different levels of refracted Snellen best-corrected visual acuity (BCVA) over time, according to first and subsequent post-treatment study visits.

Figure 4.

Cumulative self-reported numbers of anti-VEGF injections per study eye from initiation of treatment, according to first and subsequent post-treatment study visits. The boxes extend from the first to the third quartiles, while the whiskers extend from the minimum to the maximum values. The horizontal lines indicate the median values, while the crosses show the means; the means are also given numerically beside the plot.

Table 1.

Best-corrected visual acuity (BCVA) outcomes and self-reported number of anti-VEGF injections during the Age-Related Eye Disease Study 2.

	Pre- treatment visit	Post-treatment annual AREDS2 study visits				
		First	Second	Third	Fourth	Fifth
Eyes, n (%)	1105 (100)	1095 (99.1)	889 (80.5)	648 (58.6)	401 (36.3)	166 (15.0)
Mean BCVA, ETDRS letters (SD); (Snellen equivalent)	74.9 (11.8) (20/32)	68.0 (17.4) (20/40)	66.1 (19.6) (20/50)	64.7 (20.7) (20/50)	63.2 (22.1) (20/50)	61.5 (23.3) (20/60)
BCVA range, n (%)						
20/40	829 (76.4)	621 (59.3)	457 (55.1)	318 (53.5)	179 (50.6)	76 (49.7)
20/200	10 (0.9)	58 (5.5)	71 (8.6)	56 (9.4)	44 (12.4)	22 (14.4)
Maintained 20/40	-	569 (71.4)	414 (66.0)	286 (62.3)	166 (59.3)	70 (58.3)
20/20	213 (19.6)	114 (10.9)	85 (10.2)	60 (10.1)	31 (8.8)	10 (6.5)
<20/20 to 20/40	616 (56.8)	507 (48.4)	372 (44.8)	258 (43.4)	148 (41.8)	66 (43.1)
<20/40 to 20/80	203 (18.7)	246 (23.5)	212 (25.5)	142 (23.9)	86 (24.3)	40 (26.1)
<20/80 to 20/160	38 (3.5)	110 (10.5)	82 (9.9)	67 (11.3)	37 (10.4)	13 (8.5)
<20/160 to 20/500	11 (1.0)	45 (4.3)	47 (5.7)	37 (6.2)	32 (9.0)	13 (8.5)
<20/500	4 (0.4)	25 (2.4)	32 (3.9)	30 (5.0)	20 (5.6)	11 (7.2)
Mean injections per eye (self-reported) *	-	2.9	3.9	3.3	3.1	3.0
Mean cumulative injections per eye (self-reported)	-	2.9	6.8	9.9	12.5	15.8

AREDS2=Age-Related Eye Disease Study 2; BCVA=best-corrected visual acuity; ETDRS=Early Treatment of Diabetic Retinopathy Study; SD=standard deviation

* in the year preceding the visit

Comparison with literature: visual acuity outcomes and self-reported injection frequency in eyes with neovascular age-related macular degeneration undergoing anti-VEGF therapy in randomized controlled trials and real-world observational studies.

Table 2.

	Current study	Randomized controlled trial data			Real-world data						
	AREDS2	MARINA	ANCHOR	CATT		Meta-analysis (global data)	UK AMD EMR Users Group	LUMINOUS	IRIS Registry		
Treatment regimen	Any drug Any regimen	Ranibizumab Fixed monthly	Ranibizumab Fixed monthly	Ranibizumab Fixed monthly	Ranibizumab PRN	Ranibizumab Predom. PRN	Ranibizumab Predom. PRN	Ranibizumab Any regimen	Any single drug Any regimen		
Eyes at baseline (n)	1105	478	280	301	298	24,178	12,951	3379	13,859		
Mean VA: ETDRS letters (Snellen equivalent)											
Mean injections per year (n)											
Baseline	-	53.7 (20/80)	47.1 (20/120)	59.9 (20/60)	61.8 (20/60)	53.6 (20/80)	55 (20/80)	51.9 (20/100)	0.57 [*] (20/80)		
1 year	68.0 (20/40) 2.9 [†]	60.9 (20/60) 12	58.4 (20/60) 12	68.4 (20/40) 11.7	68.6 (20/40) 6.9	58.6 (20/60) 6.3 or 5.0 ^{**}	57 (20/80) Median 5	55.0 (20/80) 5.0	0.52 [*] (20/60) 6.1		
2 years	66.1 (20/50) 3.9 [†]	60.3 (20/60) 12	57.8 (20/60) 12	68.7 (20/40) 22.4 over 2y	68.5 (20/40) 12.6 over 2y	57.0 (20/80) 4.4 or 3.8 ^{**}	56 (20/80) Median 4				
3 years	64.7 (20/50) 3.3 [†]					54.7 (20/80) 3.3 or 3.8 ^{**}	53 (20/80) Median 4				
5 years	61.5 (20/60) 3.0 [†]			58.9 (20/60) Mean 15.4 over mean 3.5y (after RCT exit); mean '4 to 5' per year (CATT Follow-up Study, i.e. routine clinical care after RCT; n=647)							
7 years		45.7 (20/120) Mean 6.8 over mean 3.4y (after HORIZON exit); mean 1.6 per year (SEVEN-UP study, i.e. routine clinical care after RCT; n=65)									

* LogMAR VA

[†] Mean self-reported number of injections per year

^{**} Random-effects estimate and weighted mean, respectively

ANCHOR=Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration; AREDS2=Age-Related Eye Disease Study 2; CATT=Comparison of Age-Related Macular Degeneration Treatments Trial; ETDRS=Early Treatment of Diabetic Retinopathy Study; IRIS=Intelligent Research in Sight; MARINA=Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration; PRN=*Pro Re Nata*; RCT=Randomized Controlled Trial; SEVEN-UP=Seven-Year Observational Update of Macular Degeneration Patients Post-MARINA/ANCHOR and HORIZON Trials; UK AMD EMR Users Group=United Kingdom Age-Related Macular Degeneration Electronic Medical Record Users Group