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Real-world Outcomes of Anti–Vascular Endothelial Growth Factor Therapy in Neovascular Age-Related Macular Degeneration in the United States

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Purpose: Real-world visual outcomes of anti–vascular endothelial growth factor (anti-VEGF) therapy for neovascular age-related macular degeneration (nAMD) have been reported in cohorts outside of the United States. This study sought to assess the relationship between presenting visual acuity (VA) and visual outcomes, as well as the potential impact of loss to follow-up, in real-world anti-VEGF–treated nAMD patients from the United States.

Design: Retrospective study of aggregated, longitudinal electronic medical records obtained from a geographically diverse sample of US retina specialists and included in the Vestrum Health Retina Database.

Participants: Inclusion criteria were a diagnosis of nAMD, no previous treatment, and ≥3 monthly anti-VEGF injections in the first 4 months from diagnosis in patients diagnosed between January 2011 and July 2013.

Methods: To model loss to follow-up, mutually exclusive cohorts of nAMD patients with loss to follow-up after specific time points of 6 and 12 months (i.e., no follow-up beyond) were compared with a separate cohort of patients who completed 24 months of follow-up ending prior to July 2015 (n = 2213).

Main Outcome Measure: VA outcomes were assessed on each cohort as a whole, with additional stratification by baseline VA.

Results: The 6-, 12-, and 24-month cohorts received means of 5.4, 7.3, and 12.1 injections and showed no change, no change, and a mean change of +3.1 letters from baseline (95% confidence interval 1.8–4.4 letters, $P < 0.01$), respectively. When stratified by baseline VA, nearly all groups lose VA at their respective follow-up periods, except for those with baseline VA of 20/200 or worse.

Conclusions: Real-world nAMD patients in the United States receive fewer anti-VEGF injections and experience worse visual outcomes compared with patients in randomized clinical trials, consistent with non-US studies. Patients with better VA at presentation tend to be particularly vulnerable to vision loss. Compared with other patients, those ultimately lost to follow-up have worse visual outcomes at, or prior to, their final visit, suggesting that loss to follow-up may lead to overestimation of visual outcomes in clinical studies of nAMD. *Ophthalmology Retina 2018;■:1–9 © 2018 by the American Academy of Ophthalmology*

Anti–vascular endothelial growth factor (anti-VEGF) therapy is currently the standard of care for neovascular age-related macular degeneration (nAMD). The original ranibizumab registration trials ANCHOR (Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration Study) and MARINA (Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of nAMD) yielded improvement of 11.3 and 7.2 Early Treatment Diabetic Retinopathy Study letters, respectively, at 1 year with monthly treatment,[1,2] and subsequent randomized controlled trials (RCTs) have demonstrated similar efficacy among commonly used anti-VEGF therapies.[3,4] However, large real-world studies of anti-VEGF therapy in nAMD, which are based on chart reviews, electronic medical records (EMRs), or claims analyses, have reported less favorable visual outcomes.[5–17] These real-world studies originate from outside the United States and demonstrate that nAMD patients generally lose vision within 2 to 5 years of diagnosis, despite anti-VEGF therapy.[5,8–12,15,16] Although the cause of discrepancies between these non-US real-world studies and RCTs is unknown, possibilities include patient characteristics and undertreatment associated with variable-frequency treatment regimens (e.g., not regularly repeating monthly injections for ranibizumab or bevacizumab, or bimonthly for aflibercept).[6–8,12,13] Furthermore, these non-US real-world nAMD studies suggest that patients with better baseline visual acuity (VA) experience greater loss of vision than those patients with worse baseline VA, despite treatment with anti-VEGF therapy.[11,13,15,17] Finally, several of these non-US real-world nAMD studies have observed high loss to follow-up, between approximately 20% and

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30% of patients in the first year,[7,9,13,15] and some studies suggest that, compared with other patients, those ultimately lost to follow-up have worse visual outcomes at or prior to their final visit.[9,11,13,18]

In the current study, we sought to determine whether the real-world nAMD experience with anti-VEGF therapy in the United States was similar to that reported in patient populations outside of the United States, where the health care systems, treatment availability, and treatment regimens may differ. We also sought to assess the influence of patients' loss to follow-up under anti-VEGF treatment on the study end point of visual outcome. In this study, we specifically assessed nAMD patients lost to follow-up after 6 and 12 months compared with those patients who were followed for 24 months in a large database of aggregated, longitudinal EMRs from a geographically and demographically diverse sample of US retina specialists.

Methods

Database

The database consisted of aggregated, longitudinal EMRs from a demographically and geographically diverse patient sample that was obtained from hundreds of US retina specialists (Vestrum Health, LLC, Knoxville, TN). Aggregated data included detailed information on in-office and outpatient pharmaceutical use, clinical findings, diagnostic-test interpretation, ocular and systemic diagnoses, surgical utilization, outcomes, and adverse events. All information was deidentified, in accordance with the regulations of the Health Insurance Portability and Accountability Act of 1996, by a proprietary process during which patient identifiers are removed and replaced with an alphanumeric identifier that was generated using an industry-standard 1-way algorithm. The names of treating physicians and practices were removed from the data. The formula used to convert Snellen visual acuity measurements to ETDRS letter scores was 85 + 50 x log (Snellen fraction). The database is refreshed on a weekly basis.

Study Design, Dates for Data Collection, and Inclusion Criteria

This project was considered exempt from institutional review board review, as all patient information was deidentified as noted previously. This retrospective, uncontrolled review studied treatment-naïve nAMD patients who were diagnoses during the period from January 2011 to July 2013 and whose records were included in the Vestrum Health Retina Database. At the time of the analysis, there were 77 985 nAMD patients in the database. Inclusion criteria were as follows: a diagnosis of nAMD, no previous treatment, ≥3 monthly anti-VEGF injections in the first 4 months from diagnosis between January 2011 and July 2013. To model patient loss to follow-up, mutually exclusive cohorts of patients lost to follow-up after specific time points of 6 and 12 months (i.e., no follow-up beyond) were compared with a separate cohort of patients who completed 24 months of follow-up that ended prior to July 2015. Age, gender, number of treatments, and VA were extracted from the database. VA measurements were not standardized in this retrospective uncontrolled review.

Analysis

The patients were divided into 3 cohorts: those with records that included VA measurements up to and including 6 months from diagnosis but were lost to follow-up beyond (6-month cohort), up to and including 12 months from diagnosis but lost to follow-up beyond (12-month cohort), and those up to and including 24 months from diagnosis (24-month cohort), with each cohort being mutually exclusive of the others. Any patient who died, relocated, or transferred care was classified as lost to follow-up for the purposes of this analysis. VA outcomes were assessed on each cohort as a whole and stratified by baseline VA.

Baseline characteristics were summarized with descriptive statistics. Mean values for patient demographics, number of injections, and baseline and final VA measurements (letters) were calculated. VA outcomes compared with baseline VA were assessed with inferential statistics. The mean change in VA from baseline was calculated, along with 95% confidence intervals and *P* values, using paired *t* tests. This analysis was also performed after stratifying the patients by baseline VA within each of the cohorts.

Results

Demographics

At the time of the analysis, there were 77 985 nAMD patients in the Vestrum Health Retina Database. Based on the inclusion criteria, 2213 nAMD patients were eligible for this study: 97 (4%) in the 6-month cohort, 195 (9%) in the 12-month cohort, and 1921 (87%) in the 24-month cohort. Baseline demographics are summarized in Table 1. The overall mean age was 82 years, with 36% male patients and 63% female patients; the mean age and sex ratios were similar across cohorts. The initial anti-VEGF agent was aflibercept in 13% of patients, ranibizumab in 17%, and bevacizumab in 70%, which was similar across cohorts, except for within the 6-month cohort, which had a greater proportion of aflibercept use at 20%. The baseline means VA of the 6-, 12-, and 24-month cohorts were 39.3, 43.1, and 47.5 letters, respectively.

Injection Frequency and Visual Outcomes

In general, patients who received variable-frequency anti-VEGF injections experienced worse outcomes compared with those of patients receiving fixed, frequent therapy (regularly repeating monthly injections for ranibizumab or bevacizumab, or bimonthly injections for aflibercept) in RCTs (Table 1). The 6-month cohort presented with a baseline mean VA of 39.3 letters, received a mean of 5.4 injections, and showed a final mean VA of 38.7 letters (95% confidence interval for change in VA in letters −6.1 to 4.9, $P = 0.41$, i.e., no significant difference from baseline). The 12-month cohort presented with a baseline mean VA of 43.1 letters, received a mean of 7.3 injections, and showed a final mean VA of 42.4 letters (95% confidence interval for change in VA in letters −4.4 to 2.9, $P = 0.34$, i.e., no significant difference from baseline). The 24-month cohort presented with a baseline mean VA of 47.5 letters, received a mean of 12.1 injections and showed a final mean VA of 50.6 letters, for a net gain of 3.1 letters (95% confidence interval 1.8−4.4 letters, $P < 0.01$). There were no significant differences in the number of injections among intracohort baseline VA groups.

Baseline VA and Visual Outcomes

Better baseline VA trended with increased risk of vision loss during anti-VEGF therapy for nAMD, but it also trended with better final VA compared with that of patients with worse baseline VA (Table 2 and Figure 1). When stratified by baseline VA, nearly all groups lose VA, except for those with poor baseline VA (20/200 or worse, Figure 2). These results were slightly statistically significant for most baseline VA subgroups in the

Table 1. Patient Demographics, Treatments, and Visual Outcomes*

	Overall	24-Month Cohort	12-Month Cohort	6-Month Cohort
Number of patients	2213	1921	195	97
Mean age at initial treatment, yrs	82	82	83	81
Sex				
Female, %	63	63	59‡	63
Male, %	36	36	38	32
Sex unidentified, %	1	1	2	5
Anti-VEGF Agent†				
Aflibercept, %	13	12	12	20
Ranibizumab, %	17	17	18	15
Bevacizumab, %	70	71	70	65
Mean Number of Injections		12.1	7.3	5.4
Baseline Mean VA, letters		47.5	43.1	39.3
Final Mean VA, letters		50.6	42.4	38.7
Change in Mean VA, letters		+3.1	−0.7	−0.6
95% Confidence Interval, Change in Mean VA, letters		1.8 to 4.4	−4.4 to 2.9	−6.1 to 4.9
P value, Change in Mean VA		<0.01	0.34	0.41

EMR = electronic medical record; nAMD = neovascular age-related macular degeneration; VA = visual acuity; VEGF = vascular endothelial growth factor.

*Treatment-naïve nAMD patients diagnosed from January 2011 to July 2013 included in the Vestrum Health Retina Database.

†The breakdown of anti-VEGF agents prescribed in this study is affected by the study inclusion dates (between January 2011 and July 2013), given that aflibercept was not approved until late 2012, and the distribution of EMRs included in the Vestrum Health Retina Database at the time of the study. This breakdown is similar to preferred first-line therapy in the United States according to the American Society of Retina Specialists 2015 "Preferences and Trends" survey: 64% bevacizumab, 14% ranibizumab, 21% aflibercept. After accounting for baseline VA distribution, the choice of initial anti-VEGF therapy had no meaningful effect on visual outcomes in any of the cohorts.

‡Sum of Sex percentages in the 12-Month Cohort is low due to rounding.

24-month cohort and in some of the baseline VA subgroups in the 12-month cohort, as described in Table 2. Additionally, after accounting for baseline VA distribution, the choice of initial anti-VEGF therapy had no effect on visual outcomes in any of the cohorts.

In the 24-month cohort, patients with baseline VA of 20/70 or better experienced loss of VA from baseline by the 2-year time point (Figures 1 and 3). Notably, the group with baseline VA of 20/40 or better showed visual loss at all time points. In this 24-month cohort, the mean final change in VA was −5.2 letters

Table 2. Mean Letters Gained or Lost in Each Cohort, Stratified by Baseline Visual Acuity

24-Month Cohort	N	Change in VA from Baseline to Month 24, letters	*P* value	95% Confidence Interval, letters
All eyes	1921	3.1	<0.01	1.8 to 4.4
Baseline VA 20/40 or better	409	−5.2	<0.01	−6.7 to −3.5
Baseline VA 20/41 to 20/70	559	−1.2	0.10	2.9 to 0.6
Baseline VA 20/71 to 20/200	588	2.6	0.02	0.2 to 5.0
Baseline VA 20/201 or worse	365	19.9	<0.01	15.7 to 23.4
12-Month Cohort	**N**	**Change in VA from Baseline to Month 12, letters**		**95% Confidence Interval, letters**
All eyes	195	−0.7	0.34	−4.4 to 2.8
Baseline VA 20/40 or better	34	−4.5	0.01	−8.8 to −0.6
Baseline VA 20/40 to 20/70	55	−5.6	0.08	−13.6 to 2.4
Baseline VA 20/70 to 20/200	61	−1.3	0.35	−8.0 to 5.4
Baseline VA 20/200 or worse	45	8.9	0.02	0.9 to 16.9
6-Month Cohort	**N**	**Change in VA from Baseline to Month 6, letters**		**95% Confidence Interval, letters**
All eyes	97	−0.6	0.41	−6.1 to 4.9
Baseline VA 20/40 or better	12	−5.2	0.21	−18.9 to 8.5
Baseline VA 20/40 to 20/70	22	−1.9	0.31	−9.7 to 5.9
Baseline VA 20/70 to 20/200	38	−4.6	0.18	−14.9 to 5.6
Baseline VA 20/200 or worse	25	8.8	0.07	−3.1 to 20.7

VA = visual acuity.

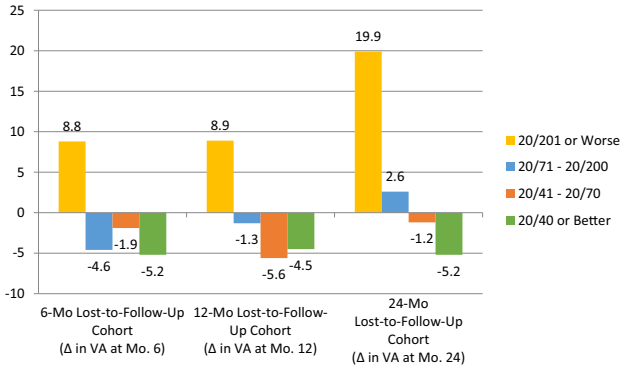

Figure 1. Mean letters gained or lost in each cohort, stratified by baseline visual acuity (VA). The figure shows the mean change in VA at 6, 12, and 24 months, respectively, stratified by baseline VA. Those patients with baseline VA of 20/201 or worse gain VA over time in each of the cohorts, whereas those patients with better baseline VA generally lose VA over time.

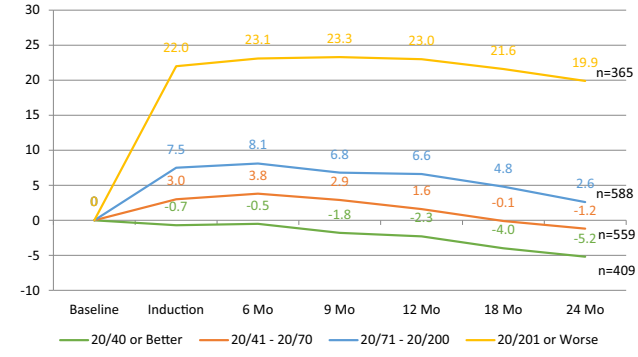

Figure 3. Visual outcomes in the 24-month cohort. Mean visual acuity (VA) over time, stratified by baseline VA, is depicted for the patients of the 24-month cohort. In this cohort, patients with better baseline VA showed worse visual outcomes at each time point than patients with better baseline VA showed. Patients with a baseline VA of 20/70 or better experienced loss of VA from baseline at the 2-year time point. Those patients with baseline VA of 20/40 or better showed visual loss at all time points.

in patients with baseline VA 20/40 or better, −1.2 letters in those with 20/40 to 20/70, +2.6 letters in those with 20/70 to 20/200, and +19.9 letters in those with 20/200 or worse (Figures 1 and 3). This result did not correlate with the relative number of injections administered (Figure 4), as these patients all received a similar number of injections on average. In particular, those patients with baseline VA of 20/40 or better and 20/40 to 20/70 received a similar number of injections (12.1 and 12.9 injections, respectively) as those patients with baseline VA of 24/70 to 20/200 and 20/200 or worse (12.4 and 10.2 injections, respectively).

In the 12-month cohort, the mean final change in VA was −4.5 letters in patients with baseline VA of 20/40 or better, −5.6 letters in those 20/40 to 20/70, −1.3 letters in those 20/70 to 20/200, and +8.9 letters in those 20/200 or worse (Figures 1 and 5). On average, each of these groups received a similar number of injections. In this 12-month cohort, all 3 patient groups with baseline VA better than 20/200 actually lost VA by the time they were lost to follow-up. Vision in this group was lost at an earlier time point compared with that of the 24-month cohort.

In the 6-month cohort, there was a similar trend, although it was not statistically significant (Figures 1 and 6). Like in the other cohorts, each of these subgroups received a similar number of injections on average.

Loss to Follow-up and Visual Outcomes

Patients who were lost to follow-up at earlier time points (i.e., 6- and 12-month cohorts) experienced worse relative visual outcomes compared with those of patients treated for longer duration (the 24-month cohort; Table 1). As noted previously, each cohort was mutually exclusive of the others and best VA outcomes were evident in the 24-month cohort, with +3.1 letters gained at month 24 from baseline, compared with the 6-month and 12-month cohorts, which showed no difference from baseline VA. Moreover, loss was observed across all baseline VA groups of 20/200 or better for the 6- and 12-month cohorts by the 6-month time point from baseline (Figures 1 and 6).

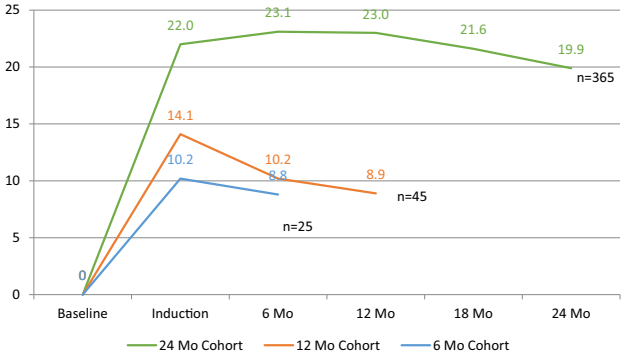

Figure 2. Visual acuity (VA) improves in patients with baseline VA of 20/201 or worse. Mean VA over time is depicted in those patients from each cohort with baseline VA of 20/201 or worse. Each cohort was mutually exclusive of the others. Patients lost to follow-up at earlier time points (i.e., 6- and 12-month cohorts) experienced worse relative visual outcomes compared with patients treated for longer duration (the 24-month cohort).

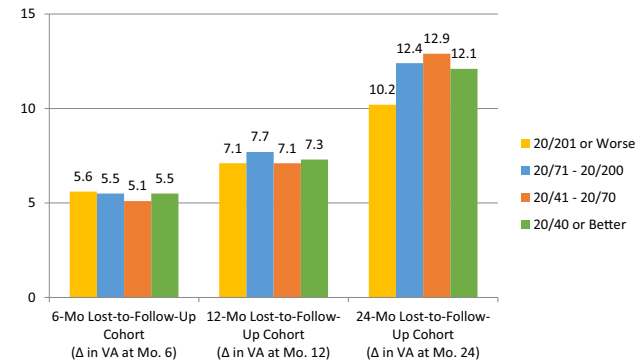

Figure 4. The mean number of treatments for each cohort stratified by baseline visual acuity (VA). The mean number of treatments for each cohort stratified by baseline VA is depicted. Inclusion required previously treatment-naïve patients with neovascular age-related macular degeneration (nAMD) to have received ≥3 monthly injections of anti–vascular endothelial growth factor in the first 4 months from diagnosis. Within the 6- and 12-month cohorts, there were no differences in the mean number of treatments when results were stratified by baseline VA. Within the 24-month cohort, although those patients with baseline VA of 20/201 or worse showed the greatest gain in VA, they received fewer treatments on average than patients with better baseline VA.

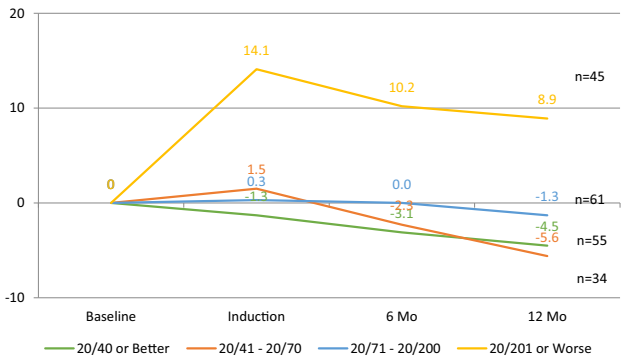

Figure 5. Visual outcomes in the 12-month cohort. Mean visual acuity (VA) over time, stratified by baseline VA, is depicted for patients from the 12-month cohort. Those patients with baseline VA of 20/40 or better showed visual loss at all time points. Vision in this 12-month cohort was lost at an earlier time point than in the 24-month cohort.

Discussion

This study specifically assesses the relationship of visual outcomes and duration of follow-up in real-world anti-VEGF–treated nAMD patients from the United States. The real-world sample was derived from a database of aggregated, longitudinal EMRs representing a geographically and demographically diverse group of patients who were examined by retina specialists in the United States.

Naturally, compared with RCTs, these real-world studies are prone to worse therapeutic outcomes, given more-diverse patient presentations that likely include advanced disease states that are not consistently eligible for RCTs. This real-world study is also limited by its retrospective nature, utilization of aggregated data from numerous clinical sites, and nonstandardized VA assessment among the sites. Specifically, inferential testing in retrospective studies is inherently limited by selection bias, and consequently, the resulting *P* values are only nominal in nature. Furthermore, the patient sample may not have entirely resembled real-world patients, given the eligibility requirement for ≥3 monthly anti-VEGF injections in the first 4 months from diagnosis, although many retina specialists in the United States do include a series of initial monthly injections as part of an induction regimen. In addition, the 6-month cohort included a smaller number of patients, and the study involved differing anti-VEGF agents analyzed without distinction; in particular, there was predominant real-world use of bevacizumab, which has been shown to be non-inferior to ranibizumab,[19,20] and various regimens of aflibercept have also been shown to be noninferior to monthly ranibizumab injections.[4,21]

Although mining EMR has numerous limitations, the resulting data may yield important longitudinal insights into patient outcomes in clinical practice. Most important, this study reveals 3 pertinent insights. First, in the United States, real-world nAMD patients experience worse visual outcomes and receive fewer anti-VEGF injections compared with patients receiving fixed, frequent therapy in RCTs. Second, eyes with better VA at presentation tend to be particularly vulnerable to vision loss compared with eyes with worse VA at presentation. Last, compared with other patients, those ultimately lost to follow-up tend to demonstrate worse visual outcomes at, or prior to, their final visit, suggesting that loss to follow-up may lead to overestimation of visual outcomes in clinical studies of nAMD. In particular, because many real-world and long-term nAMD studies show significant loss to follow-up, this study suggests that anti-VEGF treatment outcomes in nAMD may be worse than reported in many cases.

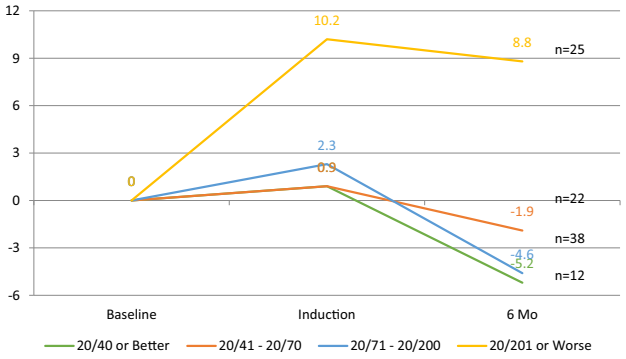

Figure 6. Visual outcomes in the 6-month cohort. Mean visual acuity (VA) over time, stratified by baseline VA, is depicted for patients from the 6-month cohort. In this cohort, vision loss generally occurs at an even earlier time point than in the 12-month cohort.

Real-world nAMD Patients Experience Worse Outcomes Compared with RCTs

Real-world nAMD patients in our US-based study experienced worse visual outcomes and received fewer anti-VEGF injections compared with patients receiving fixed, frequent therapy in RCTs. When stratified by baseline VA, nearly all groups in this real-world US study lose VA, even at the 6-month time point, except for those with baseline VA of 20/200 or worse. Moreover, each intracohort baseline VA group received a similar number of injections. Numerous non-US studies, where health care systems and treatment approaches differ, have also revealed real-world outcomes that are worse than those in RCTs.[5–16]

One possible explanation for this less favorable outcome is undertreatment. A prior US-based retrospective analysis of medical claims from 2006 to 2011 similarly showed that, compared with RCTs, patients in the United States received fewer anti-VEGF treatments and less-frequent monitoring.[22] Multiple published reports have revealed a direct relationship between the number of injections and visual outcome, with fewer injections associated with worse VA.[6–8,12,15,23] Specifically, when the number of injections per year drops below 5 to 6, VA is usually lost by year 2.[6–8,12,15,23] A pertinent non-US multicountry real-world analysis of 2227 medical records showed collectively that patients who received a mean of 5.5 and 2.2 injections in the first and second years gained only 2.4 and 0.6 letters from baseline, respectively.[8] Furthermore, that study revealed that mean letters gained at 24 months was greater in countries in

which patients received a greater number of injections on average.[8]

One reason for fewer injections in the real-world compared with the number in RCTs involves the adoption of variable-frequency anti-VEGF treatment regimens that aim to decrease treatment burden for nAMD patients. The 2015 American Society of Retina Specialists "Preferences and Trends" survey of >2700 retina specialists in 60 countries revealed that >90% of retina specialists, both in the United States and internationally, utilize OCT-guided variable-frequency anti-VEGF treatment protocols for nAMD. In the current study, both the 12- and 24-month cohorts received a mean number of injections similar to that found in the prior US claims analysis and similar to that used in the as-needed treatment arms of CATT (Comparison of AMD Treatment Trials).[3,19,22] These findings confirm that US physicians are generally employing variable-frequency treatment regimens for nAMD.

Multiple prospective RCTs have demonstrated that variable frequency anti-VEGF therapy for nAMD results in a less favorable visual outcome compared with that of fixed, frequent anti-VEGF suppression. In CATT, patients assigned to monthly treatment regimens of ranibizumab or bevacizumab experienced a statistically significant greater benefit in VA gain compared with those receiving as-needed therapy (difference of 2.4 Early Treatment Diabetic Retinopathy Study letters at 2 years, $P = 0.046$).[19] The HARBOR (Phase III, Double-Masked, Multicenter, Randomized, Active treatment-controlled Study of the Efficacy and Safety of 0.5 mg and 2.0 mg Ranibizumab Administered Monthly or on an As-needed Basis in Patients With Subfoveal nAMD Study) and IVAN (Alternative Treatments to Inhibit VEGF in Age-Related CNV) prospective RCTs also suggested inferior visual outcomes with as-needed treatment compared with those of monthly treatment, although the results did not achieve statistical significance.[20,24] Furthermore, in CATT, those patients rerandomized from monthly to as-needed treatment at month 12 experienced a mean loss of 2.2 letters by month 24 ($P = 0.03$).[19] Similarly, in the VIEW (VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD) trials, when variable-frequency treatment regimens were adopted at month 12, mean VA declined in both the ranibizumab and aflibercept treatment arms by month 24.[21] A number of other prospective RCTs have studied a fixed, less frequent regimen in which treatment frequency is reduced to every 3 months after the initial 3 monthly induction injections. For example, in the PIER (Phase IIIb, Multicenter, Randomized, Double-Masked, Sham Injection-Controlled Study of the Efficacy and Safety of Ranibizumab in Participants With Subfoveal CNV With or Without Classic CNV Secondary to AMD) study, which treated patients monthly for 3 months followed by quarterly, VA had improved by 4.3 letters at month 3 but declined by month 12 to a net loss of 0.2 letters from baseline.[25,26] Likewise, in the Efficacy and Safety of Ranibizumab in Patients with Subfoveal CNV Secondary to AMD study, the identical regimen yielded similar results at month 12.[27]

Another variable-frequency regimen, treat and extend (TAE), seems to perform relatively well in practice, based mainly on retrospective studies, 1 large, noncomparative study (LUCAS [Comparison of ranibizumab and bevacizumab for neovascular age-related macular degeneration according to LUCAS treat-and-extend protocol]),[28] and 1 small, prospective, controlled study (TREX [Prospective Trial of Treat-and-Extend versus Monthly Dosing for Neovascular Age-Related Macular Degeneration]),[29] but the level of evidence is not as strong without large-scale, controlled trials. However, in these studies that have shown good visual outcomes with the TAE regimen, the mean number of treatments in the first year was 10.1 in the TREX study[29] and 8.0 and 8.9 for ranibizumab and bevacizumab respectively in the LUCAS study.[28] Like the fixed frequent regimens, the treatment intensity in these TAE studies also exceeds that of the current study, further supporting the relative undertreatment in the real-world. Consequently, it is not surprising that longer term outcomes in studies with variable-frequency regimens relying on investigator discretion for treatment are suboptimal. For example, the open-label extension trial of the ANCHOR and MARINA studies (HORIZON [An Open-Label Extension Trial of Ranibizumab for Choroidal Neovascularization Secondary to Age-Related Macular Degeneration]) showed insidious loss of vision with variable-frequency therapy, yielding a net mean VA improvement of only 2 letters 4 years after initiating ranibizumab therapy.[30] More recently, in a follow-up study of CATT, patients experienced a net mean loss of 3 letters with variable-frequency therapy 5 years after initiating anti-VEGF treatment.[31]

nAMD Patients With Better VA at Presentation Tend to be Particularly Vulnerable to Vision Loss

This study corroborates findings of prior non-US studies by showing that nAMD patients with good baseline VA tend to be particularly vulnerable to vision loss despite treatment with anti-VEGF therapy, although they show better final VA compared with those patients with worse baseline VA.[8,11,13,15,17,32] Apparently, nAMD patients with better baseline VA may have greater potential magnitude for loss of VA than patients with worse baseline VA, and they may be more sensitive to variable-frequency anti-VEGF treatment regimens. Furthermore, other studies have shown that a significant percentage of nAMD patients being treated with variable-frequency therapy who then experience only a modest drop in VA never recover, despite subsequent implementation of more-intensive anti-VEGF treatment regimens.[33] Consequently, appropriate treatment for nAMD patients with better baseline VA is crucial, given the importance of preserving and improving vision, which is strongly associated with independence and employment.

Real-world nAMD Patients Lost to Follow-up Tend to Experience Worse Outcomes

Multiple real-world studies of anti-VEGF therapy for nAMD have observed a high rate of patients lost to follow-up, ranging from approximately 20% to 30% of patients lost in the first year.[7,9,13,15] In nAMD, loss of patients to follow-up is often related to poor response to treatment, transportation issues, cost, older age, treatment

fatigue, illness, or death.[8,9,11,14,30] Moreover, it has been observed that nAMD patients who are ultimately lost to follow-up have worse evolving visual outcomes compared with that of other patients.[9,11,13]

This study corroborates these prior studies; compared with other patients, those ultimately lost to follow-up have worse visual outcomes at, or prior to, their final visit. Furthermore, this result was noted regardless of baseline VA. In particular, this observation held despite worse baseline VA in the 6- and 12-month cohorts compared with that of the 24-month cohort, suggesting that the association between loss to follow-up and worse visual outcome is stronger than the inverse relationship between baseline VA and visual outcome. Limited patient compliance may account for the association between loss to follow-up and worse visual outcome, as patients with poorly evolving outcomes may not return for treatment. This finding is supported by 2 real-world non-US studies of anti-VEGF therapy in nAMD, which noted that, of those patients who failed to return for follow-up, approximately 30% to 40% cited poor visual outcomes.[9,11] These same studies also showed that lack of disease activity, defined as absence of exudation on OCT results, accounted for 30% to 45% of the cases lost to follow-up.[9,11] However, as demonstrated in 1 non-US study of anti-VEGF therapy in nAMD, regular follow-up remains important even when exudation is absent on OCT results, as inactive eyes no longer undergoing treatment often experience subsequent disease recurrence with poor visual outcomes.[11]

In this study, nAMD patients who are ultimately lost to follow-up tend to experience worse visual outcomes compared with those of patients who continue with follow-up, suggesting that clinical studies of nAMD with high loss to follow-up may overestimate visual outcomes. For example, 1 recent real-world nAMD study with an aflibercept bimonthly regimen showed a mean VA gain of approximately 5 letters in patients with 1 year of follow-up visits, which is less than the gains observed in RCTs.[13] Notably, 28% of patients who entered the study did not have 12-month data and were not included in the primary VA analysis. This group had a lower mean VA at their last measured time point compared with that of all other patients at baseline. Eliminating these "lost to follow-up" patients from the final VA analysis actually suggests that the 5-letter top line gain reported is an overestimation of the true real-world VA outcome in this group of patients.

Loss to follow-up has important implications, not only for real-world nAMD studies, but for all nAMD RCTs. In the follow-up study conducted 3 years after the large 2-year prospective RCT of anti-VEGF therapy in nAMD (CATT), those patients who participated showed a mean VA improvement of 7.5 letters at the conclusion of the original 2-year RCT, which was better than that of the non-participants (5.2 letters) and those who had died (3.9 letters) before the follow-up study.[31] Consequently, as acknowledged by the authors, excluding the 42% of patients lost to follow-up in the 5-year VA analysis results in an overestimation of the visual outcome at 5 years.[31] A similar scenario resulted from the 32% loss to follow-up at 4 years in the HORIZON study.[30] The nonparticipants in that extension study had worse VA values at 2 years compared with those of the participants, implying that the reported net mean improvement of 2 letters after 4 years from the initiation of treatment also overestimates the true mean VA of the total study cohort.[30] Consequently, both real-world and long-term visual outcomes in anti-VEGF treatment of nAMD are likely worse than reported in many instances.

Properly addressing the issue of missing data in clinical trials is a major concern for statisticians and regulatory agencies. In the past, addressing missing data through analysis of an intention-to-treat population, with the last observation carried forward (LOCF), was commonly performed. For example, a Danish study showed a mean VA gain of 1 letter in the 192 of 600 nAMD eyes actively treated over 4 years. However, the entire cohort of 600 nAMD eyes, including 145 eyes of patients who were either lost to follow-up or died, showed a mean VA loss of 3 letters using LOCF.[11] The LOCF imputation approach relies on the erroneous assumption that vision remains constant after loss to follow-up.[34–37] However, as the current study demonstrates, nAMD participants who are ultimately lost to follow-up are often experiencing more poorly evolving visual outcomes, compared with other patients, despite anti-VEGF therapy. Employing the LOCF approach would carry these VA outcomes to the study end point, prior to likely further deterioration of VA in these participants, and this finding consequently suggests that an overestimation of final visual outcomes in nAMD may occur. Furthermore, as demonstrated in the multiple prior examples, a per protocol approach, in which nAMD participants lost to follow-up are excluded from analysis, yields an even greater overestimation of visual outcomes. This result occurs because a per protocol approach relies on the erroneous assumption that loss to follow-up happens randomly, independent of outcomes.[34] Additional methods such as multiple imputation utilize other data within the study to estimate the missing data.[34,38] Nevertheless, clinical trial design and clinical trialists should vigorously minimize loss to follow-up, and those nAMD clinical trials with high loss to follow-up may have significant limitations, despite statistical methods for handling missing data.

In summary, real-world nAMD visual outcomes are relatively poor in the United States, despite anti-VEGF therapy, compared with those of RCTs. This study reveals 3 notable insights regarding these poor outcomes. First, real-world nAMD patients experience worse visual outcomes and receive fewer anti-VEGF injections compared with patients receiving fixed, frequent therapy in RCTs, similar to the non-US experience, where health care systems and treatments may differ. Second, compared with nAMD patients with worse VA at presentation, nAMD patients with better VA at presentation tend to be particularly vulnerable to vision loss. Specifically, in the current study, vision loss from baseline was observed as early as the 6-month time point for patients with baseline VA of 20/70 or better, despite anti-VEGF therapy. Last, compared with other patients, those ultimately lost to follow-up tend to experience worse visual outcomes at, or prior to, their final visit, suggesting that high loss to follow-up in clinical studies of

nAMD may overestimate visual outcomes. Consequently, visual outcomes in both real-world and long-term extensions of RCTs may be worse than reported in many of these nAMD studies of anti-VEGF treatment, further highlighting the significant unmet need for better treatment.

References

1. Brown DM, Kaiser PK, Michels M, et al. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. *N Engl J Med*. 2006;355:1432−1444.
2. Rosenfeld PJ, Brown DM, Heier JS, et al. Ranibizumab for neovascular age-related macular degeneration. *N Engl J Med*. 2006;355:1419−1431.
3. Martin DF, Maguire MG, Ying GS, et al, CATT Research Group. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. *N Engl J Med*. 2011;364:1897−1908.
4. Heier JS, Brown DM, Chong V, et al. Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration. *Ophthalmology*. 2012;119:2537−2548.
5. Arevalo JF, Lasave AF, Wu L, et al, Pan-American Collaborative Retina Study Group (PACORES). Intravitreal bevacizumab for choroidal neovascularization in age-related macular degeneration: 5-year results of the Pan-American Collaborative Retina Study Group. *Retina*. 2016;36:859−867.
6. Cohen SY, Mimoun G, Oubraham H, et al. Changes in visual acuity in patients with wet age-related macular degeneration treated with intravitreal ranibizumab in daily clinical practice: the LUMIERE study. *Retina*. 2013;33:474−481.
7. Hjelmqvist L, Lindberg C, Kanulf P, et al. One-year outcomes using ranibizumab for neovascular age-related macular degeneration: results of a prospective and retrospective observational multicentre study. *J Ophthalmol*. 2011;2011:405724.
8. Holz FG, Tadayoni R, Beatty S, et al. Multi-country real-life experience of anti-vascular endothelial growth factor therapy for wet age-related macular degeneration. *Br J Ophthalmol*. 2015;99:220−226.
9. Krüger Falk M, Kemp H, Sørensen TL. Four-year treatment results of neovascular age-related macular degeneration with ranibizumab and causes for discontinuation of treatment. *Am J Ophthalmol*. 2013;155:89−95.e3.
10. Rakic JM, Leys A, Brié H, et al. Real-world variability in ranibizumab treatment and associated clinical, quality of life, and safety outcomes over 24 months in patients with neovascular age-related macular degeneration: the HELIOS study. *Clin Ophthalmol*. 2013;7:1849−1858.
11. Rasmussen A, Bloch SB, Fuchs J, et al. A 4-year longitudinal study of 555 patients treated with ranibizumab for neovascular age-related macular degeneration. *Ophthalmology*. 2013;120:2630−2636.
12. Souied EH, Oubraham H, Mimoun G, et al. Changes in visual acuity in patients with wet age-related macular degeneration treated with intravitreal ranibizumab in daily clinical practice: the TWIN Study. *Retina*. 2015;35:1743−1749.
13. Talks JS, Lotery AJ, Ghanchi F, et al, United Kingdom Aflibercept Users Group. First-year visual acuity outcomes in the United Kingdom of providing aflibercept according to the VIEW study protocol for age-related macular degeneration. *Ophthalmology*. 2016;123:337−343.
14. van Asten F, Evers-Birkenkamp KU, van Lith-Verhoeven JJ, et al. A prospective, observational, open-label, multicentre study to investigate the daily treatment practice of ranibizumab in patients with neovascular age-related macular degeneration. *Acta Ophthalmol*. 2015;93:126−133.
15. Writing Committee for the UK Age-Related Macular Degeneration EMR Users Group. The neovascular age-related macular degeneration database: multicenter study of 92 976 ranibizumab injections: report 1: visual acuity. *Ophthalmology*. 2014;121:1092−1101.
16. Zarranz-Ventura J, Liew G, Johnston RL, et al. The neovascular age-related macular degeneration database: report 2: incidence, management, and visual outcomes of second treated eyes. *Ophthalmology*. 2014;121:1966−1975.
17. Ross AH, Donachie PH, Sallam A, et al. Which visual acuity measurements define high-quality care for patients with neovascular age-related macular degeneration treated with ranibizumab? *Eye (Lond)*. 2013;27:56−64.
18. Gillies MC, Campain A, Barthelmes D, et al. Long-term outcomes of treatment of neovascular age-related macular degeneration: data from an observational study. *Ophthalmology*. 2015;122:1837−1845.
19. Martin DF, Maguire MG, Fine SL, et al, Comparison of Age-related Macular Degeneration Treatments Trials (CATT) Research Group. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. *Ophthalmology*. 2012;119:1388−1398.
20. Chakravarthy U, Harding SP, Rogers CA, et al. Alternative treatments to inhibit VEGF in age-related choroidal neovascularisation: 2-year findings of the IVAN randomised controlled trial. *Lancet*. 2013;382:1258−1267.
21. Schmidt-Erfurth U, Kaiser PK, Korobelnik JF, et al. Intravitreal aflibercept injection for neovascular age-related macular degeneration: ninety-six-week results of the VIEW studies. *Ophthalmology*. 2014;121:193−201.
22. Holekamp NM, Liu Y, Yeh WS, et al. Clinical utilization of anti-VEGF agents and disease monitoring in neovascular age-related macular degeneration. *Am J Ophthalmol*. 2014;157:825−833.e1.
23. Dadgostar H, Ventura AA, Chung JY, et al. Evaluation of injection frequency and visual acuity outcomes for ranibizumab monotherapy in exudative age-related macular degeneration. *Ophthalmology*. 2009;116:1740−1747.
24. Busbee BG, Ho AC, Brown DM, et al. Twelve-month efficacy and safety of 0.5 mg or 2.0 mg ranibizumab in patients with subfoveal neovascular age-related macular degeneration. *Ophthalmology*. 2013;120:1046−1056.
25. Abraham P, Yue H, Wilson L. Randomized, double-masked, sham-controlled trial of ranibizumab for neovascular age-related macular degeneration: PIER study year 2. *Am J Ophthalmol*. 2010;150:315−324.e1.
26. Regillo CD, Brown DM, Abraham P, et al. Randomized, double-masked, sham-controlled trial of ranibizumab for neovascular age-related macular degeneration: PIER Study year 1. *Am J Ophthalmol*. 2008;145:239−248.
27. Schmidt-Erfurth U, Eldem B, Guymer R, et al. Efficacy and safety of monthly versus quarterly ranibizumab treatment in neovascular age-related macular degeneration: the EXCITE study. *Ophthalmology*. 2011;118:831−839.
28. Berg K, Pedersen TR, Sandvik L, et al. Comparison of ranibizumab and bevacizumab for neovascular age-related macular degeneration according to LUCAS treat-and-extend protocol. *Ophthalmology*. 2015;122:146−152.
29. Wykoff CC, Croft DE, Brown DM, et al. Prospective Trial of Treat-and-Extend versus Monthly Dosing for Neovascular Age-Related Macular Degeneration: TREX-AMD 1-year results. *Ophthalmology*. 2015;122:2514−2522.
30. Singer MA, Awh CC, Sadda S, et al. HORIZON: an open-label extension trial of ranibizumab for choroidal

neovascularization secondary to age-related macular degeneration. *Ophthalmology*. 2012;119:1175−1183.
31. Maguire MG, Martin DF, Ying GS, et al, Comparison of Age-related Macular Degeneration Treatments Trials (CATT) Research Group. 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;123:1751−1761.
32. Lee AY, Lee CS, Butt T, et al, UK AMD EMR Users Group. UK AMD EMR USERS GROUP REPORT V: benefits of initiating ranibizumab therapy for neovascular AMD in eyes with vision better than 6/12. *Br J Ophthalmol*. 2015;99: 1045−1050.
33. Richard G, Mones J, Wolf S, et al. Scheduled versus pro re nata dosing in the VIEW trials. *Ophthalmology*. 2015;122: 2497−2503.
34. Olsen MK, Stechuchak KM, Edinger JD, et al. Move over LOCF: principled methods for handling missing data in sleep disorder trials. *Sleep Med*. 2012;13:123−132.
35. Wong WK, Boscardin WJ, Postlethwaite AE, et al. Handling missing data issues in clinical trials for rheumatic diseases. *Contemp Clin Trials*. 2011;32:1−9.
36. Hedden SL, Woolson RF, Carter RE, et al. The impact of loss to follow-up on hypothesis tests of the treatment effect for several statistical methods in substance abuse clinical trials. *J Subst Abuse Treat*. 2009;37:54−63.
37. Mallinckrodt CH, Sanger TM, Dube S, et al. Assessing and interpreting treatment effects in longitudinal clinical trials with missing data. *Biol Psychiatry*. 2003;53:754−760.
38. O'Neill RT, Temple R. The prevention and treatment of missing data in clinical trials: an FDA perspective on the importance of dealing with it. *Clin Pharmacol Ther*. 2012;91: 550−554.

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Real-world Outcomes of Anti–Vascular Endothelial Growth Factor Therapy in Neovascular Age-Related Macular Degeneration in the United States

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In real-world patients with neovascular age-related macular degeneration treated with anti–vascular endothelial growth factor, vision loss trends with subsequent loss to follow-up, potentially leading to overestimation of visual outcomes in clinical trials. Vision loss also inversely trends with presenting visual acuity.