AMERICAN ACADEMY OF OPHTHALMOLOGY®

Vision-Related Quality of Life in Patients with Diabetic Macular Edema Treated with Intravitreal Aflibercept

The AQUA Study

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Purpose: To examine vision-related quality of life in patients with diabetic macular edema (DME) treated with intravitreal aflibercept (EYLEA, Regeneron Pharmaceuticals, Inc, Tarrytown, NY).

Design: AQUA was a multicenter, open-label, single-arm, phase 4 study.

Participants: Adults 18 years of age or older with type 1 or 2 diabetes mellitus and DME.

Methods: Patients received intravitreal aflibercept 2 mg every 8 weeks for 52 weeks, after 5 initial doses every 4 weeks.

Main Outcome Measures: The primary outcome was the change in 25-item National Eye Institute Visual Function Questionnaire (NEI VFQ-25) total score from baseline to week 52. Secondary outcomes included the change in NEI VFQ-25 near and distant activities subscale scores, best-corrected visual acuity (BCVA; Early Treatment Diabetic Retinopathy Study [ETDRS] letters), and central retinal thickness (CRT) from baseline to week 52. Change in NEI VFQ-25 score at week 52 for better-seeing eyes (BSEs) and worse-seeing eyes (WSEs) also was evaluated.

Results: A total of 553 patients comprised the full analysis set, and 560 patients comprised the safety analysis set. At baseline, the mean NEI VFQ-25 total score was 70.12, mean BCVA was 61.5 ETDRS letters, and mean CRT was 464.81 μm. A mean of 8.8 injections were administered over 52 weeks. At week 52, the mean improvement from baseline in the NEI VFQ-25 total score was +6.11 (standard deviation [SD], 11.46); the corresponding improvements in near and distant activities were +11.37 (SD, 18.01) and +7.33 (SD, 17.32), respectively. Similarly, improvements in patients whose BSE and WSE were treated were 7.74 (SD, 13.59) and 5.48 (SD, 9.70), respectively. At week 52, mean change in BCVA was +10.0 ETDRS letters (SD, 8.0 ETDRS letters), and mean change in CRT was −175.38 μm (SD, 132.62 μm). Overall, 53.6% of patients reported treatment-emergent adverse events (TEAEs), of whom 26.8% experienced an ocular TEAE in the study eye. The most common serious ocular TEAE was endophthalmitis (0.5% [n = 3]). Five deaths (0.9%) were reported, but were not considered treatment related.

Conclusions: Intravitreal aflibercept was associated with clinically meaningful improvements in NEI VFQ-25 total score over 52 weeks in patients with DME; these were even more pronounced for near than for distant activities. Adverse events were consistent with the known safety profile of intravitreal aflibercept. *Ophthalmology Retina 2019;3:567-575 © 2019 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

Supplemental material available at www.ophthalmologyretina.org.

Although ophthalmologists primarily consider the efficacy and safety of therapeutic interventions as part of the clinical decision-making process, patient-reported outcomes are as important, particularly in the treatment of chronic diseases, when selecting interventions in a clinical setting.[1] Most randomized clinical trials in retinal disorders focus on functional and anatomic outcomes for primary and secondary evaluation, giving limited weight to patient-reported outcomes. However, patient-reported outcomes, including changes in quality of life (QoL), may play an important role in patient adherence to treatment.

Diabetic macular edema (DME) is a serious complication of diabetes mellitus that causes visual impairment in working-age adults.[2,3] The impact of the ocular complications of diabetes on patient QoL is considerable and ranges from preliminary symptoms to severe vision loss.[4]

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Progressive decline in visual function may impact a patient's ability to complete daily routine activities, which can impact the psychological state. Therefore, in addition to measuring the functional outcome of a therapeutic intervention, it is also important to measure a treatment's impact on vision-related QoL.[5] Quality-of-life measurements now are recognized as an integral part of health utility analyses in many countries,[6,7] and the assessment of patients' QoL is being implemented into daily clinical therapeutic decisions.[8] The 25-item National Eye Institute Visual Function Questionnaire (NEI VFQ-25) is a visual function-specific QoL assessment tool that has been validated in patients with DME and other retinal conditions.[4,5,7,9] The NEI VFQ-25 is an established survey to evaluate a patient's disease burden and vision-related QoL, and it is sensitive to the effect of different therapeutic interventions such as anti−vascular endothelial growth factor (VEGF) therapy. The NEI VFQ-25 also allows for assessment of the extent to which eye disorders impact a patient's anxiety level and routine activities, as well as social interactions.[7] It has been used to determine QoL objectively in several phase 3 trials evaluating the efficacy and safety of intravitreal anti-VEGF therapy in different retinal indications.[10,11] Visual acuity improvement in patients with DME treated with anti-VEGF agents has been found to be correlated with enhanced patient-reported visual function measured with NEI VFQ-25.[12,13]

The efficacy and safety of intravitreal aflibercept (EYLEA) in patients with DME have been established in several phase 3 trials[14]; however, limited evidence is available on the impact of intravitreal aflibercept on vision-related QoL, namely the relative influence of the visual acuity of the better-seeing eye (BSE) and worse-seeing eye (WSE) on vision-related QoL in patients with DME. The aim of the AQUA study was to assess the impact of intravitreal aflibercept treatment on vision-related QoL outcomes in patients with DME. Herein, we report the results of the AQUA study.

Methods

Study Design

The AQUA study (http://www.clinicaltrials.gov identifier, NCT02581995) was a multicenter, open-label, single-arm, phase 4 study to evaluate vision-related QoL in patients with DME who were treated with intravitreal aflibercept over 52 weeks. Patients were recruited from 78 study sites across 14 countries in Europe and Canada. The study was conducted in accordance with the tenets of the Declaration of Helsinki and the International Council for Harmonisation guideline E6: Good Clinical Practice.[15−17] Institutional review board or ethics committee approval was obtained: each site had an institutional review board or independent ethics committee that provided approval for the protocol and the protocol amendment. Country-specific institutional review boards or independent ethics committees are listed in Table 1 (available at www.ophthalmologyretina.org). All patients provided written informed consent.

Participants

Adults 18 years of age or older with type 1 or 2 diabetes mellitus and DME with central macular involvement (defined as the area of the center subfield on OCT) were eligible if best-corrected visual acuity (BCVA) was between 73 and 24 Early Treatment Diabetic Retinopathy Study (ETDRS) letters (Snellen equivalent, approximately 20/40−20/320) in the study eye. The decrease in vision in the study eye primarily had to be the result of DME. If both eyes were affected, then 1 eye was chosen by the investigator at baseline. All exclusion criteria are listed in Table 2 (available at www.ophthalmologyretina.org).

Treatment

Patients received 5 initial injections at 4-week intervals, followed by intravitreal aflibercept 2 mg every 8 weeks until week 52. Treatment was administered in accordance with the European prescribing information.[18] Laser photocoagulation or surgery could be performed if deemed necessary by the investigator. No other DME treatment could be administered in the study eye until study completion or early termination. Any approved nonsystemic treatment (including intravitreal aflibercept) could be administered to a fellow eye with DME, but only 1 eye per patient was included in the study.

Assessments

The NEI VFQ-25 was administered at screening (up to 4 weeks before baseline); at baseline (day 1, pretreatment); at weeks 4, 8, 12, and 16 (±5 days); at weeks 24 through 48 (±10 days); and at week 52 (±10 days). The NEI VFQ-25 questionnaire was presented in the local language and administered in a quiet room by a study-related person qualified to administer this type of questionnaire, preferably before other visit procedures were performed. Patients unable to read the questionnaire because of vision impairment could be assisted by a family member other legal representative of the patient, study nurse, or study physician in completing the questionnaire. A summary of the NEI VFQ-25 questionnaire is provided in Table 3 (available at www.ophthalmologyretina.org). Visual acuity was assessed using the ETDRS protocol. Macular and DME characteristics were evaluated using spectral-domain OCT. Additionally, the anatomic state of the retinal vasculature (study eye) was evaluated by funduscopic examination, fundus photography, and fluorescein angiography.

Safety was monitored throughout the study, and all adverse events were classified according to the Medical Dictionary for Regulatory Activities (version 20). All information on intensity, causal relationship to intravitreal aflibercept, action taken or treatment, and outcome was recorded in the electronic case report form. Treatment-emergent adverse events (TEAEs) were defined as those that started after the first intravitreal aflibercept injection, but not more than 30 days after the last injection. Potential arterial thrombotic events were evaluated by an Antiplatelet Trialists' Collaboration adjudication committee in accordance with published criteria.[19]

Statistical Analyses

The primary outcome was the change in the NEI VFQ-25 total score from baseline to week 52. Secondary outcomes included the NEI VFQ-25 subscale scores for near and distant activities, mean change in BCVA (ETDRS letters), mean change in central retinal thickness (CRT) on OCT (from baseline to week 52), and the proportion of patients progressing to proliferative diabetic retinopathy (PDR) as measured by a score of at least 61 on the ETDRS Diabetic Retinopathy Severity Scale (DRSS). The DRSS was assessed on fundus photography by the central reading center at week 52. In addition, further outcomes were prespecified, including the proportion of eyes gaining or losing 0 or more ETDRS letters, 5 or more ETDRS letters, 10 or more ETDRS letters, and 15 or more ETDRS letters at week 52

Table 4. Baseline Characteristics

Characteristic	Data
Patient characteristics	n = 560
Age (yrs), mean (SD)	64.3 (9.3)
Male gender	336 (60.0)
BMI (kg/m^2), mean (SD)	29.98 (5.17)
Race	
White	519 (92.7)
Black	3 (0.5)
Asian	4 (0.7)
American Indian or Alaska Native	0
Native Hawaiian or other Pacific Islander	0
Not reported	34 (6.1)
Ethnicity	
Hispanic or Latino	1 (0.2)
Not Hispanic or Latino	526 (93.9)
Not reported	33 (5.9)
Study eye	
Better-seeing eye	116 (20.7)
Worse-seeing eye	337 (60.2)
Equal vision	104 (18.6)
Missing	3 (0.5)
Patients with prior use of anti-VEGF agents*	140 (25.3)
Patients who had not used anti-VEGF therapy before this study*	413 (74.7)
Baseline disease characteristics	n = 560
Diabetes mellitus type 2	515 (92.0)
NEI VFQ-25 total score, mean (SD)	70.12 (19.24)
BCVA (ETDRS letters), mean (SD)	61.5 (10.9)
CRT (μm), mean (SD)	464.81 (136.21)
DRSS score (study eye)	
10, DR absent	0
15, DR questionable	2 (0.4)
35, mild NPDR	148 (26.4)
43, moderate NPDR	185 (33.0)
47, moderately severe NPDR	153 (27.3)
53, severe NPDR	48 (8.6)
61, mild PDR	8 (1.4)
65, moderate PDR	8 (1.4)
71, high-risk PDR	2 (0.4)
90, cannot grade	6 (1.1)

BCVA = best-corrected visual acuity; BMI = body mass index; CRT = central retinal thickness; DR = diabetic retinopathy; DRSS = Diabetic Retinopathy Severity Scale; ETDRS = Early Treatment Diabetic Retinopathy Study; NEI VFQ-25 = 25-item National Eye Institute Visual Function Questionnaire; NPDR = nonproliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy; SD = standard deviation; VEGF = vascular endothelial growth factor.
Values are no. (%) unless otherwise indicated.
*Full analysis set, n = 553.

and the proportion of patients with a 2-step or more or 3-step or more improvement in DRSS score (defined as patients whose DRSS category decreased by 2 or 3 levels, respectively) at week 52.

The primary and secondary efficacy outcomes were analyzed descriptively. For continuous outcomes, 95% confidence intervals (CIs) were provided based on the *t* distribution assuming that the changes from baseline are distributed normally. Missing values were imputed using the last observation carried forward approach.

The calculations for NEI VFQ-25 total and subscale scores were performed in accordance with the NEI VFQ-25 scoring algorithm (version August 2000). Previous publications also have reported that the minimal clinically important difference (MCID) for the change in the NEI VFQ-25 scores is 4 to 6.[20] Based on this, an MCID of 5 or more for change from baseline to week 52 in NEI VFQ-25 scores was used for the summaries.

Because either the BSE or the WSE could be chosen as the study eye, exploratory analyses were performed to evaluate the relative influence of the visual acuity of BSEs and WSEs on the NEI VFQ-25 total score. Impact of prior use of anti-VEGF agents on NEI VFQ-25 total score also was assessed.

All efficacy parameters were evaluated using the full analysis set (FAS), defined as all patients who received at least 1 intravitreal aflibercept injection and who completed baseline and at least 1 postbaseline NEI VFQ-25 assessment. The safety analysis set included all patients who received at least 1 intravitreal aflibercept injection.

Assuming a similar variability (standard deviation [SD], 11) as in previous studies, with the enrolled sample size of 553 patients in the full analysis set, the difference between the mean and the limits of the 95% CIs was expected not to exceed 1.0 with a probability of 90% or more. All statistical analyses were performed using SAS for Windows, version 9.3 (SAS Institute, Inc, Cary, NC).

Results

Study Population

A total of 560 patients were included in the safety analysis set and 553 patients were included in the full analysis set; 529 patients completed the study. Most premature discontinuations primarily were the result of withdrawal by patients (n = 12 [2.1%]) and adverse events (n = 6 [1.1%]); the remainder were the result of being lost to follow-up (n = 5 [0.9%]), death (n = 4 [0.7%]; 1 death occurred after the patient completed the study), sponsor decision (n = 1 [0.2%]), or other reasons (n = 3 [0.5%]).

The overall mean age was 64.3 years, and more than half of the patients (n = 336 [60.0%]) were men. Most patients were white (n = 519 [92.7%]) and non-Hispanic or Latino (n = 526 [93.9%]; Table 4). Most patients had type 2 diabetes mellitus at baseline (n = 515 [92.0%]) with a mean duration of 16.4 years. At baseline, more WSEs were treated (n = 337 [60.2%]) than BSEs (n = 116 [20.7%]); 18.6% of patients (n = 104) showed equal vision in both the study eye and the fellow untreated eye. Most patients had not used anti-VEGF agents before this study (n = 413 [74.7%]). At baseline, the mean NEI VFQ-25 total score was 70.12 (SD, 19.24), mean BCVA was 61.5 ETDRS letters (SD, 10.9 ETDRS letters; Snellen equivalent, 20/59), and mean CRT was 464.81 μm (SD, 136.21 μm). The most common DRSS score in the study eye was 43 (moderate nonproliferative diabetic retinopathy [NPDR]), occurring in approximately 33% of patients (n = 185; Table 4). Overall, 1.4% of patients (n = 8) showed a DRSS score of 61 (mild PDR) and 65 (moderate PDR) each and 0.4% of patients (n = 2) showed a DRSS score of 71 (high-risk PDR; Table 4).

Treatment Exposure

The mean number of injections over 52 weeks was 8.8 (95% CI, 8.7−8.9). Most patients (n = 508 [91.9%]) received all 9 injections per the trial's treatment regimen.

Efficacy Outcomes

Quality of Life Outcomes. The mean NEI VFQ-25 total score improved from 70.12 (SD, 19.24) at baseline to 76.33 (SD, 18.76) at

week 52. The mean change was 6.11 (SD, 11.46; 95% CI, 5.3−6.9; Fig 1; Table 5). A total of 75.2% of patients (n = 416) experienced an improvement and 23.3% (n = 129) showed a decline in NEI VFQ-25 total score at week 52. The percentage of patients with no change in NEI VFQ-25 total score was 1.4% (n = 8) at week 52 (Table 5). Approximately half of patients (50.3% [n = 278]) were able to achieve or exceed the MCID over 52 weeks.

Patients whose BSE was treated (n = 112) showed a mean improvement in NEI VFQ-25 score of 7.74 (SD, 13.59; 95% CI, 5.6−9.9), and those whose WSE was treated (n = 334) showed an improvement of 5.48 (SD, 9.70; 95% CI, 4.6−6.4) at week 52 (Fig 2; Table 5). Patients with equal vision in the study eye and the fellow untreated eye (n = 104) showed a mean improvement in NEI VFQ-25 total score of 6.47 (SD, 13.13; 95% CI, 4.3−8.6) at week 52.

Mean NEI VFQ-25 subscale score for near activities improved from 62.97 (SD, 23.48) at baseline to 74.34 (SD, 23.44) at week 52; the mean change was 11.37 (SD, 18.01; 95% CI, 10.1−12.6). For distant activities, the mean NEI VFQ-25 subscale score improved from 71.96 (SD, 23.97) at baseline to 79.30 (SD, 23.44) at week 52; the mean change was 7.33 (SD, 17.32; 95% CI, 6.1−8.5; Fig 1; Table 5). At week 52, 63.8% of patients showed improvement in the near activities subscale. Similarly, the percentage of patients who achieved or exceeded MCID for the near activities subscale at week 52 was 63.8%. For distant activities, 50.1% of patients showed improvement at week 52 and 49.5% of patients achieved or exceeded MCID at week 52.

At week 52, the subgroup of patients who had received prior anti-VEGF therapy showed a mean improvement of 5.08 (SD, 10.99; 95% CI, 3.5−6.6) from baseline (mean, 71.40; SD, 18.22) in NEI VFQ-25 total score. Patients who had not received prior anti-VEGF therapy showed a mean improvement of 6.45 (SD, 11.61; 95% CI, 5.5−7.4) in NEI VFQ-25 total score from baseline (mean, 69.82; SD, 19.56) to week 52.

Visual and Anatomic Outcomes

The mean BCVA increased to 71.5 ETDRS letters (SD, 11.5 ETDRS letters; Snellen equivalent, 20/37) at week 52, representing a mean gain of 10.0 ETDRS letters (SD, 8.0 ETDRS letters; 95% CI, 9.5−10.6 ETDRS letters) from baseline to week 52 (Fig 3; Table 6). The proportion of patients gaining 15 ETDRS letters or more, 10 ETDRS letters or more, and 5 ETDRS letters or more over 52 weeks was 26.2% (n = 145), 51.9% (n = 287), and 75.2% (n = 416), respectively (Table 6). In comparison, the proportion of patients losing 15 ETDRS letters or more, 10 ETDRS letters or more, and 5 ETDRS letters or more over 52 weeks was 0.4% (n = 2), 0.7% (n = 4), and 2.2% (n = 12), respectively (Table 6). Regression analysis illustrated the positive correlation between change in NEI VFQ-25 total score and difference in maximum BCVA in the BSE (r = 0.2005; Fig 4). At week 52, mean CRT was 289.15 μm (SD, 76.15 μm), and the mean change in CRT from baseline to week 52 was −175.38 μm (SD, 132.62 μm; 95% CI, 184.9−165.8 μm; Table 6).

Diabetic Retinopathy Severity Score Outcomes

At week 52, 2.0% of patients (n = 10) showed PDR. A total of 20.5% and 3.4% of study eyes showed a 2-step or more and 3-step or more DRSS score improvement from baseline to week 52, respectively, as assessed by the central reading center (Table 6).

Safety Outcomes

In total, 53.6% patients (n = 300) experienced a TEAE, of whom 26.8% (n = 150) experienced an ocular TEAE in the study eye, 32.3% (n = 181) experienced a nonocular TEAE, and 1.8% (n = 10) experienced a treatment-emergent Antiplatelet Trialists' Collaboration event (Table 7). Endophthalmitis was reported as being treatment emergent in 3 of 560 patients (0.5%) after the application of 4889 intravitreal aflibercept injections (0.06% of injections). Five deaths (0.9%; including 1 death that occurred after the patient completed the study) were reported during the treatment period, but none were considered to be related to treatment (Table 7).

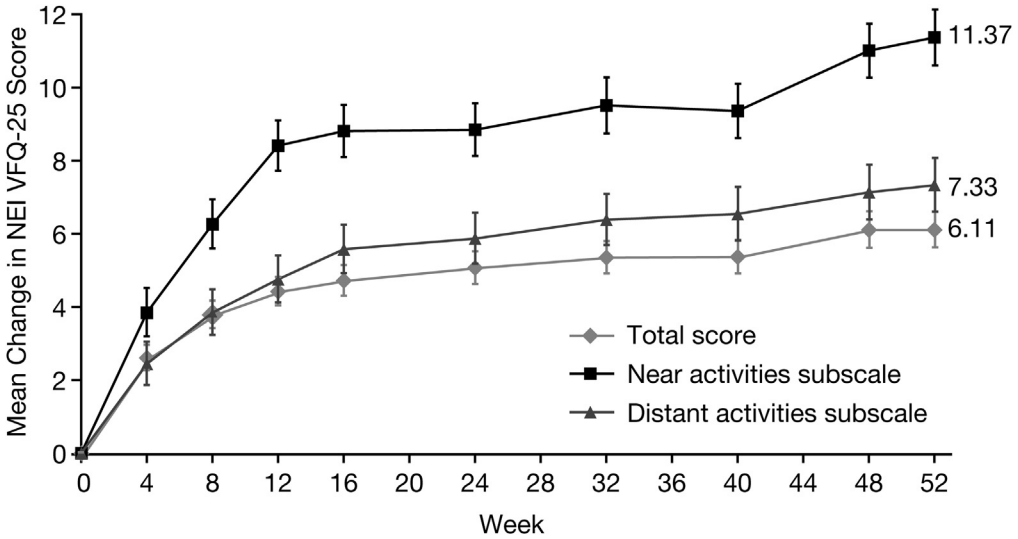

Figure 1. Graph showing mean change in 25-item National Eye Institute Visual Function Questionnaire (NEI VFQ-25) score (full analysis set, last observation carried forward).

Table 5. Quality of Life Efficacy Outcomes at Week 52

Quality of Life Outcomes, 25-Item National Eye Institute Visual Function Questionnaire Total and Subscale Scores	Intravitreal Aflibercept (n = 553)
Change in total score, mean (SD)	
All patients	6.11 (11.46)
BSE as study eye	7.74 (13.59)
WSE as study eye	5.48 (9.70)
Equal vision in study eye and fellow untreated eye	6.47 (13.13)
Improvement in total score, no. (%)	416 (75.2)
Worsening in total score, no. (%)	129 (23.3)
No change in total score, no. (%)	8 (1.4)
Change in near activities subscale score, mean (SD)	11.37 (18.01)
Change in distant activities subscale score, mean (SD)	7.33 (17.32)

BSE = better-seeing eye; SD = standard deviation; WSE = worse-seeing eye.

Discussion

The AQUA trial demonstrated that the treatment of DME with intravitreal aflibercept results in steady and substantial improvements in vision-related QoL as measured by NEI VFQ-25 total score over 52 weeks. The course of the improvement in NEI VFQ-25 closely resembled improvement in BCVA over time. A consistent increase in the mean NEI VFQ-25 total scores was observed in patients whose BSE was treated and in those whose WSE was treated throughout the study, but was more pronounced in the former. This difference can be attributed to the fact that for vision-related QoL, patient-reported outcome measures such as NEI VFQ-25 score is assessed for both eyes; however, the outcome usually is driven by the visual acuity in the BSE.[20] Nearly similar improvements (but slightly less than in patients whose BSE was treated) in NEI VFQ-25 total score were observed over 52 weeks in the subgroup of patients with equal vision in the study eye and fellow untreated eye. A slightly greater improvement in the NEI VFQ-25 subscale score for near activities than for distant activities was observed, which could be the result of a higher baseline mean NEI VFQ-25 score for distant activities than for near activities. There also may be a stronger relationship between functional outcomes and near vision compared with distance vision. More than 75% of patients experienced an improvement in NEI VFQ-25 total score at week 52. Although not specifically analyzed, it is possible that numerically lower NEI VFQ-25 total scores compared with baseline at week 52 in a subset of patients could be the result of high BCVA at screening or of comorbidities. At week 52, only 6.7% of patients lost 0 letters or more and only 2.2% of patients demonstrated a 5-letter or more loss. Prior use of anti-VEGF agents did not seem to influence the increase in NEI VFQ-25 total score greatly, because patients who had not used anti-VEGF agents before showed a slightly lower mean NEI VFQ-25 score at baseline than did those who previously had received anti-VEGF agents (69.82 [SD, 19.56] vs. 71.40 [SD, 18.22], respectively) and showed a slightly larger mean improvement (6.45 vs. 5.08) over the 52-week treatment period. A steady improvement in BCVA also was observed over the 52-week study duration. At week 52, approximately one quarter of the patients gained 15 letters or more in BCVA scores.

These results are in line with the results from the Intravitreal Aflibercept Injection in Vision Impairment due to DME (VIVID-DME) study and the Study of Intravitreal Aflibercept Injection in Patients with Diabetic Macular Edema (VISTA-DME); for near activities, the AQUA study results were more aligned with the VISTA-DME study in which the mean change in NEI VFQ-25 over 52

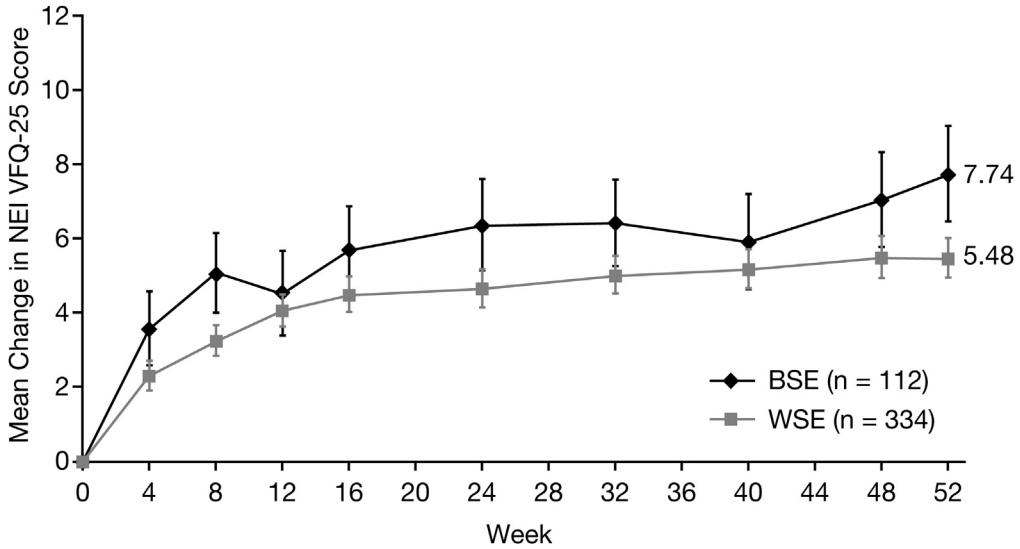

Figure 2. Graph showing mean change in 25-item National Eye Institute Visual Function Questionnaire (NEI VFQ-25) total score in the better-seeing eye (BSE) and worse-seeing eye (WSE; full analysis set, last observation carried forward).

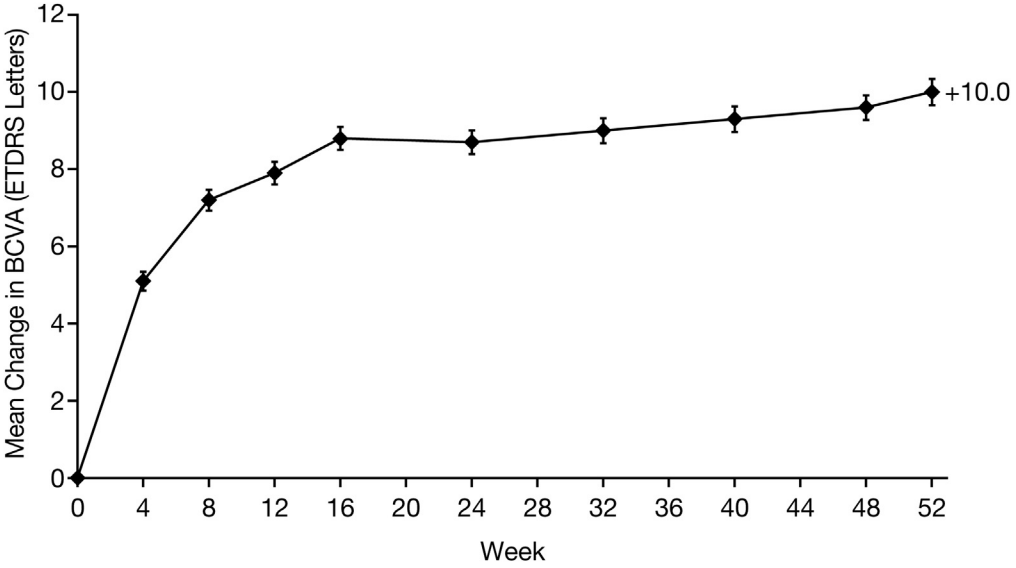

Figure 3. Graph showing mean change in best-corrected visual acuity (BCVA; Early Treatment Diabetic Retinopathy Study [ETDRS] letters; full analysis set, last observation carried forward; n = 553).

weeks was 9.4 in the intravitreal aflibercept 2 mg every 8 weeks treatment group. The corresponding mean change in the intravitreal aflibercept 2 mg every 8 weeks arm of VIVID-DME study was 5.3. Similarly, the mean change in NEI VFQ-25 score over 52 weeks for distant activities was 5.3 and 7.3 in the intravitreal aflibercept 2 mg every 8 weeks treatment group of the VIVID-DME and VISTA-DME studies, respectively.[13,21] Our findings are consistent with those of previous large clinical studies that reported improvements in vision-related QoL in patients treated with other anti-VEGF agents[22,23] and other available treatments[23] for DME and have established further the effectiveness of anti-VEGF therapy in improving vision-related QoL to a clinically meaningful extent over 52 weeks in patients with DME.

In addition to the vision-related QoL outcomes, functional outcomes of the AQUA study also were consistent with the results from VIVID-DME and VISTA-DME, in which mean change in BCVA over 52 weeks was +10.7 letters in the intravitreal aflibercept 2 mg every 8 weeks treatment group of both the studies.[13,21] These similarities among the AQUA study and VIVID-DME and VISTA-DME studies in BCVA also were accompanied by improvement in anatomic outcomes; mean change in CRT from baseline for the intravitreal aflibercept 2 mg every 8 weeks group was −192.4 μm and 183.1 μm in the VIVID-DME and VISTA-DME studies, respectively.[13,21] Comparable with the AQUA study, the proportions of patients gaining 15 letters or more were 33.3% and 31.3% in the intravitreal aflibercept 2 mg every 8 weeks groups of the VIVID-DME and VISTA-DME studies, respectively.[13,21] The corresponding percentages of eyes that gained 10 letters or more were 53.3% and 58.3% in the VIVID-DME and VISTA-DME studies, respectively. However, DRSS outcomes in the AQUA study differed slightly from those of the VIVID-DME and VISTA-DME studies; at week 52, 27.7% and 29.1% patients were 2-step or more improvers in the intravitreal aflibercept 2 mg every 8 weeks groups of the VIVID-DME and VISTA-DME studies, respectively. This variation in DRSS outcomes could be the result of differences in the distribution of baseline DRSS scores between the AQUA study and the EYLEA phase 3 trials, because baseline DR severity is a major predictor of improvement with anti-VEGF therapies. The proportion of patients with severe NPDR (DRSS score of 53) at baseline was greater in the intravitreal aflibercept 2 mg every 8 weeks group of the VIVID-DME and VISTA-DME studies than in the AQUA study (31.1% and 26.5% vs. 8.6%), whereas the proportion of patients with mild NPDR (DRSS score of 35) was lower (0.7% and 6.0% vs. 26.4%).[13,21]

Table 6. Visual and Anatomic Outcomes at Week 52

Visual and Anatomic Outcomes	Intravitreal Aflibercept (n = 553)
Change in BCVA (ETDRS letters), mean (SD)	+10 (8.0)
Change in CRT (μm), no. (%)	−175.38 (132.62)
≥15-letter gain	145 (26.2)
≥10-letter gain	287 (51.9)
≥5-letter gain	416 (75.2)
≥0-letter gain	516 (93.3)
≥0-letter loss	37 (6.7)
≥5-letter loss	12 (2.2)
≥10-letter loss	4 (0.7)
≥15-letter loss	2 (0.4)
≥2-step DRSS score improvement, no./total no. (%)	103/502 (20.5)
≥3-step DRSS score improvement, no./total no. (%)	17/502 (3.4)

BCVA = best-corrected visual acuity; CRT = central retinal thickness; DRSS = Diabetic Retinopathy Severity Scale; ETDRS = Early Treatment Diabetic Retinopathy Study; SD = standard deviation.
All data are number of patients (%) unless otherwise indicated.

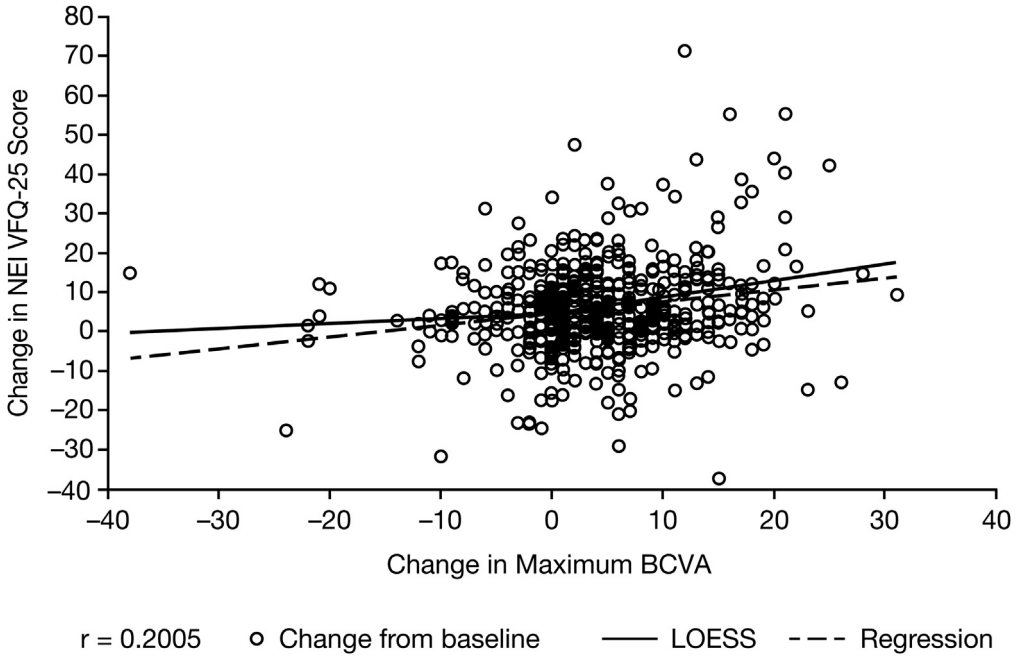

Figure 4. Scatterplot showing correlation between mean change in 25-item National Eye Institute Visual Function Questionnaire (NEI VFQ-25) score and difference in maximum best-corrected visual acuity (BCVA; Early Treatment Diabetic Retinopathy Study [ETDRS] letters; LOESS = locally estimated scatterplot smoothing; full analysis set, last observation carried forward).

No new safety signals were observed in the AQUA study, and intravitreal aflibercept was well tolerated over 52 weeks. The safety profile of intravitreal aflibercept for the treatment of DME in this study was consistent with that in other studies of intravitreal aflibercept.[13,21]

The NEI VFQ-25 assesses the impact of visual disability on patients' overall health domains, such as emotional well being, social functioning, and daily visual function.[7] Evidence from the literature suggests a strong association between visual functioning and vision-related QoL derived from ophthalmologic-specific measures, such as the NEI VFQ-25, in various retinal complications.[9] Previous research has found a correlation between decreased visual function and development of depression, which in turn affects patients' daily activities. Higher incidence of depressive disorders in patients with advanced age-related macular degeneration and other retinal diseases, comparable with rates seen in patients with life-threatening diseases such as cancer or cerebrovascular diseases, supports these observations.[24,25] Thus, improving NEI VFQ-25 scores can help clinicians to provide patients with optimized medical treatment, further increasing treatment adherence and persistence.[7]

The large patient population included in this study, the use of NEI VFQ-25 assessment score, and the prospective design are strengths of the AQUA study. However, this study did not stratify patients according to their baseline visual acuity, and there may be relevant differences in score changes in patients with a BCVA of fewer than 70 letters (Snellen equivalent, 20/40) compared with those with a BCVA of 70 letters or

Table 7. Safety Outcomes Over 52 Weeks

	Intravitreal Aflibercept (n = 560)
Any TEAE	300 (53.6)
Any treatment-emergent SAEs	66 (11.8)
Any ocular TEAE (study eye)	150 (26.8)
Treatment-emergent ocular SAEs in study eye	
Patients with at least 1 treatment-emergent ocular SAE	6 (1.1)
Eye disorders	3 (0.5)
Vitreitis	2 (0.4)
Anterior chamber inflammation	1 (0.2)
Cataract subcapsular	1 (0.2)
Posterior capsule opacification	1 (0.2)
Infections and infestations	3 (0.5)
Endophthalmitis	3 (0.5)
Any nonocular TEAE	181 (32.3)
Any treatment-emergent APTC event	10 (1.8)
Patients with SAEs with fatal outcomes, death	5 (0.9)
Cardiopulmonary failure*	1 (0.2)
Pneumonia*	1 (0.2)
Cardiorespiratory arrest	1 (0.2)
Cardiovascular insufficiency	1 (0.2)
Vascular encephalopathy	1 (0.2)
Myocardial infarction	1 (0.2)

APTC = Anti-Platelet Trialists' Collaboration; SAE = serious adverse event; TEAE = treatment-emergent adverse event.
All data are number of patients (%). All events were considered not related to study drug by the investigator.
*One patient experienced 2 events with a fatal outcome.

more. Similarly, patients were not stratified by baseline DRSS score, and there may be differences in NEI VFQ-25 score changes in patients with mild NPDR compared with those who have severe NPDR at baseline.[26] There was a difference observed in NEI VFQ-25 total score for patients who received prior anti-VEGF agents compared with those who did not, with anti-VEGF treatment-naïve patients achieving a slightly higher score. This study did not assess the correlation between letter gain categories and change in QoL scores; however, a positive correlation was observed between change in NEI VFQ-25 score and difference in maximum BCVA in the BSE. Moreover, the potential impact of comorbidities of diabetes on the NEI VFQ-25 scores has not been included.

In conclusion, use of intravitreal aflibercept was associated with clinically meaningful and patient-relevant improvements in NEI VFQ-25 total score, as well as subscale scores for near and distant vision, along with visual and functional outcomes over 52 weeks in this phase 4 study of patients with DME.

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Abbreviations and Acronyms:
ATE = arterial thrombotic event; **BCVA** = best-corrected visual acuity; **BSE** = better-seeing eye; **CI** = confidence interval; **CRT** = central retinal thickness; **DME** = diabetic macular edema; **DRSS** = Diabetic Retinopathy Severity Scale; **ETDRS** = Early Treatment Diabetic Retinopathy Study; **FAS** = full analysis set; **MCID** = minimal clinically important difference; **NEI VFQ-25** = 25-item National Eye Institute Visual Function Questionnaire; **NPDR** = nonproliferative diabetic retinopathy; **PDR** = proliferative diabetic retinopathy; **QoL** = quality of life; **SD** = standard deviation; **TEAE** = treatment-emergent adverse event; **VEGF** = vascular endothelial growth factor; **VISTA** = Study of Intravitreal Aflibercept Injection in Patients with Diabetic Macular Edema; **VIVID** = Intravitreal Aflibercept Injection in Vision Impairment due to DME; **WSE** = worse-seeing eye.

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