Graefes Arch Clin Exp Ophthalmol (2017) 255:475–484
DOI 10.1007/s00417-016-3477-9

RETINAL DISORDERS

Vision-related quality of life: 12-month aflibercept treatment in patients with treatment-resistant neovascular age-related macular degeneration

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Received: 24 January 2016 / Revised: 8 August 2016 / Accepted: 17 August 2016 / Published online: 30 August 2016

Abstract
Purpose To assess changes in vision-related quality of life (VR-QoL) among patients with treatment-resistant neovascular age-related macular degeneration (nAMD) following intravitreal aflibercept treatment over 48 weeks.
Methods We conducted a prospective study in which 49 patients with nAMD resistant to anti-vascular endothelial growth factor therapy were switched to intravitreal aflibercept. Patients were treated with three loading doses every 4 weeks followed by injections every 8 weeks, for a total of 48 weeks. Ophthalmic examinations performed at each visit included best-corrected visual acuity (BCVA) and central macular thickness (CMT) measurement. The National Eye Institute Visual Functioning Questionnaire 25 (NEI VFQ-25) was used to assess VR-QoL at baseline and weeks 24 and 48. Changes in NEI VFQ-25 composite and subscale scores were analyzed using paired *t* tests. The relationship between the change in VR-QoL and changes in BCVA and CMT, and the impact of the better-seeing eye (BSE, defined as the eye reading the greater number of letters at baseline) vs. the worse-seeing eye (WSE, the fellow eye to the BSE) were assessed.
Results Mean NEI VFQ-25 composite scores improved significantly at weeks 24 and 48 compared to baseline (4.5 ± 9.2 and 4.4 ± 11.8, respectively, all $p < 0.01$). Among subscales, general vision and near and distance activities showed significant improvements at weeks 24 and 48 (all $p < 0.05$). Improvement in the NEI VFQ-25 composite score was significantly associated with increased BCVA at week 48 (β coefficient = 0.43, $p = 0.029$), but not with change in CMT (β coefficient = −0.007, $p = 0.631$). There was no association between VR-QoL changes and BSE or WSE.
Conclusion Despite previous anti-VEGF treatment in this cohort, overall VR-QoL improved following aflibercept therapy over 48 weeks. This improvement was related to improved vision in treatment eyes regardless of whether they were the BSE or WSE.

Keywords Vision-related quality of life (VR-QoL) · Neovascular age-related macular degeneration (nAMD) · Intravitreal aflibercept · Anti-vascular endothelial growth factor (anti-VEGF) · Treatment resistant · Prospective clinical trial

Partial data from this trial were presented at:
1. Association for Research in Vision and Ophthalmology (ARVO) 2014 Annual Meeting, May 4–8, 2014, Orange County Convention Centre, South Building, Orlando, Florida, USA.
2. The Royal Australian and New Zealand College of Ophthalmologists (RANZCO) 45th Annual Scientific Congress, November 2–6, 2013, Hotel Grand Chancellor, Hobart, Australia.

This manuscript has not been published previously, and it is not simultaneously being considered for any other publication.

The trial was registered with the Australian and New Zealand Clinical Trials Registry (ACTRN 12612000666820).

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Introduction

Age-related macular degeneration (AMD) is the leading cause of visual impairment among the elderly in the developed world [1]. AMD can be classified into early (typically not visually

impairing) and late (visually impairing) stages [2, 3]. Neovascular AMD is a rapidly progressing form of late AMD associated with proliferation and intraretinal infiltration of choroidal vessels (neovascularization) resulting in an accumulation of fluid or hemorrhages in the intraretinal and subretinal space. Subsequent disruptions in retinal morphology, including macular scarring (fibrosis) and eventual atrophy, and damage to neural function, have been reported to be associated with severe loss of visual function or blindness [2].

Patients with late AMD can present with distortion or loss of sharp, fine-detailed central vision, which is important for activities such as reading, driving, recognizing faces and perceiving color [3, 4]. Visual impairment caused by neovascular AMD (nAMD) severely inhibits individuals' ability to perform activities of daily living (ADL) as well as their mobility [5], and is associated with an increased risk of social isolation, depression, loss of independence and reduction in overall quality of life (QoL) [5].

Previous findings from prospective studies have shown that aflibercept was effective in improving visual acuity (VA) and reducing central macular thickness (CMT) among patients who were resistant to other anti-vascular endothelial growth factor (anti-VEGF) agents [6, 7]. However, the impact of aflibercept treatment on vision-related quality of life (VR-QoL) has not been reported in this specific population. The National Eye Institute Visual Functioning Questionnaire 25 (NEI VFQ-25) is a validated and frequently used method of assessing VR-QoL in patients with nAMD [8–10]. It is also the most frequently used QoL measurement instrument in studies of nAMD following anti-VEGF treatment [4, 11]. The NEI VFQ-25 captures the patient's perception of visual function required to perform daily activities, and accounts for other aspects of the disease and the psychological effects of the condition. Assessment of VR-QoL in a treatment-resistant cohort can provide a more comprehensive understanding of the effects of aflibercept treatment on the daily routines of individuals with nAMD [11, 12].

The purpose of this study was to prospectively evaluate changes in VR-QoL following aflibercept treatment in previously treatment-resistant nAMD patients, using the NEI VFQ-25 questionnaire. We also assessed correlations between a patient's VR-QoL and visual function, including both the better-seeing eye (BSE, defined as the eye reading the greater number of letters at baseline) and worse-seeing eye (WSE, the fellow eye to the BSE), and macular anatomical changes.

Methods

Study design

This was a prospective open-label clinical trial conducted at a single tertiary retina clinic, with VR-QoL as one of the secondary outcomes assessed. The study was approved by the local institutional human research ethics committee (Bellberry Limited), and was conducted in accordance with the tenets of the Declaration of Helsinki. The trial is registered with the Australian and New Zealand Clinical Trials Registry (ACTRN 12612000666820).

Patients and clinical procedures

After providing written informed consent, 49 participants previously resistant to treatment with other anti-VEGF agents were recruited into the study between August and October 2012. Treatment resistance was defined as known choroidal neovascularization (CNV) secondary to AMD as demonstrated by fluorescein angiography (FA), prior treatment with at least four injections of anti-VEGF agents within the past 6 months, and persistent intraretinal or subretinal fluid, or both, on spectral-domain optical coherence tomography (SD-OCT) during this period [6]. The inclusion and exclusion criteria and study protocol were described previously [6]. At each visit, patients underwent a full ophthalmic examination, including best-corrected visual acuity (BCVA) measured using the Early Treatment of Diabetic Retinopathy Study (ETDRS) charts, and measurement of CMT using SD-OCT (Heidelberg Spectralis, Heidelberg, Germany). FA and indocyanine green angiography were performed at baseline visits to confirm the presence of AMD-related CNV and to exclude potential masquerade lesions such as polypoidal choroidal vasculopathy and retinal angiomatous proliferation. All participants were prospectively assessed every 4 weeks, and were treated with three loading doses of 2.0 mg intravitreal aflibercept every 4 weeks, followed by injections every 8 weeks, over a 48-week period. This regime was the regulatory authority-approved treatment regime for intravitreal aflibercept to treat nAMD patients, following the early clinical data and the findings of the VIEW 1 and VIEW 2 studies [11].

VR-QoL instrument

The NEI VFQ-25 self-administered format (Version 2000) was used in this study. The form includes 25 questions that assess the following 12 aspects of ADL: general health, general vision, ocular pain, near vision activities, distance vision activities, social functioning, vision-specific role difficulties, vision-specific mental health, dependency due to vision, driving, peripheral vision and color vision [8, 9].

The NEI VFQ-25 questionnaire was distributed and collected at the baseline, week 24 and week 48 visits. The results were analyzed in accordance with the published guidelines for the NEI VFQ-25 [9]. Each individual response was converted to a score between 0 and 100, with a higher score reflecting better vision-related function. Items within the NEI VFQ-25 questionnaire were categorized into 12 subscales by grouping related questions together and calculating each subscale score

by averaging all related question scores in this specific subscale. The NEI VFQ-25 composite score was calculated by averaging scores of all subscales excluding general health.

Statistical analysis

Participant baseline characteristics and NEI VFQ-25 composite scores were summarized using mean and standard deviation or proportions, whichever was appropriate. Changes in mean NEI VFQ-25 composite scores from baseline at weeks 24 and 48 were evaluated using paired *t* tests. The association between changes in NEI VFQ-25 composite score and changes in BCVA (expressed as number of ETDRS letters read) or CMT (in micrometers) over 24 and 48 weeks was evaluated using Pearson correlations. It was further assessed using linear regression models that accounted for possible baseline confounders including age, sex, baseline BCVA and CMT, smoking status, history of underlying systemic disease, and previous anti-VEGF treatment duration and number of injections. If patients did not attend a scheduled visit, the last-observation-carried-forward method was used for BCVA and CMT analysis, whereas patients with missing NEI VFQ-25 score(s) were removed from the analysis at the relevant time points.

Because VR-QoL usually involves vision changes in both eyes, additional sub-analysis was performed on the number of BCVA letters read at baseline for BSE and WSE. The BSE of a participant was defined as the eye with more BCVA letters read at baseline, and consequently the other eye, with fewer letters read, was considered the WSE. In the case of both eyes of a participant reading an equal number of letters at baseline, the study eye was chosen as the BSE. In addition, to evaluate whether there was an impact on VR-QoL scores from a VA change in the fellow eye (non-study eye), changes in BCVA in fellow eyes were also assessed.

To investigate the response difference in VR-QoL change in relation to vision improvement and treatment, the participants were grouped into "good" and "poor" responders, based on the improvement in their BCVA at 48 weeks compared to baseline. Good responders were those with >5 letter improvement (primary outcome of the original trial) and poor responders were those with ≤5-letter improvement in BCVA after 48 weeks of aflibercept treatment. The differences between the two responder groups in baseline characteristics, as well as the changes in NEI VFQ-25 composite and subscale scores at weeks 24 and 48, were compared using the two-sample *t* test.

The minimum clinically meaningful changes in NEI VFQ-25 scores were estimated by a distribution-based method which involves multiplying the standard deviation (SD) by 0.2 (0.2SD) [13, 14]. In our study, it was calculated using baseline SD and SD changes at weeks 24 and 48. The SD changes were also calculated for the individuals whose BCVA was confirmed to have improved (good responders) and the individuals not expected to change (poor responders). A change in NEI VFQ-25 composite and subscale scores of 4–6 points was defined as minimum clinically important difference (MCID) in this study [4, 15, 16].

Analyses presented here were performed using SPSS statistical software (version 20.0; IBM Corp, Armonk, NY, USA). A p value of less than 0.05 was considered statistically significant in all analyses.

Results

Forty-nine patients were recruited into the study and completed the 48-week follow-up. Two participants had missing NEI VFQ-25 data at week 24, and another participant missed the week 48 follow-up visit, resulting in 47 participants at week 24 and 48 participants at week 48 with complete data for analysis. Table 1 shows the baseline characteristics of the 49 participants by good and poor responders. At baseline, mean NEI VFQ-25 composite scores were similar between the good and poor responder subgroups [69.1 ± 17.7 vs. 70.7 ± 22.2 (mean ± SD)]. Participants in the poor responder group had better vision at baseline than good responders (65.2 ± 15.8 vs. 54.2 ± 14.8, $p = 0.017$). In addition, 18 of 28 (64.3 %) patients in the poor responder group had baseline BCVA better than the overall mean value of 60.5 letters, compared to 8 of 21 (38.1 %) participants in the good responder group with above-average vision ($p = 0.005$). There was a significant difference in general health scores at baseline between the good and poor responders (65.5 ± 20.1 vs. 51.8 ± 25.4, $p = 0.05$). The interval between prior anti-VEGF treatment and baseline was longer in the poor responder group than in the good responder group (32.7 ± 5.2 vs. 38.0 ± 9.6 days, $p = 0.03$). There was no significant difference between the good and poor responder groups with respect to any other baseline factors studied (Table 1).

The mean interval between the last injection of previous anti-VEGF treatment and baseline aflibercept was 35.7 ± 8.4 days. All 49 patients received ranibizumab in the 6 months before switching to aflibercept, and three patients (6.1 %) were treated with both ranibizumab and bevacizumab during that period. No other anti-VEGF treatment had been given in the 6 months prior to the commencement of aflibercept. The mean number of injections during the 6 months before switching to aflibercept was 5.3 ± 1.4. Patients' history of underlying systemic disease at baseline included six cases of diabetes, three heart attacks, three strokes, 33 with hypertension and 18 with hypercholesterolemia. None of these conditions had a statistically significant association with study outcomes.

Visual acuity and anatomical changes

The mean BCVA in treatment eyes at baseline was 60.5 ± 16.2 letters, and this improved by an average of 6.9 ± 8.1 letters by

Table 1 Baseline characteristics of 49 participants and responder subgroups

Characteristics	Participant groups [number (%) or mean ± SD]			
	Total ($n = 49$)	Good responder[a] ($n = 21$)	Poor responder[b] ($n = 28$)	p value[c]
Age (years)	77.3 ± 7.5	76.1 ± 7.8	78.3 ± 7.2	0.23
Sex (female)	28 (57)	11 (39)	17 (61)	0.58
Treatment eye (right)	23 (46.9)	9 (39)	14 (61)	0.75
Better-seeing eye in treatment	24 (49)	9 (38)	15 (62)	0.46
Interval between prior anti-VEGF treatment and baseline (days)	35.7 ± 8.4	32.7 ± 5.2	38.0 ± 9.6	0.03
Treatment with both ranibizumab and bevacizumab in the prior 6 months	3 (6)	1 (2)	2 (4)	–
Mean number of injections in the prior 6 months	5.3 ± 1.4	5.2 ± 1.3	5.4 ± 1.5	0.71
Duration of ranibizumab treatment (years)	3.4 ± 1.7	3.7 ± 1.6	3.1 ± 1.8	0.34
Total ranibizumab injections	34.9 ± 16.1	36.9 ± 14.6	33.4 ± 17.2	0.46
Smoking status:				
Non-smoker	19 (39)	9 (47)	10 (53)	1.00
Ex-smoker	28 (57)	12 (43)	16 (57)	1.00
Current smoker	2 (4)	0 (0)	2 (100)	–
BCVA (no. of letters read)	60.5 ± 16.2	54.2 ± 14.8	65.2 ± 15.8	0.02
BCVA >60.5 letters[d]	26 (53)	8 (31)	18 (69)	0.02
CMT (μm)	448.4 ± 141.2	450.2 ± 149.9	447.1 ± 137.2	0.94
NEI VFQ-25 score (points scored out of 100)	70.0 ± 20.1	69.1 ± 17.7	70.7 ± 22.2	0.78
NEI VFQ-25 general health sub-score	57.7 ± 24.0	65.5 ± 20.1	51.8 ± 25.4	0.05

SD = standard deviation, n = sample size, BCVA = best-corrected visual acuity, CMT = central macular thickness, NEI VFQ-25 = National Eye Institute Visual Function Questionnaire 25

[a] Good responders defined as participants with >5-letter improvement at week 48 compared to baseline

[b] Poor responders defined as participants with ≤5-letter improvement at week 48 compared to baseline

[c] p value for comparison between good responder and poor responder participant groups

[d] Average number of letters read at baseline among total population = 60.5

week 24 and 4.7 ± 9.1 letters by week 48 (both $p < 0.001$). The mean BCVA of fellow eyes at baseline and at weeks 24 and 48 was 61.0 ± 22.0 ($n = 48$), 63.5 ± 24.3 ($n = 47$) and 62.1 ± 23.3 letters ($n = 48$), respectively ($p < 0.001$ for week 24 and $p > 0.05$ for week 48). There was no significant BCVA improvement in fellow eyes over the 12-month period (mean change 1.1 ± 5.4 letters, $p > 0.05$). The mean CMT of study eyes at baseline was 448.4 ± 141.2 μm, which decreased to 361.7 ± 147.6 μm at week 24 and 351.1 ± 131.3 μm at week 48 (both $p < 0.001$).

Changes in NEI VFQ-25 scores

The mean NEI VFQ-25 composite score at baseline was 70.0 ± 20.1, and this increased significantly, by 4.5 ± 9.2 points ($p = 0.002$) at week 24 and 4.4 ± 11.8 points ($p = 0.012$) at week 48. Table 2 presents a summary of the NEI VFQ-25 composite and subscale scores at baseline and the mean changes from baseline to weeks 24 and 48. At week 24, subscales showing significant improvement included general vision, near activities, distance activities, social functioning and mental health (all $p < 0.05$). Similar results were observed at week 48 except for social functioning. The role difficulties subscale also showed significant improvement at week 48 (all $p < 0.05$). Mental health showed borderline statistical significance ($p = 0.056$). The distribution-based MCID for the NEI VFQ-25 scores is shown in Table 3.

Relationship of NEI VFQ-25 scores with BCVA and CMT

An increase in the NEI VFQ-25 composite score was moderately associated with an improvement in BCVA at week 48 compared to baseline, after adjusting for age, gender, baseline BCVA and CMT (β coefficient = 0.43, $p = 0.029$). However, this positive association was not detected at week 24 (β coefficient = 0.05, $p = 0.81$). There was no impact on the results associated with previous anti-VEGF treatment duration or number of injections, or with smoking status. There was also no association between the increase in the NEI VFQ-25 composite score and reduction in CMT at either week 24 or week

Table 2 The distribution of NEI VFQ-25 subscale scores and mean changes at week 24 and week 48

NEI VFQ-25[a] questionnaire scores	Baseline ($n = 49$)[b]	Mean change week 24 vs. baseline ($n = 47$)[c]		Mean change week 48 vs. baseline ($n = 48$)[d]	
	Mean ± SD	Mean ± SD	*P* value	Mean ± SD	*p* value
NEI VFQ-25 composite score	70.0 ± 20.1	4.5 ± 9.2	0.002	4.4 ± 11.8	0.01
Subscale scores					
General health	57.7 ± 24.0	−1.1 ± 20.2	0.72	1.0 ± 19.3	0.71
General vision	58.8 ± 19.3	6.4 ± 16.2	0.01	5.8 ± 13.7	0.01
Ocular pain	89.9 ± 16.2	−2.1 ± 9.8	0.15	−2.5 ± 13.3	0.20
Near activities	56.4 ± 26.2	6.4 ± 15.0	0.01	8.7 ± 17.9	0.00
Distance activities	64.1 ± 25.1	7.2 ± 14.7	0.00	7.7 ± 20.3	0.01
Social functioning	83.3 ± 22.2	4.0 ± 13.3	0.05	3.4 ± 20.9	0.27
Mental health	67.5 ± 24.3	6.2 ± 13.3	0.00	4.3 ± 15.2	0.06
Role difficulties	63.0 ± 26.9	6.5 ± 27.6	0.12	11.3 ± 29.1	0.01
Dependence	80.1 ± 28.9	3.1 ± 12.9	0.10	2.1 ± 15.7	0.36
Driving	61.6 ± 33.5	1.7 ± 19.8	0.62	−2.1 ± 16.9	0.47
Colour vision	84.7 ± 25.4	5.9 ± 20.3	0.06	7.3 ± 26.8	0.07
Peripheral vision	74.0 ± 25.0	1.1 ± 20.2	0.72	5.7 ± 20.8	0.06

n = sample size, SD = standard deviation

[a] The empirical range for the NEI VFQ-25 scores is 0 to 100. A higher score indicates better vision-related quality of life

[b] Reduced sample size for role difficulties ($n = 47$) and driving ($n = 36$) subscales

[c] Reduced sample size for distance activities ($n = 46$), role difficulties ($n = 46$) and driving ($n = 34$) subscales

[d] Reduced sample size for role difficulties ($n = 46$), dependency ($n = 47$) and driving ($n = 34$) subscales

Table 3 The distribution of clinically meaningful change in NEI VFQ-25 subscales

NEI VFQ-25 questionnaire subscales	Clinically meaningful change in NEI VFQ-25 scores (points)[a]						
	SD at baseline ($n = 49$)	SD change in NEI VFQ-25 score from baseline to week 24			SD change in NEI VFQ-25 score from baseline to week 48		
		Total population ($n = 47$)	Poor responder[b] ($n = 26$)	Good responder[c] ($n = 21$)	Total population ($n = 48$)	Poor responder ($n = 27$)	Good responder ($n = 21$)
General health	4.8	4.0	4.2	3.3	3.9	4.3	3.3
General vision	3.9	3.2	3.8	2.5	2.7	2.9	2.5
Ocular pain	3.2	2.0	1.6	2.4	2.7	2.1	3.2
Near activities	5.2	3.0	2.6	3.5	3.6	3.5	3.8
Distance activities	5.0	2.9	3.2	2.7	4.1	4.8	2.9
Social functioning	4.4	2.7	2.9	2.4	4.2	4.7	3.6
Mental health	4.9	2.7	2.7	2.8	3.0	3.0	2.9
Role difficulties	5.4	5.5	6.1	5.0	5.8	6.6	4.7
Dependence	5.8	2.6	2.8	2.3	3.1	3.2	3.1
Driving	6.7	4.0	4.2	3.8	3.4	3.5	2.9
Colour vision	5.1	4.1	3.9	4.3	5.4	5.8	4.6
Peripheral vision	5.0	4.0	4.7	3.0	4.2	4.5	3.7
NEI VFQ-25 composite score	4.0	1.8	1.9	1.8	2.4	2.6	2.0

SD = standard deviation, n = sample size

[a] Minimum change estimated as 0.2 × SD

[c] Good responders defined as participants with improvement of >5 letters at week 48 compared to baseline

48 (β coefficient = −0.008, $p = 0.487$ and β coefficient = −0.007, $p = 0.631$, respectively), after adjusting for all baseline factors.

There was a significant positive linear relationship between an improvement in mental health score and an increase in BCVA between baseline and week 48 ($r = 0.33$, $p = 0.02$). However, this relation was not able to be statistically detected at week 24 ($r = 0.22$, $p = 0.14$). There was no significant correlation between changes in any other subscale score and BCVA at week 24 or 48 (all $p > 0.05$).

The improvement in color vision score was negatively correlated with reduction in CMT at week 24 ($r = -0.42$, $p = 0.003$), and the increase in dependency score was negatively correlated with a decrease in CMT at week 48 ($r = -0.42$, $p = 0.003$). There was no other noticeable relationship between the change in any other subscale and CMT at week 24 or 48 (all $p > 0.05$).

Relationship between NEI VFQ-25 scores and better-seeing vs. worse-seeing treatment eyes

At baseline, 24/49 (49 %) treatment eyes were BSE, with 9/24 (38 %) BSE found within the good responder group and 15/24 (62 %) within the poor responder group (Table 1). Three eyes progressed from BSE to a WSE over the 48-week study period. In the treatment eyes, the mean improvement in vision from baseline in eyes with BSE status was 4.4 ± 7.2 and 3.4 ± 6.6 letters at weeks 24 and 48, respectively ($p < 0.01$ for all). The eyes with WSE status showed more significant mean improvement from baseline at weeks 24 and 48, with values of 9.5 ± 8.4 and 6.2 ± 10.6 letters, respectively (all $p < 0.01$). The mean improvement in NEI VFQ-25 composite score from baseline in treatment eyes with BSE status was 4.1 ± 11.1 and 2.7 ± 14.1 points, respectively (all $p > 0.05$), while the mean improvement in eyes with WSE status was 3.7 ± 6.6 and 5.0 ± 9.5 points at weeks 24 and 48, respectively (all $p < 0.05$). Although WSE showed greater improvement in BCVA over 48 weeks compared to BSE, such differences between WSE and BSE eyes were not statistically significant ($p > 0.05$). This may be due to the small sample size. In addition, the improvement in BCVA from baseline in treatment eyes had no statistically significant association, in either BSE or WSE, with mean changes in NEI VFQ-25 composite score at weeks 24 and 48 (β coefficient = 0.005, $p = 0.569$ and β coefficient = 0.007, $p = 0.336$).

VR-QoL results in good and poor responder groups

Compared to baseline, both good ($n = 21$, 45 %) and poor ($n = 26$, 55 %) responders showed a significant improvement in NEI VFQ-25 composite scores at week 24 (4.4 ± 8.9 vs. 4.6 ± 9.6, both $p < 0.03$). Among good responders, general health, distance activities and mental health subscales improved significantly. Among poor responders, general vision, near activities, distance activities and mental health subscales showed a significant improvement at week 24 (all $p < 0.05$).

Good responders also showed a significant increase in the NEI VFQ-25 composite score at week 48 compared to baseline (6.8 ± 10.1 points, $p = 0.01$). However, poor responders ($n = 27$, 56 %) showed no significant improvement over the same period (2.5 ± 12.7 points, $p = 0.32$). Significant improvement at week 48 was shown for distance activities, mental health, role difficulties, color vision and peripheral vision in good responders, and for general vision, ocular pain and near activities in poor responders (all $p < 0.05$). Figure 1 shows the distribution of mean changes in NEI VFQ-25 subscale scores in the two responder groups over the 48-week study period. General health at week 24 and mental health mean scores at week 48 were significantly different between the good responders and poor responders ($p = 0.02$). The observed differences in mean change in other subscales were not significant.

Anatomical changes in good and poor responders

In good responders, mean CMT at baseline was 450.2 ± 149.9 μm, and CMT decreased by 97.8 ± 190.6 μm ($p = 0.029$) and 129.2 ± 171.8 μm ($p = 0.003$) at weeks 24 and 48, respectively. In poor responders, mean CMT was 447.1 ± 137.2 μm at baseline, and decreased by 78.5 ± 110.3 μm ($p = 0.001$) and 73.3 ± 127.9 μm ($p = 0.005$) at weeks 24 and 48, respectively. However, differences in CMT changes between good and poor responders were not significant at either week 24 ($p = 0.657$) or week 48 ($p = 0.198$) compared to baseline.

Discussion

Previous studies have documented extensive evidence that improved visual and anatomic outcomes are associated with anti-VEGF treatment, including bevacizumab, ranibizumab and aflibercept, in patients with AMD [17–19]. Change in VA is often used to measure the clinical effectiveness of treatment in AMD. However, VA and other clinical measurements for assessing AMD, including OCT, used alone do not capture how the patients' visual function affects their ADLs [5]. Although VA and QoL are suggested to be strongly correlated in patients with AMD [20–22], from the patient's perspective, an improvement in psychological well-being and the ability to perform ADLs that are dependent on visual function may be equally or even more important than the clinical assessment of VA itself [5]. Increasing attention has been given to the assessment of health-related QoL outcomes in patients with eye disease [4, 12, 16].

Improvements in VR-QoL have been reported previously among treatment-naïve nAMD patients undergoing anti-VEGF therapy such as pegaptanib [23], ranibizumab [24] and

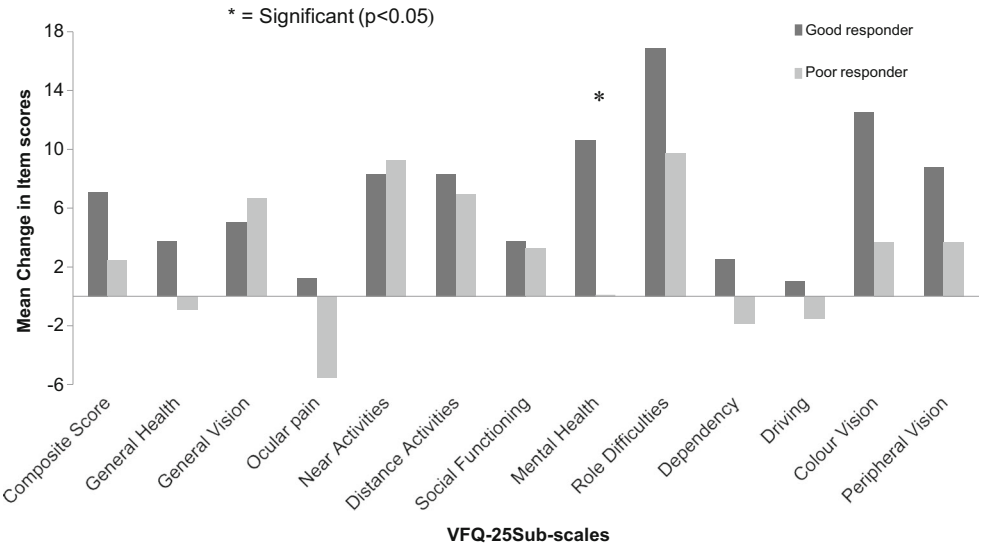

Fig. 1 The mean change in VFQ-25 subscale scores between baseline and week 48 by responder status

aflibercept [11]. However, to our knowledge, there are no previous reports regarding VR-QoL in anti-VEGF treatment-resistant patients in a prospective switching study. In our cohort, the mean interval between the last injection of previous anti-VEGF treatment and baseline aflibercept was 35.7 ± 8.4 days, which reflects treatment resistance. The baseline NEI VFQ-25 composite score of our cohort and subsequent improvement by an average of 4.5 points at week 24 and 4.4 points at week 48 after switching to aflibercept treatment are comparable to the results reported in VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD studies (VIEW 1 and VIEW 2) at 5.1 ± 14.7 and 4.9 ± 14.7, respectively [11]. The improved near activities (8.7 points) and distance activities subscales (7.7 points) at week 48 are also comparable to the results observed in the VIEW 1 and VIEW 2 studies (range of 4.8 to 8.6) [5, 11]. These similar VR-QoL outcomes between treatment-naïve and treatment-resistant patients suggest that there is still potential for VR-QoL improvement in patients who have responded poorly to previous anti-VEGF treatments and switch their treatment regime to aflibercept.

Distribution-based methods were used to estimate MCID for the composite and subscale scores in our study. The 0.2SD values are general benchmarks for facilitating decisions regarding the clinical importance of observed changes in relation to measurement variability. Standard deviation estimates for individuals are not expected to reflect the amount of spurious change in the NEI VFQ-25 score and are helpful in determining whether the observed change is a true change. Our results suggest that a 4–6-point change in the NEI VFQ-25 composite and subscale scores obtained from the study would be considered too large to be spurious. Thus, these are clinically significant improvements [4, 16].

Patients with eye disease often have a BSE and a WSE. Cross-sectional and longitudinal studies have reported that the VR-QoL has a closer relationship with the vision change in the WSE than the BSE [25–27, 29].

Data from the Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD (MARINA) and the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration (ANCHOR) with intravitreal ranibizumab treatment showed that the VR-QoL measured with the VFQ-25 was improved regardless of whether the treated eye was the BSE or the WSE, although two-thirds of the treatment eyes were the WSE [24]. Another study also confirmed that an improvement in VR-QoL may be related to an improvement in vision, and maintained in the treatment eye irrespective of whether the WSE or the BSE was treated [28]. In our study, the treatment eyes with WSE status demonstrated greater improvement in mean BCVA and NEI VFQ-25 scores than eyes with BSE status over a 48-week treatment period, although there was no statistically significant association found between BSE or WSE. In addition, there was no statistically significant mean change in NEI VFQ-25 composite score in either WSE or BSE at weeks 24 and 48 compared to baseline. It should be noted that 51 % of the treatment eyes in our cohort were the WSE at baseline, and this number increased to 57 % at week 48. As BCVA in the fellow eye did not show a significant change from baseline at week 48, the VR-QoL improvement would be associated with the BCVA improvement in the treatment eye only. In nAMD patients with bilateral eye disease, whose daily life may be constrained by inconvenience, cost or risk of additional medications/injections, effective treatment regardless of BSE or WSE would improve VR-QoL and relieve the disease burden [29]. Evidence from our study strongly suggests that patients should have access to treatment and care when the function in either eye is affected, even in treatment-resistant cohorts.

A number of studies have reported that AMD may lead to high levels of emotional distress and reduced QoL [30–33], and studies have reported that a high proportion of people with AMD suffer from depression and mental disorders [30, 34]. Brady et al. [34] found a strong association between depression and lower NEI VFQ-25 scores in AMD patients, but only a weak association between VA and depression. Several studies have suggested a possible reciprocal relationship between visual disability and depression (disability leads to depression and depression influences disability) [30, 35]. Our study demonstrated a high level of mental health subscale improvement in the group that also had a high level of VA improvement after 48 weeks of aflibercept treatment. This is comparable to the results of the MARINA and ANCHOR studies [36, 37]. A weak positive correlation between the mental health subscale scores and BCVA improvement was also detected in our study, and is similar to the results reported by Brody et al. [34]. This suggests that the improvement in vision may have a positive impact on the patient's mental well-being.

There was no significant correlation between NEI VFQ-25 composite score and reduction in CMT in our study, although BCVA and CMT were found to be closely related [38]. This result is consistent with the findings in the study conducted by Bressler et al. [24, 26], and suggests that the anatomical changes observed over the study period did not have a sufficient impact on the functional aspects of daily living. However, changes in color vision and dependency subscales were moderately and negatively correlated with a reduction in CMT. Whether the improvement in color vision subscale reflects an improvement in cone photoreceptor function secondary to a reduction in macular thickness [2] is not yet known and should be evaluated in future studies. The relationship between the dependency subscale and anatomical changes also warrants further investigation.

Evaluation of the effects of treatment with respect to VR-QoL in our study showed that patients who responded well to the treatment (good responders) had a greater improvement in NEI VFQ-25 composite score than those patients who did not respond well to the treatment (poor responders), despite a positive correlation between NEI VFQ-25 composite score and BCVA improvement. This is also supported by a recent publication by Finger et al. [28], who demonstrated that treatment for nAMD improved patient VR-QoL in those who gained and maintained visual acuity. These results provide further evidence that the NEI VFQ-25 is responsive to visual acuity changes in patients receiving aflibercept therapy for previously treatment-resistant nAMD. It further confirms that NEI VFQ-25 would be a reliable instrument for assessing treatment effectiveness in addition to VA and OCT evaluation [10].

The lack of statistically significant improvement in most of the subscales for both good and poor responder groups, and the lack of significant differences in improvement in subscale scores between good and poor responder groups, requires further investigation with a larger patient cohort. As discussed previously, although there is a clear correlation between an improvement in VR-QoL composite score and increased BCVA, the BCVA is not the only factor affecting VR-QoL. Both good and poor responders showed significant improvements in the NEI VFQ-25 composite and subscale scores in general health, distance activities and mental health at week 24, and poor responders showed significant improvement in near activity at week 24. These subscale changes in the poor responder group were not associated with improvement in BCVA (all $p > 0.05$). There may be a ceiling effect arising from a higher baseline mean BCVA (65.2 vs. 54.2 letters) and a higher percentage of participants with better baseline BCVA (64.3 % vs. 38.1 %) in poor responders than in good responders. These high baseline values in the poor responder group could limit the potential for detecting further improvement in these measures. The small case numbers may also contribute to the difficulty in detecting the differences. We note that the interval between the last injection in the previous anti-VEGF treatment and commencement of baseline aflibercept was longer in the poor responder group than in the good responder group (38.0 ± 9.6 vs. 32.7 ± 5.2 days, $p = 0.03$). This suggests that a longer interval between last injection and baseline switching treatment may have had an influence on VR-QoL responses. It further suggests that treatment-resistant patients may benefit from switching earlier rather than later in order to preserve visual function and improve daily quality of life.

The limitations of this study include the lack of a control group and the small size of the study sample used to assess outcome variables. As the study was the first prospective switching study in the world, the study group and the number of study participants were limited by the aflibercept supply at the time of recruitment. The small population size has limited statistical differentiation power to detect any subtle differences in the NEI VFQ-25 analysis, especially in the subscales. However, the prospective nature of the study design, patient assessment and follow-up using reliable and valid instruments, and the standardized manner of data collection are key strengths of this study. The use of MCID also helps to determine whether the observed changes are true changes and are clinically relevant.

In conclusion, this study provides evidence that aflibercept therapy can improve VR-QoL in a specific cohort of previously anti-VEGF treatment-resistant patients with nAMD, without significant adverse events. The improvement in VR-QoL was associated with increased vision in treatment eyes, regardless of whether they were better-seeing or worse-seeing eyes. Patients with greater visual gain showed a greater improvement in VR-QoL. These results may provide useful information for understanding the effect of aflibercept treatment among patients with treatment-resistant nAMD. It also suggests that patients should have access to treatment and care

when the function in either eye is affected, even in a treatment-resistant cohort. Measurement of VR-QoL may also be helpful for monitoring disease progression and guiding future treatment regimes for treatment-resistant nAMD, as it is a useful assessment tool in addition to vision and OCT measurements in this cohort of patients.

Compliance with ethical standards

Funding Financial support was provided in part by Bayer Corporation. The sponsor had no role in the design or conduct of this research. The authors have full control of all primary data, and we agree to allow Graefe's Archive for Clinical and Experimental Ophthalmology to review our data upon request.

Conflict of interest Dr. Andrew Chang has acted as a consultant for Alcon, Bayer and Novartis. All other authors state that they have no proprietary interests or conflicts of interest related to this submission.

Ethical approval All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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