Patient-reported outcomes from a phase IV study of aflibercept in patients with refractory retinal vein occlusions

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Abstract:
PURPOSE: To determine the patient-centered effectiveness of switching patients with persistent macular edema due to retinal vein occlusion (RVO) to aflibercept using the National Eye Institute Visual Function Questionnaire 25 (NEI-VFQ-25).
MATERIALS AND METHODS: Prospective study of eyes with persistent cystoid macular edema due to RVO despite regular treatment with bevacizumab or ranibizumab switched to aflibercept. Three loading doses of intravitreal aflibercept were administered every 4 weeks and thereafter every 8 weeks until week 48. Vision-related quality of life (VRQoL) using NEI-VFQ-25 was measured at baseline, 24 weeks, and 48 weeks following the switch. Baseline scores were compared to week 24 and 48 using paired t-test. Relationship between best-corrected visual acuity (BCVA) in the study eye and the NEI-VFQ-25 composite and subscale scores was investigated.
RESULTS: Eighteen patients with RVO were enrolled in the study with a mean age of 70.3 ± 8.6 years. The mean change in BCVA and central macular thickness (CMT) from baseline to 48 weeks was +20.6 ± 5.2 Early Treatment of Diabetic Retinopathy Score letters and −109.2 ± 82.8 μm, respectively. VRQoL improved significantly, with an increase of mean NEI-VFQ composite score of 11.5 ± 9.5; the corresponding improvements in near and distant activities were 13.3 ± 19.4 and 8.4 ± 10.4, respectively (P < 0.001 for both). Logistic regression analysis demonstrated that BCVA gain of >15 letters and CMT < 300 μm at the end of the study predicted a higher change in VFQ-25.
CONCLUSION: Switching eyes with persistent macular edema due to RVO to aflibercept resulted in significant improvement in visual function and patient satisfaction.

Keywords: Aflibercept, antivascular endothelial growth factor, macular edema, quality of life, retinal vein occlusion, treatment resistance

Introduction
Macular edema is the major cause of vision loss in eyes with retinal vein occlusion (RVO). Vascular endothelial growth factor (VEGF) inhibitors have been shown to be effective in the management of macular edema due to RVO. However, not all eyes respond optimally to one agent and may respond better to another anti-VEGF. We have previously reported improvement in best-corrected visual acuity (BCVA) and reduction in central macular thickness (CMT) in eyes with persistent macular edema due to RVO switched to aflibercept despite prior treatment with bevacizumab or ranibizumab.

Results from the SCORE2 report that RVO has a major impact on patient-reported vision-related quality of life (VRQoL),...
despite RVO being predominantly a unilateral disease, 93% of those participants in SCORE2 had bilateral disease.\textsuperscript{[13]} There are little data on the effects of switching treatment from a patient’s perspective. Patient-reported outcome measures are increasingly recognized as necessary for determining the usefulness of interventions in all aspects of clinical care.\textsuperscript{[14]}

The National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25) is a well-established and validated survey to objectively evaluate a patients' perceived disease burden and to determine VRQoL and has been used to judge the effect of interventional therapy.\textsuperscript{[15-18]} The aim of this study was to better assess patient-centered effectiveness of switching to aflibercept in patients with persistent macular edema secondary to RVO.

Even when a treatment considered effective based on the reduction in CMT and improvement in vision, it is possible for patients to continue to suffer symptoms, such as metamorphopsia, poor vision, and relative scotoma, which may lead to poorer VRQoL scores.

We investigated the NEI-VFQ-25 scores and their relationship to response to treatment, that is, BCVA change and CMT. We compared the results where the study eye was the better-seeing eye to where the study eye was the worse-seeing eye. Accordingly, we investigated the relations between BCVA, CMT, and VFQ to elucidate an enhanced appreciation of the functional impact of macular edema on a cohort of treatment-resistant RVO patients.

**Methods**

The present study was a 48-week clinical trial that evaluated the efficacy of switching to 2 mg aflibercept (Eylea: Regeneron, Tarrytown, NY, USA) in patient’s refractory to bevacizumab (Avastin: Genentech, San Francisco, CA, USA) or ranibizumab (Lucentis: Genentech, San Francisco, CA, USA) for the treatment of macular edema secondary to RVOs. The study was conducted in accordance with the Declaration of Helsinki and was approved by relevant Health Research Ethics Committee (Bellberry Limited, approval number : 2017-11-837). Patients gave written informed consent. The trial was registered on the Australian and New Zealand Clinical Trials Registry (ACTRN 12617001487303).

**Protocol synopsis**

The eligibility criteria have been detailed previously.\textsuperscript{[19]} Briefly, participants had center involving macular edema due to RVO confirmed by fundus fluorescein angiography; BCVA between 34 and 73 letters (Snellen equivalent of between 20/200-20/40); presence of central edema >320 µm as measured on spectral domain optical coherence tomography (SD OCT) with documented prior suboptimal response. Suboptimal response was defined as ≤5 letter gain (and vision loss) in BCVA, or reduction of <20% CMT on SD OCT after at least 4 previous intravitreal injections of bevacizumab and/or ranibizumab in the 6 months prior to baseline. Baseline measurements included BCVA with ETDRS charts by standardized staff. CMT was measured by SD-OCT using the Heidelberg Spectralis (Heidelberg Engineering, Heidelberg Germany) and repeated every 4 weeks by the same technician.

A loading dose of three intravitreal aflibercept injections (2.0 mg/0.1 mL) at 4-week intervals were given (i.e., at baseline, week 4, and week 8). Subsequent aflibercept injections were administered 8-weekly until week 48. The intravitreal aflibercept (2 mg) protocol was standard across all patients. After topical anesthesia with oxybuprocaine, the eyelids and conjunctiva were cleansed with povidone-iodine solution, and a lid speculum was inserted. A 30-gauge needle was inserted through the pars plana 3.5 mm posterior to the limbus, and 0.05 mL of aflibercept (2 mg) therapy was administrated into the vitreous cavity. Patients were given prophylactic ocular lubricants postinjection for discomfort.

**Patient-reported visual function**

Subjective patient-reported visual quality of life (QoL) was evaluated by the 25-item NEI-VFQ-25 at baseline, week-24, and week-48. The questionnaire was administered by a single, trained interviewer. The NEI-VFQ-25 comprises 25 base questions that comprise 12 areas of vision-specific function: general health, quality of vision (including near and distance), driving, dependency, role function, social function, mental health, limitation with peripheral vision and color vision, and ocular pain. Six additional appendix questions from the NEI-VFQ-25 were added to enhance the consistency and sensitivity of both the near and distance visual subscales.

Scores range from 0 (worst score) to 100 (best score). The composite and each subscale score for the NEI-VFQ-25 were calculated according to published algorithms. While there is no recognized benchmark for a clinically significant change in the NEI-VFQ-25 scores, studies have suggested that a 4- to 6-point improvement is correlated with a 15-letter (3 points) difference in VA.\textsuperscript{[17]}

**Statistical analyses**

All analyses were performed using SPSS software (version 24.0, SPSS Inc., Chicago, IL, USA). Normal distribution of data was confirmed using Shapiro-Wilk tests. BCVA was performed on an ETDRS chart and given a corresponding letter score for statistical analysis.\textsuperscript{[20]} Results were presented as...
the mean ± standard deviation. Paired t-tests were used to compare differences in means of BCVA, CMT, composite, and subscale scores in the VFQ-25. Cronbach’s standardized α was calculated to assess the internal consistency of the subscale scores. Usually, Cronbach’s values of 0.7 or higher are deemed standard.

The relationship between NEI-VFQ-25 scores and baseline factors of BCVA and CMT was assessed using Pearson’s correlation coefficients. P < 0.05 was deemed statistically significant.

Results

A total of 18 eyes from 18 subjects (14 BRVO and 4 CRVO) were included in our study, and all patients answered the questionnaire at all time points. The mean age of these 18 patients was 70.3 ± 8.6 years (range: 54–85) at study entry. Patient demographics and baseline characteristics are shown in Table 1. The mean number of previous injections was 50.3 ± 16.9 and 36.9 ± 3.3 over a period of 102.7 ± 31.9 and 67.5 ± 44.2 months in the CRVO and BRVO groups, respectively.

The BCVA for the total patient sample was 65.3 ± 4.6 letters at baseline and showed a significant improvement at week 1 and remained up to week 48, for a final mean BCVA of 84.8 ± 8.8 letters (P < 0.001) [Figure 1]. The mean baseline CMT was 393.2 ± 116.4 μm; similarly, the results demonstrated a significant reduction in CMT measured by OCT at week 48 (−109.2 ± 82.8 μm, P < 0.001). All patients received 8 aflibercept injections over 48 weeks of the study.

VFQ

The mean ten-subscale composite NEI-VFQ-25 score at baseline was 82.9 ± 8.2 (range, 64.4–92.1). Overall, general health, general vision, and driving were the areas patients declared the most affected. In contrast, peripheral and color vision and social functioning are least affected, followed by vision-specific dependency. Changes in composite and subscale scores at 24 and 48 weeks are summarized in Table 2. There was a significant improvement from baseline to week 48 in general vision (P < 0.001), role difficulties (P < 0.001), and near vision (P < 0.001).

The responsiveness of VFQ scores was increased in patients for whom the study eye was worse-seeing eye at baseline (+14.6 ± 6.1 vs. 7.5 ± 3.6, P = 0.02). Furthermore, the improvement in composite scores was more evident in BRVO than CRVO eyes (+13.5 ± 8.4 vs. 4.4 ± 5.7, P < 0.001).

Relationship between visual acuity, central macular thickness, and VFQ

To explore the association of vision change and QoL, we used the vision score from the study eye only. There was a significant correlation between the BCVA and the ten-subscale composite scores (r = 0.84, P = 0.03) [Table 3]. A moderate correlation was demonstrated between the BCVA of the study eye and the patients’ subjective handicap (NEI VFQ 25 “Composite Score”). Correlations with the functional variables were demonstrated: “distance activities” (r = 0.765, P = 0.001) as well as “peripheral vision” (r = 0.951, P = 0.017) were positively correlated with BCVA. Role difficulties and driving had a nonsignificant negative correlation with BCVA. Dependence scores had a weak significant negative correlation with final BCVA change (r = −0.196, P = 0.04).

None of the baseline characteristics such as age and gender were significant predictors of improvement in

Table 1: Baseline characteristics of included patients

| Characteristic                                    | BRVO (n=14) | CRVO (n=4) |
|--------------------------------------------------|-------------|------------|
| Age (years), mean±SD                             | 71.5±8.8    | 66.0±5.5   |
| Male, n (%)                                      | 4 (28.6)    | 3 (75)     |
| Systolic blood pressure (mmHg), mean±SD          | 135.6±16.6  | 132.8±10.8 |
| Hypertension, n (%)                              | 13 (92.9)   | 4 (100.0)  |
| Hyperlipidemia, n (%)                            | 6 (42.9)    | 3 (75.0)   |
| NIDDM, n (%)                                     | 2 (14.3)    | 2 (50.0)   |
| Known glaucoma/ocular hypertension, n (%)        | 3 (20.0)    | 0 (0)      |
| Duration of anti-VEGF treatment (months), mean±SD| 67.5±44.2   | 102.7±31.9 |
| Total number of anti-VEGF injections, mean±SD    | 36.9±17.7   | 50.3±16.9  |
| Interval between last anti-VEGF and baseline aflibercept (days), mean±SD | 44.7±3.3 | 38.0±8.8 |
| Ischemia, n (%)                                  | 4 (28.6)    | 2 (50)     |
| BCVA, letter score, mean±SD                      | 65.3±3.8    | 64.3±6.4   |

BRVO: Branch retinal vein occlusion, CRVO: Central retinal vein occlusion, SD: Standard deviation, BCVA: Best-corrected visual acuity, VEGF: Vascular endothelial growth factor, NIDDM: Noninsulin-dependent diabetes mellitus
**Table 2: Changes in visual function questionnaire-25 scores during the study period**

| VFQ-25 subscale          | Baseline score, mean±SD (n=18) | Change at 24-weeks (n=18) | Change at 48-weeks (n=18) |
|--------------------------|---------------------------------|---------------------------|--------------------------|
|                          | Mean±SD                         | P                          | Mean±SD                  | P                          |
| Composite score          | 82.9±8.2                        | 8.8±6.8                    | <0.001                   | 11.5±9.5                   | <0.001                    |
| Subscales                |                                 |                            |                          |                            |
| General health           | 63.9±17.6                       | 4.2±19.6                   | 0.381                    | 16.7±20.4                  | 0.014                     |
| General vision           | 65.6±13.4                       | 14.4±13.4                  | <0.001                   | 19.7±21.0                  | 0.001                     |
| Ocular pain              | 84.0±14.1                       | 11.8±13.2                  | 0.001                    | 15.0±16.5                  | 0.001                     |
| Near activities          | 79.6±20.1                       | 12.0±13.5                  | 0.001                    | 13.3±19.4                  | 0.002                     |
| Distance activities      | 87.5±12.5                       | 10.6±11.7                  | 0.001                    | 8.4±10.4                   | 0.002                     |
| Social functioning       | 94.4±9.8                        | 5.6±9.8                    | 0.028                    | 4.2±9.0                    | 0.049                     |
| Mental health            | 82.3±11.2                       | 10.8±10.2                  | <0.001                   | 12.0±12.9                  | 0.020                     |
| Role difficulties        | 79.9±19.7                       | 12.5±22.7                  | 0.032                    | 19.2±21.6                  | <0.001                    |
| Dependence               | 90.7±10.3                       | 9.3±10.3                   | 0.001                    | 7.2±9.4                    | 0.001                     |
| Driving                  | 77.3±19.9                       | 5.6±21.4                   | 0.285                    | 13.3±15.7                  | 0.001                     |
| Color vision             | 98.6±5.9                        | 1.4±5.9                    | 0.331                    | 1.7±6.5                    | 0.331                     |
| Peripheral vision        | 91.7±14.9                       | 7.9±13.9                   | 0.026                    | 7.8±13.9                   | 0.276                     |

VFQ-25: Visual function questionnaire-25, SD: Standard deviation

**Table 3: Visual function questionnaire outcomes and correlation with best-corrected visual acuity and central macular thickness at baseline and 48 weeks**

| NEI-VFQ-25 | Correlation of baseline value with BCVA at baseline | Correlation of 48-week value with BCVA at 48-weeks | Correlation of change in value with change in BCVA at 48-weeks |
|------------|-----------------------------------------------------|---------------------------------------------------|---------------------------------------------------------------|
|            | Pearson’s correlation coefficient | P                          | Pearson’s correlation coefficient | P                          | Pearson’s correlation coefficient | P                          |
| Composite score | 0.84            | 0.03                  | 0.72                           | 0.0091                  | 0.57                           | 0.05                        |
| General health        | 0.65            | 0.015                 | 0.974                          | 0.008                   | 0.937                          | 0.022                       |
| General vision         | 0.78            | 0.05                  | 0.813                          | 0.045                   | 0.74                           | 0.015                       |
| Ocular pain            | 0.30            | 0.13                  | 0.564                          | 0.146                   | 0.344                          | 0.209                       |
| Near activities        | 0.72            | 0.02                  | 0.87                           | 0.04                    | 0.687                          | 0.013                       |
| Distance activities    | 0.64            | 0.019                 | 0.835                          | 0.05                    | 0.765                          | 0.001                       |
| Social functioning     | 0.157           | 0.53                  | 0.564                          | 0.146                   | 0.295                          | 0.290                       |
| Mental health          | −0.370          | 0.13                  | 0.612                          | 0.007                   | 0.502                          | 0.188                       |
| Role difficulties      | −0.205          | 0.415                 | −0.267                         | 0.285                   | −0.204                         | 0.466                       |
| Dependence             | −0.417          | 0.085                 | −0.412                         | 0.09                    | −0.196                         | 0.04                        |
| Driving                | −0.227          | 0.365                 | −0.56                          | 0.08                    | 0.89                           | 0.037                       |
| Color vision           | 0.618           | 0.026                 | 0.535                          | 0.059                   | 0.466                          | 0.02                        |
| Peripheral vision      | 0.611           | 0.029                 | 0.502                          | 0.169                   | 0.951                          | 0.017                       |

| NEI-VFQ-25 | Correlation of baseline value with CMT at baseline | Correlation of 48-week value with CMT at 48-weeks | Correlation of change in value with change in CMT at 48-weeks |
|------------|-----------------------------------------------------|---------------------------------------------------|---------------------------------------------------------------|
|            | Pearson’s correlation coefficient | P                          | Pearson’s correlation coefficient | P                          | Pearson’s correlation coefficient | P                          |
| Composite score | 0.693          | 0.03                  | 0.743                          | 0.001                   | 0.524                          | 0.027                       |
| General health        | 0.998          | 0.001                 | 0.538                          | 0.015                   | 0.736                          | 0.095                       |
| General vision         | 0.793          | 0.022                 | 0.704                          | 0.001                   | 0.761                          | 0.086                       |
| Ocular pain            | 0.187          | 0.326                 | 0.246                          | 0.325                   | 0.064                          | 0.821                       |
| Near activities        | 0.827          | 0.019                 | 0.482                          | 0.043                   | 0.532                          | 0.017                       |
| Distance activities    | 0.845          | 0.016                 | 0.769                          | 0.02                    | 0.7312                         | 0.006                       |
| Social functioning     | 0.511          | 0.166                 | 0.776                          | 0.072                   | 0.793                          | 0.074                       |
| Mental health          | 0.254          | 0.308                 | 0.391                          | 0.109                   | 0.245                          | 0.379                       |
| Role difficulties      | 0.408          | 0.093                 | 0.242                          | 0.290                   | 0.271                          | 0.304                       |
| Dependence             | 0.332          | 0.243                 | 0.265                          | 0.08                    | 0.531                          | 0.176                       |
| Driving                | 0.332          | 0.178                 | 0.593                          | 0.135                   | 0.565                          | 0.162                       |
| Color vision           | 0.734          | 0.08                  | 0.813                          | 0.06                    | 0.970                          | 0.010                       |
| Peripheral vision      | 0.697          | 0.099                 | 0.722                          | 0.001                   | 0.774                          | 0.081                       |

NEI-VFQ-25: National eye institute visual function questionnaire 25, BCVA: Best-corrected visual acuity, CMT: Central macular thickness
the NEI-VFQ-25 composite. For the total composite score, baseline score was positively associated with scores at 48 weeks ($P = 0.05$), as well as distance, near, and mental health. Baseline BCVA was a positive predictor of VFQ outcomes ($P < 0.001$). Logistic regression analysis demonstrated that BCVA gain of $>15$ letters and CMT $<300$ μm at the end of study predicted a higher change in VFQ-25.

When we stratified the 18 eyes according to the number of letters gained, eyes gaining $>15$ letters had almost double the gain in overall composite score, compared to those who gained $<15$ letters ($P = 0.02$). Other significant gains for eyes that gain greater vision included general health ($P = 0.04$), general vision ($P = 0.01$), and near activities ($P = 0.01$) [Table 4].

The change in social functioning, dependence, and role difficulty scores for all patients showed a low correlation with change in BCVA. Similarly, when we stratified patients into two groups according to the number of letters gained, no relationship was found.

In the group with the greater BCVA gain, there was a strong correlation between letters gained and distance and near activities and general vision (range, $r = 0.75–0.91$; $P = 0.002$). Comparatively, in the group who gained $<15$ letters, there was moderate association between vision change and distance and near activities (range, $r = 0.55–0.67$; $P = 0.001$).

**Discussion**

This prospective study evaluated patient-reported VRQoL among subjects with persistent macular edema due to RVO, before and after switch to aflibercept. BCVA and NEI-VFQ results were evaluated as the main functional outcome variables. The NEI-VFQ-25 is a patient-reported tool that measures binocular function, demonstrated responsiveness to changes in BCVA, a monocular measured outcome, in the treatment of refractory macular edema in the study eye. A statistically significant improvement in BCVA was observed at all time points, with a mean gain of 20 letters at the conclusion of the study, corresponding to an improvement in NEI-VFQ-25 overall composite score of 11 points. These results are noteworthy, especially in light of the study eye being the worse eye at baseline in the majority of subjects (83%).

Results of the present study showed that RVO has a significant impact on patient-reported visual function, despite the condition being predominately unilateral. Similar results were seen in the SCORE2, CRUISE, and GALILEO studies. Being aware of a patient’s subjective vision-related QoL and burden of disease, as objectively evaluated with the NEI-VFQ, is crucial to understanding a patient’s anxieties, in order to encourage compliance with intravitreal therapy and for continued monitoring.

Previous reports evaluated the impact of treatment outcomes of the better-seeing and worse-seeing eyes on VFQ-25 results. It was shown that an impaired QoL is even evident if only one eye is affected by the underlying disease, with unimpaired vision of the better-seeing eye. Thus, it can be seen that the worse-seeing eye can have a substantial impact on QoL. The impact of CRVO on VRQoL was greater than BRVO eyes, which is consistent with findings from other studies. This may be due to the disease being more chronic in the included CRVO patients, who had almost 25% more injections than the included BRVO patients, and had a significantly longer duration of disease. As such, those with CRVO may have had limited improvement in their subjective functional vision and limited potential for visual recovery.

When the data were stratified by BCVA status of the study eye relative to the fellow eye at baseline, an improvement

| Table 4: Visual function questionnaire scores in patients stratified for vision gain |
|-----------------------------------|------------------|-----------------|-----------------|
| VFQ-25 subscale | Stratified for BCVA | ≥ 15 letters gain | <15 letters gain | $P$ of difference |
| Composite score | 13.3±9.8 | 7.7±6.9 | 0.02 |
| Subscales | | | |
| General health | 20.0±22.9 | 10.0±13.7 | 0.04 |
| General vision | 23.0±22.0 | 13.0±19.2 | 0.01 |
| Ocular pain | 18.8±17.9 | 7.5±11.2 | 0.03 |
| Near activities | 18.3±20.7 | 3.3±12.6 | 0.01 |
| Distance activities | 10.8±11.1 | 3.7±7.3 | 0.03 |
| Social functioning | 3.8±8.4 | 5.0±11.2 | 0.55 |
| Mental health | 14.6±13.9 | 6.7±9.6 | 0.03 |
| Role difficulties | 21.3±22.1 | 15.1±22.4 | 0.11 |
| Dependence | 7.5±9.2 | 6.7±10.9 | 0.32 |
| Driving | 14.2±11.8 | 11.7±23.3 | 0.57 |
| Color vision | 5.0±4.5 | 2.3±3.7 | 0.02 |
| Peripheral vision | 9.2±15.4 | 5.0±11.2 | 0.04 |

VFQ-25: Visual function questionnaire-25, BCVA: Best-corrected visual acuity
in the overall composite score was observed, irrespective of whether the BCVA in the study eye was better or worse than the fellow eye. However, this improvement was of greater magnitude when the fellow eye was the better-seeing eye. Nevertheless, even when the study eye was the better eye, there was a notable improvement in the overall composite score of 7.5 points, indicating that the impact of improved binocular function is captured in the NEI-VFQ-25 measurement.

Following efficacious treatment, resolution of macular edema frequently precedes significant gains in BCVA. In general, the effectiveness of these treatments is assessed centered on a change in the CMT as evaluated by OCT and concurring with BCVA measurements. However, visual acuity only reflects central macular function. In a real-world clinical setting, some patients continue to experience symptoms of metamorphopsia, blurred vision and scotomata even though the macular edema has resolved and visual acuity recovered.

These findings suggest that retinal function at the fovea may have been relatively well maintained in these patients with treatment-resistant macular edema. Patients with RVO are generally younger and have a healthier retinal pigment epithelium and, therefore, better potential for visual recovery. However, the small number of patients, lack of control group, means that further investigation is needed to reinforce the functional results seen here with the recurrence of macular edema after aflibercept switch in RVO patients.

**Conclusion**

Clinical management of eyes demonstrating an insufficient response to anti-VEGF therapy remains a clinical challenge. Switching to aflibercept in these cases has shown good anatomical improvements, but not always associated functional improvements are seen. We present additional data of the advantage of changing therapy to aflibercept in these patients. Switching to aflibercept demonstrated strong functional improvements, including patients own subjective gain in vision-related QoL. Patient’s own subjective appraisal of visual function is a valuable tool as a gross assessment in the effect of aflibercept therapy on a patient’s visual function.

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**Conflicts of interest**

The authors declared that there are no conflicts of interests of this paper.

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