Original Article

Taiwan J Ophthalmol 2021;11: 244-250

Access this article online

Quick Response Code:

Website:
www.e-tjo.org

DOI:
10.4103/tjo.tjo_19_20

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

Kimberly Spooner[1,2,3], Samantha Fraser-Bell[1,3], Thomas Hong[1,2], Andrew Chang[1,2,3]*

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).[1] Vascular endothelial growth factor (VEGF) inhibitors have been shown to be effective in the management of macular edema due to RVO.[2-4] However, not all eyes respond optimally to one agent and may respond better to another anti-VEGF.[5-11] 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.[12]

Results from the SCORE2 report that RVO has a major impact on patient-reported vision-related quality of life (VRQoL),

[1]Sydney Retina, [2]Sydney Institute of Vision Science, [3]University of Sydney, NSW, Australia

***Address for correspondence:**
Dr. Andrew Chang, Sydney Retina, Level 13, Park House 187 Macquarie Street, Sydney NSW, Australia 2000.
E-mail: achang@sydneyretina.com.au

Submission: 11-02-2020
Accepted: 09-04-2020
Published: 03-06-2020

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Spooner K, Fraser-Bell S, Hong T, Chang A. Patient-reported outcomes from a phase IV study of aflibercept in patients with refractory retinal vein occlusions. Taiwan J Ophthalmol 2021;11:244-50.

© 2020 Taiwan J Ophthalmol | Published by Wolters Kluwer - Medknow

despite RVO being predominantly a unilateral disease, 93% of those participants in SCORE2 had bilateral disease.[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.[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.[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.[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 cleaned 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 administered 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 lines) difference in VA.[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.[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 ($P < 0.001$).

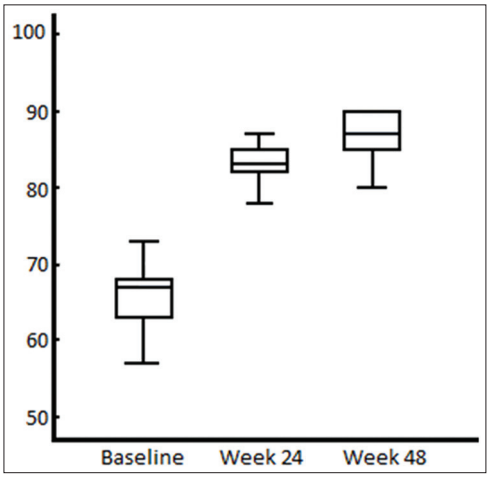

Figure 1: Best-corrected visual acuity results. 48-week follow-up of functional outcome during switch to aflibercept. Error bars represent mean values and 95% confidence intervals

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.[21-23] 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.[24] 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.[25] 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.[26,27] 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.[27-31] 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.[32,33]

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.

Financial support and sponsorship

Bayer Corporation Global provided financial support in the form of an unrestricted grant. The sponsor had no role in the design, conduct or analysis of this research or in the preparation of the manuscript. None of the authors have any proprietary interest in any material or method presented.

Conflicts of interest

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

References

1. Rogers S, Mcintosh RL, Cheung N, Lim L, Wang JJ, Mitchell P, *et al*. The prevalence of retinal vein occlusion: Pooled data from population studies from the United States, Europe, Asia, and Australia. Ophthalmology 2010;117:313-90.
2. Ogura Y, Roider J, Korobelnik JF, Holz FG, Simader C, Schmidt-Erfurth U, *et al*. Intravitreal aflibercept for macular edema secondary to central retinal vein occlusion: 18-month results of the phase 3 galileo study. Am J Ophthalmol 2014;158:1032-8.
3. Brown DM, Campochiaro PA, Singh RP, Li Z, Gray S, Saroj N, *et al*. Ranibizumab for macular edema following central retinal vein occlusion: Six-month primary end point results of a phase III study. Ophthalmology 2010;117:1124-330.
4. Algvere Pv, Epstein D, Von Wendt G, Seregard S, Kvanta A. Intravitreal bevacizumab in central retinal vein occlusion: 18-month results of a prospective clinical trial. Eur J Ophthalmol 2011;21:789-95.
5. Pfau M, Fassnacht-Riederle H, Becker MD, Graf N, Michels S. Clinical outcome after switching therapy from ranibizumab and/or bevacizumab to aflibercept in central retinal vein occlusion. Ophthalmic Res 2015;54:150-6.
6. Eadie JA, Ip MS, Kulkarni AD. Response to aflibercept as secondary therapy in patients with persistent retinal edema due to central retinal vein occlusion initially treated with bevacizumab or ranibizumab. Retina 2014;34:2439-43.
7. Wirth MA, Becker MD, Graf N, Michels S. Aflibercept in branch retinal vein occlusion as second line therapy: Clinical outcome 12 months after changing treatment from bevacizumab/ranibizumab-a pilot study. Int J Retina Vitreous 2016;2:20.
8. Tagami M, Sai R, Fukuda M, Azumi A. Prolongation of injection interval after switching therapy from ranibizumab to aflibercept in Japanese patients with macular edema secondary to branch retinal vein occlusion. Clin Ophthalmol 2017;11:403-8.
9. Lehmann-Clarke L, Dirani A, Mantel I, Ambresin A. The effect of switching ranibizumab to aflibercept in refractory cases of macular edema secondary to ischemic central vein occlusion. Klin Monbl Augenheilkd 2015;232:552-5.
10. Cohen MN, Houston SK, Juhn A, Ho AC, Regillo CD, Vander J, *et al*. Effect of aflibercept on refractory macular edema associated with central retinal vein occlusion. Can J Ophthalmol 2016;51:342-7.
11. Papakostas TD, Lim L, van Zyl T, Miller JB, Modjtahedi BS, Andreoli CM, *et al*. Intravitreal aflibercept for macular oedema secondary to central retinal vein occlusion in patients with prior treatment with bevacizumab or ranibizumab. Eye (London, England) 2016;30:79-84.
12. Spooner K, Hong T, Bahrami B, Chang A. A meta-analysis of patients with treatment-resistant macular oedema secondary to retinal vein occlusions following switching to aflibercept. Acta Ophthalmol 2019;97:15-23.
13. Scott IU, Figueroa MJ, Oden NL, Ip Ms, Blodi BA, Vanveldhuisen PC, *et al*. Score2 report 5: Vision-related function in patients with macular edema secondary to central retinal or hemiretinal vein occlusion. Am J Ophthalmol 2017;184:147-56.
14. Doward LC, Gnanasakthy A, Baker MG. Patient reported outcomes: Looking beyond the label claim. Health Qual Life Outcomes 2010;8:89.
15. Khadka J, Mcalinden C, Pesudovs K. Validation of the national eye institute visual function questionnaire-25 (NEI VFQ-25) in age-related macular degeneration. Invest Ophthalmol Vis Sci 2012;53:1276.

16. Revicki DA, Rentz AM, Harnam N, Thomas VS, Lanzetta P. Reliability and validity of the national eye institute visual function questionnaire-25 in patients with age-related macular degeneration. Invest Ophthalmol Vis Sci 2010;51:712-7.
17. Suñer IJ, Bressler NM, Varma R, Dolan CM, Ward J, Turpcu A. Responsiveness of the national eye institute visual function questionnaire-25 to visual acuity gains in patients with diabetic macular edema: Evidence from the ride and rise trials. Retina 2017;37:1126-33.
18. Suñer IJ, Kokame GT, Yu E, Ward J, Dolan C, Bressler NM. Responsiveness of nei vfq-25 to changes in visual acuity in neovascular amd: Validation studies from two phase 3 clinical trials. Invest Ophthalmol Vis Sci 2009;50:3629-35.
19. Spooner K, Fraser-Bell S, Hong T, Chang A. Prospective study of aflibercept for the treatment of persistent macular oedema secondary to retinal vein occlusions in eyes not responsive to long-term treatment with bevacizumab or ranibizumab. Clin Exp Ophthalmol 2019;48:53-60.
20. Gregori NZ, Feuer W, Rosenfeld PJ. Novel method for analyzing snellen visual acuity measurements. Retina 2010;30:1046-50.
21. Scott IU, Vanveldhuisen PC, Barton F, Oden NL, Ip MS, Blodi BA, *et al*. Patient-reported visual function outcomes after anti-vascular endothelial growth factor therapy for macular edema due to central retinal or hemiretinal vein occlusion: Preplanned secondary analysis of a randomized clinical trial. JAMA Ophthalmol 2019. doi: 10.1001/jamaophthalmol.2019.1519. [Epub ahead of print].
22. Varma R, Bressler NM, Suñer I, Lee P, Dolan CM, Ward J, *et al*. Improved vision-related function after ranibizumab for macular edema after retinal vein occlusion: Results from the bravo and cruise trials. Ophthalmology 2012;119:2108-18.
23. Holz FG, Roider J, Ogura Y, Korobelnik JF, Simader C, Groetzbach G, *et al*. Vegf trap-eye for macular oedema secondary to central retinal vein occlusion: 6-month results of the phase III galileo study. Br J Ophthalmol 2013;97:278-84.
24. Hirneiss C. The impact of a better-seeing eye and a worse-seeing eye on vision-related quality of life. Clin Ophthalmol 2014;8:1703-9.
25. Awdeh RM, Elsing SH, Deramo VA, Stinnett S, Lee PP, Fekrat S. Vision-related quality of life in persons with unilateral branch retinal vein occlusion using the 25-item national eye institute visual function questionnaire. Br J Ophthalmol 2010;94:319-23.
26. Paulose R, Chhablani J, Dedhia CJ, Stewart MW, Mansour AM. Intravitreal ziv-aflibercept for macular edema following retinal vein occlusion. Clin Ophthalmol 2016;10:1853-8.
27. Campochiaro PA, Sophie R, Pearlman J, Brown DM, Boyer DS, Heier JS, *et al*. Long-term outcomes in patients with retinal vein occlusion treated with ranibizumab: The retain study. ophthalmology 2014;121:209-19.
28. Campochiaro PA, Brown DM, Awh CC, Lee SY, Gray S, Saroj N, *et al*. Sustained benefits from ranibizumab for macular edema following central retinal vein occlusion: Twelve-month outcomes of a phase iii study. ophthalmology 2011;118:2041-9.
29. Brown DM, Campochiaro PA, Bhisitkul RB, Ho AC, Gray S, Saroj N, *et al*. Sustained benefits from ranibizumab for macular edema following branch retinal vein occlusion: 12-month outcomes of a phase iii study. Ophthalmology 2011;118:1594-602.
30. Heier JS, Campochiaro PA, Yau L, Li Z, Saroj N, Rubio RG, *et al*. Ranibizumab for macular edema due to retinal vein occlusions: long-term follow-up in the horizon trial. Ophthalmology 2012;119:802-9.
31. Clark WL, Boyer DS, Heier JS, Brown DM, Haller JA, Vitti R, *et al*. Intravitreal aflibercept for macular edema following branch retinal vein occlusion: 52-week results of the vibrant study. Ophthalmology 2016;123:330-6.
32. Elliott DB, Hurst MA, Weatherill J. Comparing clinical tests of visual function in cataract with the patient's perceived visual disability. Eye (Lond) 1990;4(Pt 5):712-7.
33. Stifter E, Sacu S, Thaler A, Weghaupt H. Contrast acuity in cataracts of different morphology and association to self-reported visual function. Invest Ophthalmol Vis Sci 2006;47:5412-22.