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Optical-coherence tomography angiography and ultrawide-field angiography findings in eyes with refractory macular edema secondary to retinal vein occlusion switched to aflibercept: A subanalysis from a 48-week prospective study

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Abstract:

PURPOSE: To evaluate anatomical changes on ultra-wide-field fluorescein-angiography and optical coherence angiography (OCT-A) among a cohort with treatment-resistant macular edema secondary to retinal vein occlusions (RVO) switched to aflibercept.

MATERIALS AND METHODS: Patients with persistent macular edema despite previous bevacizumab and/or ranibizumab were switched to aflibercept in a 48-week prospective trial. Ultra-wide-field fluorescein angiography (UWFFA) and OCT-A were performed at baseline, week-24 and week-48. The ischemic index was calculated from UWFFA and the areas of vascular perfusion. The foveal avascular zone (FAZ) were quantitatively evaluated on OCT-A.

RESULTS: Eighteen patients (mean age, 70.3±8.6 years) were recruited. Mean central macular thickness (CMT) was significantly reduced at 48-weeks compared to baseline (-87.6±48.8 µm, $P < 0.001$ and -191.0±128.3µm, $P < 0.001$ among BRVO and CRVO eyes, respectively). The mean baseline ischemic index as measured on Optos wide-field angiography was 10.9%±8.3 and decreased to 5.7%±4.2 ($P = 0.028$), at week 48. The mean FAZ areas of the SCP and DCP reduced by -0.06 ± 0.12 mm 2 and -0.17± 0.45 mm 2 , respectively. FAZ area on OCT-A was stable in eyes with stable or improved vision but increased in size in eyes with baseline macular ischemia and those with lower gains in BCVA at week 48 (R 2 =0.719, $P = 0.05$ and R 2 =0.516, $P = 0.01$).

CONCLUSION: There was a reduction in macular edema measured on OCT at 48-weeks in eyes switched to aflibercept with chronic macular edema due to retinal vein occlusion. There was also a reduction in retinal ischemia as measured using UWFFA.

Keywords:

Anti-vascular endothelial growth factor, recalcitrant, aflibercept, macular edema, retinal vein occlusion

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Introduction

Retinal vein occlusion (RVO) is the second-most prevalent type of retinovascular disease behind diabetic retinopathy.[1] RVO affects venous outflow, leading to the areas of retinal nonperfusion and macular edema, which, in turn, causes significant visual impairment.[2-5] Distinguishing areas of nonperfusion are

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useful to evaluate the prognosis and progression of the disease.

The treatment of macular edema due to RVO with vascular endothelial growth factors (VEGFs) inhibitors has dominated management strategies in the past decade.[6] There is a subset of patients who do not respond completely to one antiangiogenic therapy and may respond better to another.[7,8]

Optical-coherence tomography (OCT) and fundus fluorescein angiography (FA) are the standard investigations for evaluating macular edema and retinal nonperfusion in RVO. Recently, ultrawide-field angiography using the optos-scanning laser ophthalmoscope (Optos PLC, Dunfermline, UK) has enabled imaging of the far peripheral retina, and standard OCT-angiography (OCT-A) allows the noninvasive assessment of the superficial and deep retinal layers of the macula.

We have previously reported the results of best-corrected visual acuity (BCVA) and central macular thickness (CMT) changes over 48 weeks postswitch. The purpose of this subanalysis was to quantitatively assess the anatomical alteration during the switch of anti-VEGF switch to aflibercept (Eylea: Regeneron, Tarrytown, NY, USA) over 48 weeks in a cohort of treatment-resistant macular edema secondary to RVO.

Methods

Study design

This prospective, open-label, single-arm, clinical study recruited patients from a tertiary referral center in Sydney, Australia. The present study was registered on the Australian and New Zealand Clinical Trials Registry (ACTRN 12617001487303). This study obtained ethical approval from the local Institutional Review Board (Bellberry Limited, approval number: 2017-11-837), with all patients providing written informed consent and study adhering to the tenets of the declaration of Helsinki.

The study protocol, inclusion and exclusion criteria have previously been published.[9] Briefly, the participants were enrolled with persistent macular edema secondary to RVO despite at least 4 prior intravitreal bevacizumab (Avastin: Genentech, San Francisco, CA, USA) and/or ranibizumab (Lucentis Genentech, San Francisco, CA, USA) in the 6 months before baseline, having a BCVA of between 34 and 73 early treatment of diabetic retinopathy letter score and a CMT of >320 μm.

Follow-up visits and treatment protocol

All patients had ultrawide-field fluorescein angiography (UWFFA) before aflibercept initiation, for the analysis of perfusion status, and at week 24 and week 48 for the analysis of change in perfusion. At each follow-up visit, all patients underwent a complete slit-lamp examination, BCVA testing, fundus examination and OCT, and OCT-A by Heidelberg Spectralis OCT (Heidelberg Engineering, Heidelberg Germany).

All patients were given three initial loading doses of aflibercept 2 mg every 4 weeks, and then, every 8 weeks until week 48. The treatment protocol was standardized across all patients. Subsequent to topical anesthesia with oxybuprocaine, the eyelids and conjunctiva were prepared with povidone-iodine solution. A 0.05 mL dose of aflibercept was delivered into the vitreous cavity through a 30 G needle inserted though the pars plana 3.5 mm posterior to the limbus.

Optical-coherence tomography analysis

Baseline and 4 weekly follow-up scans were obtained to measure CMT, which was defined as the distance from the inner-limiting membrane to Bruch's membrane in the central 1-mm centered on the fovea. Segmentation lines were manually modified in the instances of software error. If the fovea could not be accurately detected, the scan was omitted from the analysis. Follow-up scans were obtained by the use of the inbuilt progression scanning tool. All imaging was independently assessed by two-image graders, and a third-grader arbitrated in the event of incongruity.

The inner segment/outer segment (IS/OS) line was evaluated considering its continuity in the central fovea, any disruption in the line, which was defined as the loss of back-reflection line. Macular volume (MV) measurements were recorded at the initial presentation and each 4 weekly follow-up visit thereafter. Two graders reviewed all enhanced-depth imaging-OCT scans together and any disagreements on measuring end points were resolved by third interpreter who were all blinded to the patient clinical data. In such cases, the third reviewer's measurement was used for the data analysis.

Optical coherence tomography-angiography

Patients were evaluated using the Spectralis OCT-A (Spectralis OCT2; Heidelberg Engineering, Heidelberg, Germany). A 15° × 10° area volume scan area was obtained. The OCT-A software (Heyex Software version 1.9.201.0; Heidelberg Engineering, Heidelberg, Germany) affords an automated segmentation algorithm for the retinal and choroidal layers. All the OCT-A scans were vigilantly assessed to identify the possible segmentation errors. In which case, an expert grader executed a manual adjustment of the segmentation lines. Microvascular measurements such as area of the foveal avascular zone (FAZ) in the

Table 1: Baseline Characteristics

Characteristic	BRVO (*n*=14)	CRVO (*n*=4)	All (*n*=18)
Age (years), mean±SD	71.6±9.2	66.0±5.5	70.3±8.6
Male, *n* (%)	4 (28.6)	3 (75)	7 (39)
Duration of anti-VEGF treatment (months), mean±SD	67.5±44.2	102.7±31.9	75.6±43.3
Total number of anti-VEGF injections, mean±SD	38.8±18.0	50.3±16.9	40.0±17.8
Ischaemia, *n* (%)	4 (28.6)	2 (50)	6 (33.3)
BCVA, ETDRS Letters	65.3±3.8	64.3±6.4	65.1±4.3
CMT, μm	367.9±49.2	482.0±229.7	393.2±116.4
Subfoveal Choroidal Thickness, μm	219.1±50.6	232.5±65.2	222.1±52.4
Macular Volume	9.0±0.6	9.9±2.4	9.2±1.2
FAZ area, mm2			
Superficial	0.5±0.2	0.7±0.1	0.6±0.2
Deep	0.7±0.3	1.4±0.7	0.8±0.5
Ischaemic Index, %	7.9±5.9	16.1±10.3	10.9±8.3
Prior laser therapy, *n* (%)	4 (28.6)	1 (25.0)	5 (27.8)

superior and deep capillary plexuses were measured by manually delineating the area [Figure 1]. Disruptions of the FAZ, such as capillary dropout and anastomotic arcade disruptions, were noted during the grading of the FAZ.[10] In cases of sectoral disruptions, these were included in the FAZ delineation.

Ultrawide-field fluorescein angiography

UWFFA was performed using the Optos 200Tx device using a standardized protocol. Study eyes were dilated with tropicamide 1% and phenylephrine 2.5%, and then, ultrawide-field (UWF) pseudocolor images were obtained centered on the fovea of the study eye. Subsequent to intravenous administration of 5 mL of 10% sodium fluorescein dye, images were captured throughout the early, middle, and late phases of the angiography.

Analyses were performed using the prior published methods.[11,12] A single-central image obtained from the late arteriovenous or early midphase was chosen for manual demarcation of areas of nonperfusion by an experienced grader. The image chosen was based on the largest field of view and the greatest image clarity.

The definition of nonperfusion was modified from the Standard Care versus Corticosteroid for RVO study.[12] Nonperfusion areas were distinguished as the areas of capillary loss differentiated by a dark zone without any flow signal, with the loss of speckled hyperreflectance consistency, surrounded by large retinal vessels and not congruent with artifacts. Using the review software (V2 Vantage, Optos, Dunfermline, UK), the areas of nonperfusion were manually encircled for the calculation of area size. The ischemic index (ISI) was calculated by dividing the area of nonperfusion by the total gradable area [Figure 2]. Ischemic type of central retinal vein occlusion (CRVO) was defined as retinal nonperfusion area of ≥10-disc diameters, which could involve the periphery and/or macular. Macular ischemia was defined as a FAZ of ≥1000 μm and broken capillary rings at the borders of the FAZ with distinct areas of capillary nonperfusion.[13,14]

The results from two independent masked graders were compared. If the difference in quantitative results between graders was <20%, the individual grader results were averaged. If the difference was ≥20%, a third examiner adjudicated a consensus among graders.

Statistical analyses

Statistical analysis was executed using the SPSS software (version 24.0, SPSS Inc., Chicago, IL, USA). Shapiro–Wilk normality test was used to examine the distribution normality of continuous variables. Descriptive data were described as means and standard deviation. Paired *t*-test was used to evaluate the variables between baseline and follow-up visits. Interobserver concordance was calculated using the interclass correlation coefficient. To evaluate the association with BCVA and other parameters, the Pearson correlation coefficient was used.

Univariate linear regression analysis and stepwise multivariate linear regression analyses were executed to evaluate the influence of each baseline characteristic, such as the superficial and deep FAZ, area of nonperfusion, CMT, MV, and choroidal thickness. $P < 0.05$ was deemed statistically significant. Mean ± standard deviation was used to report the findings.

Results

Study patients

The baseline characteristics of the patients are summarized in Table 1. Eighteen eyes of 18 patients (7 men and 11 women) with RVO were examined in this study. The mean age was 70 years. Four patients (22%) had CRVO, and the remaining 14 patients (78%) had BRVO.

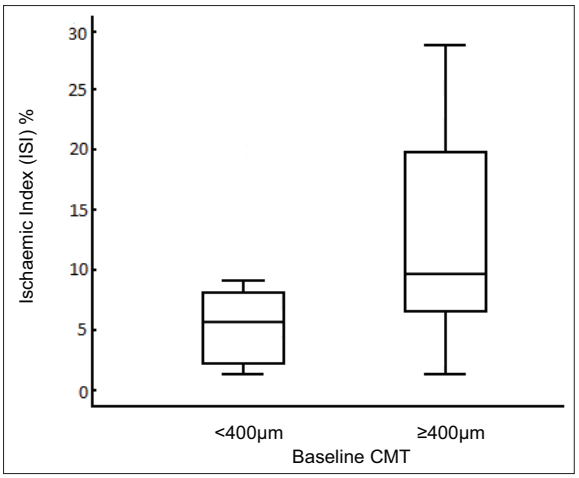

Figure 1: Comparison of ischemic index with baseline central macular thickness

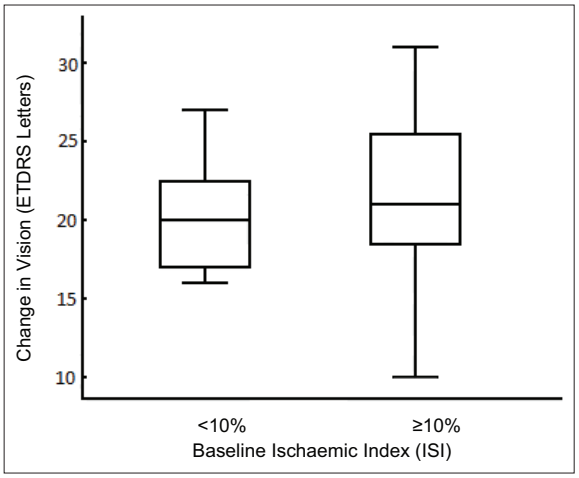

Figure 2: Change in BCVA by baseline ischaemic index

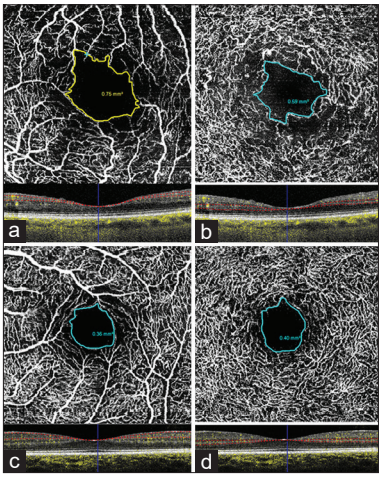

Figure 3: (a-d) Representative images of the FAZ area and their corresponding segmentation in two patients. In the eye of a 70-year old man with CRVO with a BCVA of 68 ETDRS letters (Snellen equivalent 20/40), the FAZ area was 0.75 mm2 in the superficial capillary plexus layer (a) and 0.59 mm2 in the deep capillary plexus layer (b). The corresponding segmentation lines are shown below. In the eye of a healthy 68-year-old woman with a BCVA of 84 ETDRS letters (Snellen equivalent 20/20), the FAZ area was 0.36 mm2 in the superficial capillary plexus layer (c) and 0.40 mm2 in the deep capillary plexus layer (d). The corresponding segmentation lines are shown below

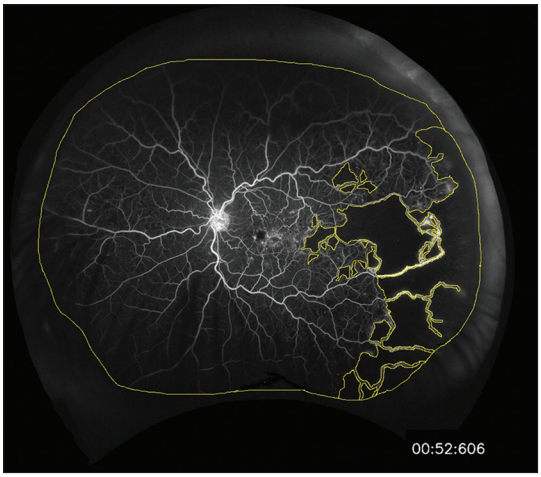

Figure 4: An example of our method for calculating the ischemic index. The total fundus area was encircled, and the area of nonperfusion was delineated. Ischemic index was the ratio of the area of nonperfusion over the total fundus area

Optical-coherence tomography angiography

Macular ischemia was present in 9 eyes (50%) on OCT-A at baseline. The IS/OS line was incomplete or absent in 56% of these eyes but intact in all eyes without macular ischemia. Final BCVA was less in eyes with macular ischemia than those eyes without macular ischemia: 73.1 and 86.0 letters (P = 0.04), respectively. There was no significant difference in the reduction of macular edema in eyes with macular ischemia versus those without macular ischemia, P = 0.15.

It was easier to identify nonperfused areas of the macula using OCT-A than UWFFA. Our OCT-A device was not able to detect nonperfused areas in the peripheral retina. On OCT-A, the mean change in FAZ area at 48 weeks was − 0.06 ± 0.12 mm^2 (range: –0.35–0.14 mm^2) in the superficial capillary plexus (SCP) and − 0.17 ± 0.45 mm^2 (range: –0.74–0.39 mm^2) in the deep capillary plexus (DCP) [Figure 3]. A univariate linear regression model similarly demonstrated that FAZ changes in the SCP and DCP were correlated with baseline macular ischemia on OCT-A and final BCVA (R^2 = 0.719, P = 0.05 and R^2 = 0.516, P = 0.01). Hence, eyes with greater macular ischemia and lower gain in BCVA demonstrated a significant increase in the FAZ area over the 48-week follow-up period. Intergrader agreement for measuring FAZ area was excellent, with intraclass correlation coefficient of 0.94.

A significant reduction in CMT occurred at all times points compared to baseline (P < 0.001). At week 48, reduction in mean CMT in BRVO eyes was 87.6 ± 48.8 µm, P < 0.001 and 191.0 ± 128.3 µm, P < 0.001 in CRVO eyes.

Based on a multiple regression analysis, better baseline BCVA and macular ischemia were significantly associated

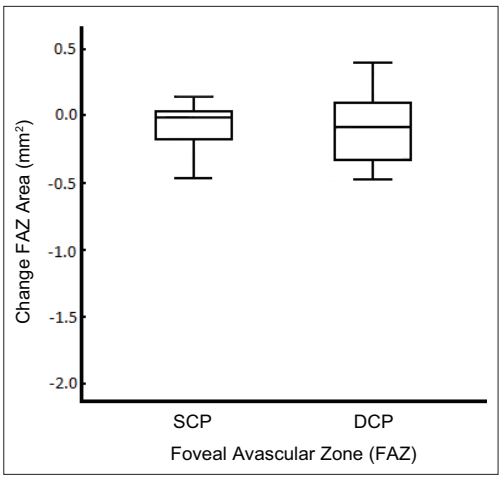

Figure 5: Change in FAZ area at the level if the SCP and DCP

with a greater reduction in CMT at 48 weeks ($P < 0.05$ and $P = 0.03$ respectively) and CRVO but not BRVO ($P = 0.34$).

Ultrawide-field fluorescein angiography

At baseline examination, UWFFA revealed an ischemic CRVO in two eyes. Ischemic BRVO was present in four eyes (29%). During the study, no nonischemic CRVO eyes converted to ischemic CRVO eyes.

The mean retinal ISI at the time of switch to aflibercept was 10.9% ± 8.3%. Among all patients, the ISI was significantly larger in eyes with a CMT of >400 μm, compared to those with a lower CMT (15.0% ± 9.2% vs. 4.8.3% ± 6.9%, $P = 0.04$) [Figure 4]. Those with a higher ISI were shown to have undergone a greater number of previous injections than those with a lower ISI (42.3 ± 17.2 injections vs. 31.0 ± 15.6, $P = 0.04$).

The mean ISI decreased from baseline to week 48 (5.7% ± 4.2%, $P = 0.028$). After 48 weeks of aflibercept therapy, the reduction in CMT thickness was greater for those with a greater ISI, compared to those with smaller areas of ischemia (−191.8 ± 191.4 vs. −79.8 ± 15.9, $P = 0.02$). The improvement in ISI was most evident in the perimacular area and was evident at the week 24 visit and had little further change at week 48.

Patients with a higher ISI at baseline had a nonsignificant trend for worse BCVA in the presence of macular edema compared with those with a smaller ISI (63.6 ± 5.6 vs. 68.9 ± 2.5 letters, $P = 0.23$). These patients also experienced a larger gain in BCVA with treatment, although this was not statistically significant (+19.1 ± 3.5 vs. +16.6 ± 1.2 letters. $P = 0.23$) [Figure 5]. The intraclass correlation coefficient for ISI measurements between the two observers was 0.996.

Discussion

Macular edema is the foremost complication of RVO, leading to visual impairment. Hemodynamic alterations arising early in the course of RVO diminishing retinal perfusion and leading to increased release of VEGF. This upsurge in the level of VEGF is a key mitigator in the evolution of retinal edema.

Several studies have shown that initiating anti-VEGF treatment, thus blocking VEGF induces a significant gain in the vision and markedly decreases macular edema[15-18] which was confirmed by the present study.

The present subanalysis of a prospective 48-week study aimed to assess the morphological changes in nonresponsive eyes with RVO switched to aflibercept. We previously showed CMT reductions of 87 and 191 μm in BRVO and CRVO eyes, respectively, over 48 weeks from baseline.[9]

OCT-A is a novel modality which can be used to assess macular perfusion. OCT-A permits segmental assessment of the capillary complex that are coherent with histologic findings. OCT-A has been demonstrated to image the deep capillary network better than FA.[19]

Previous studies have reported that the FAZ is modified in RVO and correlated with visual acuity.[20] In the present study, we also report that visual acuity was correlated with vascular densities in the SCP and DCP. It is logical that FAZ size, which quantitatively measures the degree of macular ischemia, would be correlated with visual function.[21,22] The FAZ diameter measured on OCT-A of the DCP was significantly greater than the FAZ diameter at the level of the SCP supporting previous studies.[20,23]

Raised levels of VEGF and cytokines have been quantified in the vitreous of RVO eyes, which can be neutralized with the use of antiangiogenic therapies, and thus, an improvement in macular edema is seen.[24-27] We found greater improvements in the ischemic index from baseline to week 48 in eyes with BRVO compared to CRVO. This may be due to the greater VEGF activity exhibited in CRVO, although we had small numbers so this may be due to chance.[27,28] UWFFA was valuable in quantifying the amount of peripheral nonperfusion. We found no postswitch increase in nonperfusion, presumably due to the antiangiogenic effect of aflibercept.

There are some notable limitations of the present study. The present study included patients with varying previous treatments and RVO durations. In addition, confounding variables included previous laser therapy that may have altered the effect of anti-VEGF therapy. Moreover, the quantification of capillary nonperfusion and FAZ measurements is a subjective measure, as presently, there is no analytical software available. Though, notably our quantification process showed a high level of agreement between the graders.

Advancing technology like UWF-OCTA will offer more comprehensive imaging of vascular networks as assessed by 50° FA and demonstrates the capacity to detect vessel density and nonperfusion maps.[29,30]

We found significant improvements in OCT-A and UWFFFA parameters in eyes switched to aflibercept, despite these eyes being extensively treated previously. The evaluation of microvascular changes in RVO patients over time is important in following up patients with retinovascular disease. Further studies of larger population and control group are needed to provide support for these particular results.

Ethical approval

All procedures performed were in accordance with the ethical standards of the Institutional Research Committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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

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All other authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest, or nonfinancial interest in the subject matter or materials discussed in this manuscript.

Conflicts of interest

The authors declare that there are no conflicts of interest of this paper.

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