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Effects of Switching to Aflibercept in Treatment Resistant Macular Edema Secondary to Retinal Vein Occlusion

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Purpose: The aim of this study was to examine 12-month outcomes of eyes switched from intravitreal ranibizumab or bevacizumab to aflibercept for cystoid macular edema due to retinal vein occlusion (RVO).

Design: Retrospective, observation, case series.

Methods: A retrospective study was performed assessing eyes with RVO switched to aflibercept for at least 12 months. To be included in the study, eyes had to have macular edema despite treatment for at least 6 months with bevacizumab and/or ranibizumab before the switch, central foveal thickness (CFT) $\geq$300 μm at time of switch, and visual acuity (VA) $\leq$60 early treatment of diabetic retinopathy score (ETDRS) letters (20/40 Snellen equivalent). Outcome measures included change in VA (in ETDRS letters), CFT, and interval between intravitreal injections.

Results: 27 eyes of 27 patients were included in the analysis: 13 with branch RVO, and 14 with central RVO. Mean VA before switch was 54.2 ± 23.7 letters (20/80 Snellen equivalent) and mean CFT was 460.4 ± 178.2 μm. Mean number of previous anti-vascular endothelial growth factor (VEGF) injections was 29.5 ± 19.2. At 12 months, mean VA improved by 8.7 ± 13.2 letters ($P < 0.01$) and mean CFT decreased by 180.9 ± 207.7 μm compared with baseline ($P < 0.01$). Mean injection interval increased by 1.6 ± 2.0 weeks to 6.9 ± 1.2 weeks, but this was not statistically significant ($P = 0.18$).

Conclusions: In our small retrospective study, eyes switched to intravitreal aflibercept for persistent cystoid macular edema (CME) due to RVO improved vision and macular thickness; however, larger prospective studies are required to validate our findings.

Key Words: aflibercept, anti-VEGF, retinal vein occlusion, switching

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Retinal vein occlusion (RVO) is the second most prevalent retinal vascular disease, after diabetic retinopathy,[1,2] with a prevalence of 5.20 per 1000.[3] Broadly speaking, there are 2 subtypes depending upon the anatomical location of obstruction within the retinal venous system: central retinal vein occlusion (CRVO) encompassing the entire central retinal vein, and branch retinal vein occlusions (BRVO) where 1 branch is involved.[2,4] Macular edema is frequently associated with RVO, which is the predominant cause of vision loss.[5]

Numerous studies have demonstrated the role of vascular endothelial growth factor (VEGF) in the development and persistence of macular edema.[6,7] Vascular endothelial-derived growth factor inhibitors (anti-VEGF) have markedly improved anatomical and functional outcomes in the setting of RVO.[8,9] However, there is a subset of patients with persistent macular edema despite regular anti-VEGF treatment.[10,11]

When an insufficient response is observed after treatment with one anti-VEGF therapy, switching to another therapy may be considered. This strategy is based on several reports,[12–14] suggesting anatomic and visual outcome benefits after switching between anti-VEGF therapies in cases of unfavorable response to the initial treatment.

Aflibercept is a recombinant fusion protein consisting of the key human VEGF receptor extracellular domains from receptors 1 and 2 (VEGFR1 and VEGFR2) fused to the Fc domain of human IgG1. Aflibercept is hypothesized to be superior to both bevacizumab and ranibizumab owing to its higher binding affinity for VEGF-A and additionally to placental growth factors 1 and 2 (PlGF1 and PlGF2) and VEGF-B, and by having a longer half-life in the vitreous compared with ranibizumab.[15]

To further assess the efficacy of aflibercept as a further therapy option in RVO, we report clinical outcomes in RVO patients with lack or incomplete response to initial bevacizumab and/or ranibizumab treatment.

METHODS

Protocol/Inclusion and Exclusion Criteria

This is a retrospective clinical study conducted at a tertiary referral center, Sydney Retina. Ethics was approved by the

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University of Sydney local ethics committee and adhered to the tenets of the declaration of Helsinki. All patients provided informed consent. A treatment database of all patients attending the clinic between January 2015 and January 2017 requiring ongoing anti-VEGF therapy was reviewed. Patients who were switched to aflibercept from bevacizumab and/or ranibizumab were identified.

Inclusion criteria included eyes with a diagnosis of RVO, with recurrent or persistent edema on spectral domain optical coherence tomography (SD-OCT). Eyes must have received a minimum of 4 ranibizumab and/or bevacizumab injections in the preceding 6 months before switching to aflibercept. Eyes were excluded due to significant concomitant ocular pathology such as age-related macular degeneration, diabetic retinopathy, history of vitrectomy or intravitreal corticosteroids, and if <12 months of follow-up post switch was available.

On switching to aflibercept, all included eyes were treated with 3 monthly injections followed by a pro re nata regimen. Data collected on follow-up visits included corrected visual acuity (VA), intraocular pressure (IOP), and central foveal thickness (CFT) as measured with SD-OCT (Spectralis; Heidelberg Engineering, Heidelberg, Germany). Progression scans utilizing eye and landmark tracking were undertaken to ensure accurate measurement of the same anatomical location.

Endpoints of the Study

The primary outcomes were the mean change in VA, CFT, and change in injection interval at 12 months' post switch to aflibercept.

VA was performed using a Snellen chart with the patient's regular correction, where available, and complemented with pinhole correction. Values were converted to ETDRS letter score for statistical analysis.

CFT was measured using the macular volume scans obtained on Spectralis OCT. A thickness map centered on the foveal centre using the ETDRS grid. CFT was defined as the distance between the inner limiting membrane and Bruch's membrane in the central 1-mm diameter area. Foveal thickness calculations were implemented using the manufacturer's built-in software (Spectralis Acquisition and Viewing Modules, version 6.0; Heidelberg Engineering). Segmentation lines were manually adjusted in the case of software error. Follow-up scans were obtained by use of the progression scanning tool.

Statistical Analyses

Statistical analysis was performed using SPSS software (version 24.0, IBM, Armonk, NY). Descriptive data were presented as means and standard deviation. Paired *t* test was used to compare outcome variables between baseline and follow up visits. Interobserver agreement was assessed using the interclass correlation coefficient.

Linear regression was used to assess the effects of age, number of injections, baseline BCVA on both BCVA, and CFT. A 95% confidence interval with 5% level of significance was adopted; thus, P values of <0.05 were considered to be statistically significant. Missing data were imputed using the last observation carried forward method. Treatment exposure and follow-up frequency were only analyzed in patients concluding the entire 12 months of the study.

RESULTS

Study Patients

A total of 27 eyes of 27 patients with macular edema secondary to RVO were identified. 13 eyes (n = 13) were classified as BRVO and 14 eyes as CRVO. Baseline characteristics of the 27 patients are summarized in Table 1. 11 (n = 11) eyes were previously treated with bevacizumab alone, 1 patient was treated with ranibizumab alone, and 15 eyes had previous treatment with both bevacizumab and ranibizumab. Mean patient age was 73.2 ± 11.4 years. Before switching, patients had received a mean of 29.5 ± 19.2 injections over a mean period of 43.3 ± 33.3 months. 6 (43%) CRVO eyes were classified as ischemic CRVO.

A history of systemic hypertension was present in 21 (77.8%) of the patients, diabetes mellitus in 5 (18.5%), and hyperlipidaemia in 17 (62.3%). Baseline was defined as the first visit aflibercept was administered.

Visual and Anatomical Outcomes

Vision improved during the study from a mean of 54.2 ± 23.7 letters at baseline to 62.8 ± 19.4 letters at month 12 ($P < 0.01$). At 12 months, VA of 18 (67%) eyes improved by ≥5 letters and in 6 (22%) eyes VA improved by ≥15 letters. 3 (11%) eyes lost ≥1 letter. 3 (11%) eyes lost between 5 and 10 ETDRS letters, and 6 (22%) were stable compared with baseline.

Analysis by RVO subtype demonstrated a significant difference in VA at all time points. At baseline switch to aflibercept, those with CRVO had lost 6.1 letters from initiation of anti-VEGF treatment (Fig. 1). Those in the BRVO group had gained 10.4 letters since starting anti-VEGF therapy; however, in the 12 months immediately before switching (baseline), BRVO

TABLE 1. Baseline and Clinical Characteristics of Included Patients

	BRVO (n = 13)	CRVO (n = 14)	ALL (n = 27)	*P* Value
Age, y (SD)	71.5 ± 12.3	75.1 ± 10.7	73.2 ± 11.4	0.62
Male, n (%)	7 (54%)	8 (57%)	15 (55%)	
Baseline VA, ETDRS letters (SD)	72.1 ± 7.6	37.6 ± 21.3	54.2 ± 23.7	0.05
Baseline CFT, μm (SD)	359.5 ± 56.7	554.1 ± 202.2	460.4 ± 178.2	0.05
Pre-treatment CFT, μm (SD)	471.7 ± 120.3	667.6 ± 291.4	574.5 ± 251.7	0.02
Pre-switch duration of treatment, months (SD)	37.9 ± 23.9	49.0 ± 40.7	43.3 ± 33.3	0.43
Pre-switch mean injections	34.5 ± 15.2	36.0 ± 23.8	29.5 ± 19.2	0.75
Pre-switch injection interval, weeks (SD)	4.8 ± 3.0	5.9 ± 4.9	5.2 ± 5.3	0.01
Post-switch Injection Interval, weeks (SD)	7.0 ± 2.4	6.8 ± 1.8	6.9 ± 2.0	0.01
Post-switch mean injections	7.8 ± 2.1	8.1 ± 1.5	8.1 ± 1.9	0.01
Post-switch CFT, μm (SD)	297.3 ± 49.7	262.9 ± 62.4	279.5 ± 58.2	0.02

BRVO indicates branch retinal vein occlusions; CFT, central foveal thickness; CRVO, central retinal vein occlusion; VA, visual acuity.

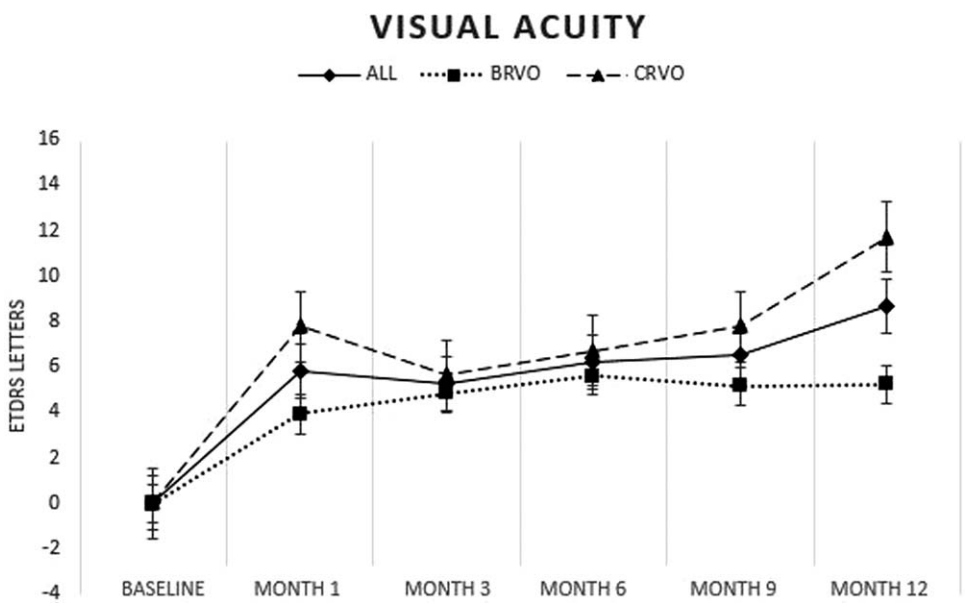

FIGURE 1. Mean change in VA in ETDRS letters from baseline to 12 months' post-switch to aflibercept. VA indicates visual acuity; ETDRS, early treatment of diabetic retinopathy score; BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion.

patients had lost 3.1 letters, and had persisting macular edema despite monthly intravitreal injections. Baseline VA in the BRVO group was 72.1 ± 7.6 letters, and 37.6 ± 21.3 letters in the CRVO group ($P = 0.018$). Eyes with BRVO gained 5.2 ± 5.7 letters at month 12 on average, compared with eyes with CRVO, which gained 11.7 ± 17.3 letters ($P = 0.006$).

Pre-treatment VA and at time of switch was not significantly different among CRVO perfusion status groups (ischemic vs non-ischemic, $P = 0.567$ and 0.968, respectively). Vision in eyes with ischemic CRVO improved by 14.8 ± 18.9 letters at month 12, compared with 9.4 ± 16.8 letters in eyes with nonischemic CRVO ($P = 0.852$) (Fig. 2).

There was a reduction in CFT from an average of 460.4 ± 178.2 μm at baseline to 279.5 ± 58.2 μm at month 12 ($P < 0.01$). This significant reduction in CFT was already apparent at 1 month [with mean reduction of 146.1 ± 171.5 μm ($P < 0.01$)] (Fig. 3).

Eyes with CRVO had a greater anatomical reduction in CFT (Table 1). There was no difference in CFT reduction among perfusion status in CRVO subgroup (Fig. 4). 16 (59%) eyes had complete resolution of macular edema at month 12. 2 (2%) eyes showed chronic thinning of the neuroretina, and 11 eyes (46%) had attenuation of the ellipsoid zone. (Fig. 5)

A multiple regression analysis was performed in which VA at 12 months was regarded as a dependent variable and the impact of the subsequent risk factors as resultant independent variables: extent of the RVO, hypertension, hyperlipidemia, and diabetes mellitus. A longer duration of RVO was associated with worse vision at 12 months after the switch ($P < 0.001$). This was repeated for analysis of CFT at 12 months, which indicated that those with RVO and hypertension have substantially thicker CFT ($P < 0.001$) than those without hypertension.

Treatment Intensity or Injection Frequency

Before baseline, patients had received a mean of 30 injections over a mean period of >3 years. The mean injection interval was 5 weeks preceding baseline. After switching to aflibercept, eyes had undergone a mean of 8.1 intravitreal injections over the 12-month study period, with a mean injection interval of 7 weeks, increasing the injection intervals by 1.6 ± 2.1 weeks ($P = 0.18$) (Table 1).

A significant correlation was found between CFT at time of switching and the total number of aflibercept injections required for resolution of macular edema ($R^2 = 0.801$). Furthermore, there was a substantial association between the duration of disease and a worse VA at time of switch ($R^2 = 0.863$).

Safety Outcomes

No eyes in the study developed significant ocular or systemic complications such as endophthalmitis, uveitis, prolonged elevation of IOP, or vascular events.

DISCUSSION

This study has demonstrated that switching to intravitreal aflibercept after suboptimal response to bevacizumab and/or ranibizumab may lead to both anatomical and functional improvement in eyes with macular edema due to RVO. On average, there was an 8.7-letter improvement in vision with 70% of patients gaining at least 5 letters (one line). There was a corresponding reduction in CFT on average of 180.9 microns.

Although bevacizumab, ranibizumab, and aflibercept have shown similar efficacy in RVO,[16–18] differences among these compounds may affect treatment outcome in this subgroup of refractory patients. The Study of Comparative Treatments for Retinal Vein Occlusion 2 studies demonstrated that aflibercept administered every 4 weeks was noninferior to monthly bevacizumab in maintaining vision in patients with treatment-naive RVO over 6 months.[10,19] However, this study did not specifically examine eyes with a poor response to bevacizumab and/or ranibizumab.

Numerous studies have investigated outcomes of aflibercept in cases of persistent macular edema despite previous bevacizumab or ranibizumab treatment in RVO,[12–14,20–24] which we recently summarized by meta-analysis.[25] Of the 8 articles identified, 7 were retrospective and 1 was prospective. A majority of the

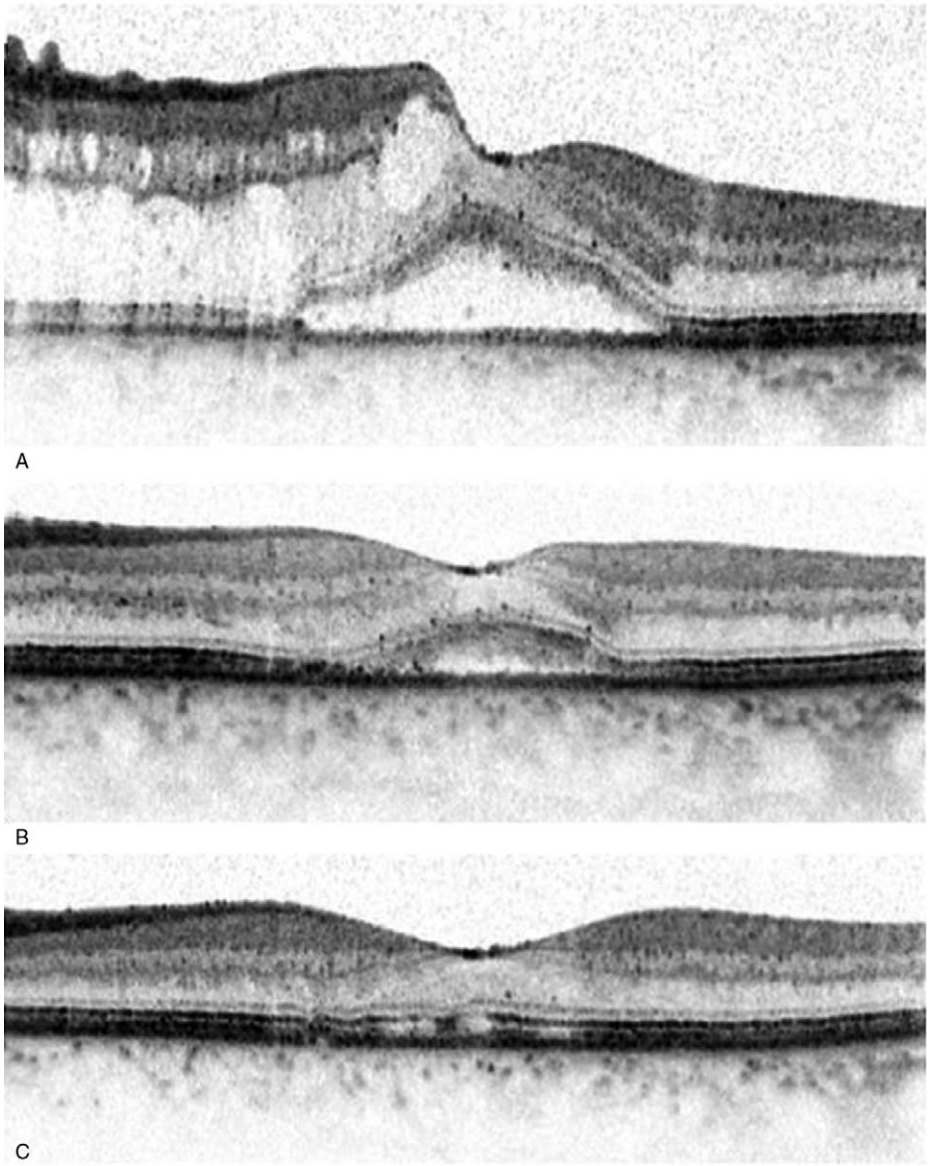

FIGURE 2. Example of treatment resistant patient at baseline (A), month 1 (B), and month 12 (C).

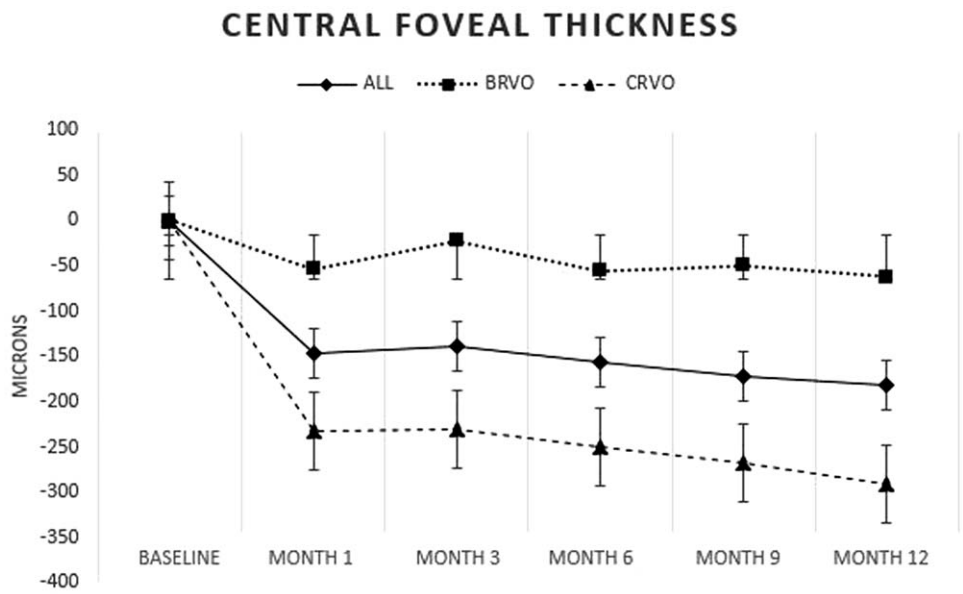

FIGURE 3. Mean change in CFT in microns from baseline to 12 months' post-switch to aflibercept. CFT indicates central foveal thickness; BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion.

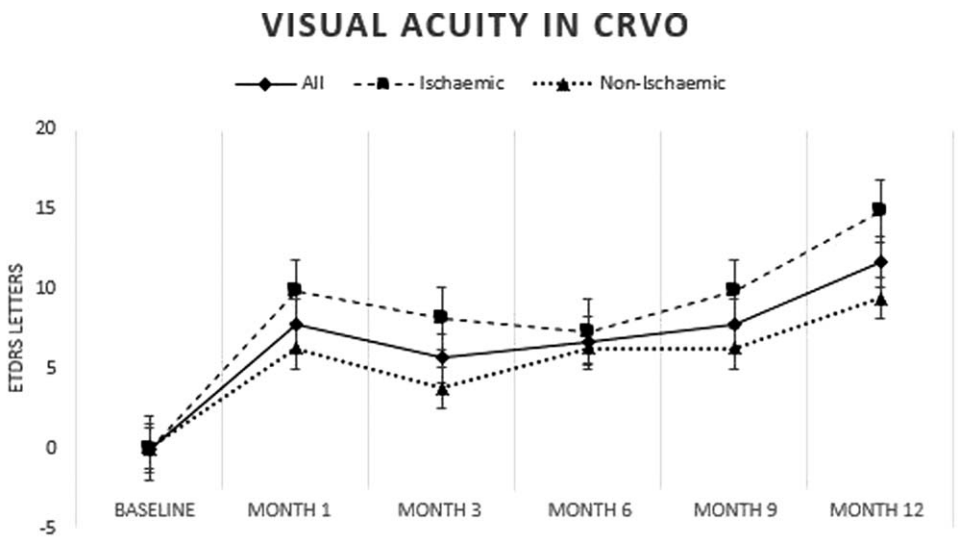

FIGURE 4. CRVO subgroup analysis -Mean change in VA in ETDRS letters from baseline to 12-months post-switch to aflibercept. CRVO indicates central retinal vein occlusion; VA, visual acuity; ETDRS, early treatment of diabetic retinopathy score.

patients were treated with first-line bevacizumab and were switched to aflibercept due to an insufficient response. Overall, there was mean reduction of 118 microns in macular thickness at 12 months and a mean improvement of 3.1 letters among these studies. This is a similar result to our study in which there was a mean reduction of 180.9 microns and mean improvement of 8.7 letters at 12 months.

However, unlike the previously reported studies, this study included eyes switched late after on average >25 previous injections. Controlling edema earlier by switching earlier may be associated with a better visual outcome with lower prevalence of thinning of the neuroretina and ischemia, which is often noted in eyes with persistent macular edema.[26,27] Despite this, the extent of visual gains demonstrated in this study are in the same order of previous studies where aflibercept was initiated after shorter periods of first-line therapy. Thus, conceivably, the benefit of early rather than delayed conversion to aflibercept is not reflected in the absolute visual gain after the conversion.

The outcomes presented here suggest that by switching anti-VEGF therapy to aflibercept in eyes with chronic disease, and persistent macular edema due to RVO, a prolongation of the treatment interval can be attained, and improvements in both functional and anatomical outcomes, despite extensive previous treatment. A spontaneous deterioration in the natural disease process of CME as expressed by Rogers et al[28] seems relatively improbable due to inclusion of patients with recurrent chronic macular edema.

Possible explanations for these findings may be aflibercepts' higher binding affinity and the added binding to PlGF, compared with ranibizumab and bevacizumab.[15] Aflibercept has also demonstrated a prolonged intravitreal retention time compared with bevacizumab and ranibizumab,[29] and longer half-life.[30]

Functional and anatomic outcomes showed small but significant gains over the course of the 12-month study period after switching to aflibercept associated with the ability to extend injection intervals.

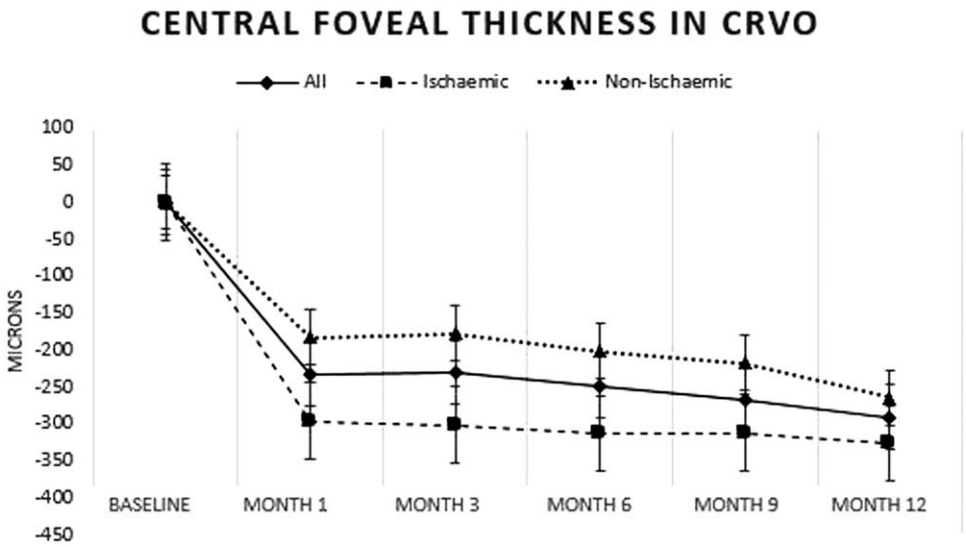

FIGURE 5. CRVO subtype analysis. Mean change in CFT in microns from baseline to 12-months post-switch to aflibercept. CFT indicates central foveal thickness; CRVO, central retinal vein occlusion.

The main limitations of this study are its retrospective nature, absence of control group, small sample size, and limited follow-up period. Larger, longer, prospective clinical studies are required.

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