

# One-year outcomes of Aflibercept for refractory diabetic macular edema in Bevacizumab nonresponders

Ali Salimi<sup>1</sup>, Natalia Vila<sup>1</sup>, Milad Modabber<sup>1</sup>, Michael Kapusta<sup>1,2</sup>

**Purpose:** A sub-population of patients with diabetic macular edema (DME) responds less effectively to off-label use of Bevacizumab. Approval of Aflibercept for DME has offered Bevacizumab nonresponders an alternative therapeutic option. Herein, we investigate the anatomical and functional changes associated with Aflibercept treatment in Bevacizumab nonresponders with chronic DME in a Canadian setting. **Methods:** A retrospective study of eyes with persistent DME that were switched to Aflibercept due to nonresponse following  $\geq 6$  consecutive monthly Bevacizumab injections was performed. Anatomical and functional changes and the predictors of response were assessed using patients' characteristics prior to receiving their first (baseline) and seventh consecutive Aflibercept injections (follow-up). **Results:** Twenty-four eyes were included, with a mean age of  $63.9 \pm 10.7$  years, an average of  $16.8 \pm 8.5$  Bevacizumab injections prior to switching to Aflibercept, and mean follow-up duration of  $11.8 \pm 1.7$  months following switching to Aflibercept. Best-corrected visual acuity (BCVA) improved significantly from  $0.49 \pm 0.13$  to  $0.41 \pm 0.11$  logMAR ( $P < 0.001$ ) and central subfield thickness (CST) decreased by  $119.4 \mu\text{m}$  from  $409.4 \pm 85.8 \mu\text{m}$  to  $290.0 \pm 64.5 \mu\text{m}$  ( $P < 0.001$ ), with 50% of eyes showing complete anatomical response. Worse BCVA and higher CST at baseline predicted greater vision improvements ( $P = 0.001$  and  $P = 0.035$ , respectively) while a larger decrease in CST was associated with greater baseline CST ( $P = 0.001$ ) and better glycemic control ( $P = 0.039$ ). **Conclusion:** Our data from a real-world clinical setting highlight the efficacy of Aflibercept as an alternative therapeutic option for DME recalcitrant to Bevacizumab, with potential additional benefit to those with worse vision, greater CST, and better glycemic control at baseline.

**Key words:** Aflibercept, anti-VEGF, Bevacizumab, diabetic macular edema, refractory

Diabetic macular edema (DME) causes significant vision loss, diminished quality of life, and psychological distress. The individual and psychosocial burden of DME underlines the importance of optimizing treatment options for these patients, particularly those with more challenging and less responsive cases.

Current DME guidelines recommend anti-vascular endothelial growth factor (anti-VEGF) therapy with or without adjunct laser photocoagulation for those with center-involved DME (CI-DME).<sup>[1]</sup> Off-label use of Bevacizumab (Avastin<sup>®</sup>) has shown to be effective in treating DME<sup>[2]</sup>; however, a subpopulation of patients is considered poor responders – for which there exists no uniform definition in the literature. In cases of poor response, switching to a different therapy, such as corticosteroids<sup>[3]</sup> or an alternative anti-VEGF agent is usually a viable step.<sup>[4]</sup>

Aflibercept (Eylea<sup>®</sup>) is an anti-VEGF agent approved for the treatment of DME. It is characterized by a greater binding affinity to VEGF as well as a longer half-life and has shown to be efficacious in treating DME.<sup>[5]</sup> A few studies have

investigated the outcomes related to switching to Aflibercept in DME patients refractory to Bevacizumab therapy<sup>[6-14]</sup>; however, the number of pre-switch Bevacizumab injections and the post-switch follow-up duration was limited in the majority of these studies. Further, the morphometric features of the macula and the predictors of response in this therapeutically challenging sub-population remains understudied.

In 2014, Health Canada approved Aflibercept for treatment of DME; however, switching to this anti-VEGF was set back because of limited provincial drug funding for this drug.<sup>[15]</sup> Hence, switching to Aflibercept was delayed until more recently, when Canadian provincial health insurances approved Aflibercept coverage for DME nonresponders. Here, we assessed the 1-year anatomical and functional vision outcomes of switching to Aflibercept among a Canadian cohort of chronic DME patients recalcitrant to Bevacizumab therapy and investigated the predictors of response and morphometric features of the macula following switching to Aflibercept.

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:** WKHLRPMedknow\_reprints@wolterskluwer.com

**Cite this article as:** Salimi A, Vila N, Modabber M, Kapusta M. One-year outcomes of Aflibercept for refractory diabetic macular edema in Bevacizumab nonresponders. Indian J Ophthalmol 2021;69:360-7.

Access this article online

Website:

www.ijo.in

DOI:

10.4103/ijo.IJO\_459\_20

Quick Response Code:



<sup>1</sup>Department of Ophthalmology, McGill University, <sup>2</sup>Eye Health MD, Montreal, Quebec, Canada

**Correspondence to:** Dr. Ali Salimi, Department of Ophthalmology, McGill University, Montreal, Quebec, Canada. 5252 Boulevard de Maisonneuve O, Montréal, QC H4A 3S9. E-mail: ali.salimi@mail.mcgill.ca

Received: 04-Mar-2020

Revision: 19-May-2020

Accepted: 28-Sep-2020

Published: 18-Jan-2021

## Methods

**Participants:** We performed a retrospective review of all patients who received Bevacizumab injections for reduced vision from CI-DME and were switched, due to poor response to this medication, to Aflibercept at a single ophthalmology clinic. The inclusion criteria consisted of persistent CI-DME defined by central subfield thickness (CST)  $\geq 300 \mu\text{m}$ <sup>[10]</sup> with persistent or increasing subretinal or intraretinal fluid despite a minimum of six consecutive monthly intravitreal Bevacizumab injections (1.25 mg/0.05 mL), and decreased vision from CI-DME defined by BCVA  $\leq 20/40$ . Exclusion criteria consisted of the following prior to switching: retinal vascular diseases other than DME, dense cataracts, recent history of panretinal or macular laser in the study eye ( $< 3$  months), recent cerebrovascular accident or myocardial infarction within 3 months of screening. Prior history of pars plana vitrectomy was not considered an exclusion criterion, and both vitrectomized and nonvitrectomized eyes were included in the study.

**Imaging:** The retinal imaging was done using the Cirrus HD-OCT (Carl Zeiss Meditec, Dublin, CA). The Cirrus HD-OCT Macular Analysis software automatically analyzed the macular thickness (the distance between the inner limiting membrane and the Bruch's membrane) in all nine regions of the macula, defined by the Early Treatment Diabetic Retinopathy Study (ETDRS) map. All subjects underwent imaging prior to receiving each injection, which served as the basis to evaluate the anatomical characteristics of patients' macula, including CST (average thickness in the central 1 mm diameter circle of the ETDRS grid), average macular thickness (AMT) (average retinal thickness in all nine ETDRS sections), and average macular volume (AMV) (average volume in all nine ETDRS sections).

Presence or absence of the following morphometric features was evaluated: diffuse retinal thickening characterized by a uniformly increased retinal thickness of greater than  $200 \mu\text{m}$  and decreased intra-retinal reflectivity, hyper-reflective dots, hard exudates, ellipsoid zone disruption, epiretinal membrane, sponge-like retinal swelling, subretinal fluid, vitreomacular traction and adhesion, disruption of the external limiting membrane, as well as intra-retinal cystoid space which was categorized based on its horizontal width (small:  $< 250 \mu\text{m}$ , medium:  $250\text{-}500 \mu\text{m}$ , and large:  $\geq 500 \mu\text{m}$ ). Cone outer segment tip (COST) status – an early marker of photoreceptor damage<sup>[16]</sup> – was classified into distinct, discernible, obscured, disrupted. Ellipsoid zone status – a predictor of functional vision – was classified according to the degree of disruption (0%, up to 25%, 25-50%, and  $\geq 50\%$ ).

**Visual exam:** At every visit, prior to receiving the injection, subjects were evaluated for BCVA using the Snellen chart. To ensure the continuity of the data, the BCVA scores were converted to the logarithm of minimal angle of resolution (LogMAR), and letters of vision gained were calculated in visual acuity rating scale (VAR) using the following formula:  $\text{VAR} = 100 - 50(\log\text{MAR})$ .

**Injection procedure:** Using sterile technique and following application of topical anesthetic (Tetracaine) and Povidone-iodine 5% (Betadine) drops onto the ocular surface, the injection site was marked at 3.5- or 4-mm posterior to the limbus (pseudophakic or phakic status, respectively).

The injection site was inferotemporal and 0.05 mL of Bevacizumab (1.25 mg/0.05 mL) or Aflibercept (2 mg/0.05 mL) was injected through pars plana using a 30-gauge needle. Following the injection, a drop of povidone-iodine 5% and antibiotic drops were instilled. The switch from bevacizumab to Aflibercept occurred according to the following regimen: the first six Aflibercept injections were administered through a fixed regimen at 8-week intervals (loading dose) and the subsequent ones were administered according to a treat and extend regimen.

**Data Extraction and Statistical Analyses:** We extracted the clinical characteristics including the hemoglobin A1C (HbA1C), BCVA, intraocular pressure, and the OCT-derived anatomical data from patients' medical records, prior to receiving their first and seventh consecutive Aflibercept injections, serving as the baseline and the follow-up data points, respectively. The outcomes of interest were improvements in functional vision and macular structures. Vision changes were also broadly categorized as improved (change in LogMAR  $< -0.01$ ), stable (change in LogMAR between  $-0.01$  and  $0.01$ ), and deteriorated (change in LogMAR  $> 0.01$ ). Complete anatomical response to Aflibercept was defined by CST  $< 300 \mu\text{m}$  at follow-up with a reduction greater than 10% compared to baseline in the absence of sub-retinal fluid.<sup>[10]</sup>

Changes from baseline (immediately prior to switching to Aflibercept) to the follow-up (following 6 consecutive Aflibercept injections) were evaluated using repeated-measure ANOVA (continuous variables), McNemar (dichotomous variables), and Wilcoxon test (ordinal variables). Predictors of response were evaluated using linear regression models. All analyses were performed using SPSS Statistics 26.0, with  $P < 0.05$ . The study adhered to the tenets of the Declaration of Helsinki and was approved by the local ethics committee.

## Results

### Baseline characteristics

Data of 24 eyes from 17 patients who met the above-cited inclusion criteria were extracted and analyzed. The demographic and baseline clinical features of the patients are presented in Table 1. There were no missing data for any patient. The average age was  $63.9 \pm 10.7$  years, mean diabetes duration was  $20.4 \pm 11.7$  years, and the average number of Bevacizumab injections prior to switching to Aflibercept was  $16.8 \pm 8.5$  (the last six of which were administered monthly). At baseline, the average BCVA was  $0.49 \pm 0.13$  LogMAR, mean CST was  $409.4 \pm 85.8 \mu\text{m}$ , AMT was  $324.3 \pm 45.6 \mu\text{m}$ , and AMV was  $11.7 \pm 1.7 \mu\text{L}$ . Half of the eyes ( $n = 12$ ), had proliferative diabetic retinopathy (PDR), all of which had undergone panretinal photocoagulation (PRP). None of the patients had severe epiretinal membrane involving the macular center or vitreomacular traction that required vitrectomy. At follow-up, all eyes had received six intravitreal Aflibercept injections with an average injection interval of  $7.8 \pm 1.2$  weeks and a mean follow-up duration of  $11.8 \pm 1.7$  months.

### Functional and anatomical vision outcomes

Changes in functional and anatomical characteristics of patients from baseline to follow-up are compared and presented in Table 2. Statistically significant improvements were observed in both vision and macular swelling. BCVA

**Table 1: Patients' baseline demographics, clinical features, and OCT-derived morphometric characteristics (n=24)**

Variables		Range [min-max]
Age (years)	63.9±10.7	46-98
Sex (M:F)	16:8	
Study Eye (OD: OS)	14:10	
Hypertension, n (%)	17 (71%)	
Diabetes duration (years)	20.4±11.7	7-39
Hemoglobin A1C (%)	8.0±1.5	5.5-11.2
Number of Bevacizumab injections	16.8±8.5	10-36
Bevacizumab therapy duration (months)	39.7±23.6	11-91
Proliferative diabetic retinopathy	12 (50%)	
History of panretinal photocoagulation	12 (50%)	
Previous Triamcinolone treatment, n (%)	2 (8%)	
Previous modified grid laser treatment	15 (63%)	
History of vitrectomy, n (%)	4 (17%)	
Best-corrected visual acuity (logMAR)	0.49±0.13	0.30-0.70
Intraocular pressure (mmHg)	17.0±3.7	11.0-24.0
Central Subfield Thickness (µm)	409.4±85.8	302-659
Average Macular Thickness (µm)	324.3±45.6	259-429
Average Macular Volume (µl)	11.7±1.7	8.7-15.4
Diffuse retinal thickening, n (%)	24 (100%)	
Hyper-reflective dots, n (%)	24 (100%)	
Intra-retinal cystoid space size (none : small <250 µm: medium=250-500 µm: large ≥500 µm)	0:8:8:8	
Hard exudates, n (%)	21 (88%)	
Cone outer segment tips (Distinct : Discernible : Obscured : Disrupted)	3:1:6:14	
Ellipsoid zone disruption (no : 0-25% : 25-50% : >50%)	8:5:8:3	
Epi-retinal membrane, n (%)	12 (50%)	
External limiting membrane disruption, n (%)	4 (17%)	
Vitreomacular adhesion, n (%)	4 (17%)	
Sponge-like retinal swelling, n (%)	1 (4%)	
Subretinal fluid, n (%)	1 (4%)	
Vitreomacular traction, n (%)	0 (0%)	
Tractional retinal detachment, n (%)	0 (0%)	

The continuous and discrete data are presented as mean±standard deviation and frequency (percentage), respectively

improved from  $0.49 \pm 0.13$  LogMAR to  $0.41 \pm 0.11$  ( $P < 0.001$ , Eta-squared = 0.479), and on average patients gained 4 letters of acuity. Proportional analyses showed that vision improved in 58% of the patients, remained stable in 38%, and deteriorated in 4%.

In terms of anatomical changes, CST decreased by  $119.4 \mu\text{m}$  (29% reduction), from  $409.4 \pm 85.8 \mu\text{m}$  to  $290.0 \pm 64.5 \mu\text{m}$  ( $P < 0.001$ , Eta-squared = 0.550) and 71% of eyes experienced a reduction greater than  $50 \mu\text{m}$ . In addition, the overall edema in macula improved, as the AMT decreased by 10% from  $324.3 \pm 45.6 \mu\text{m}$  to  $290.3 \pm 29.5 \mu\text{m}$  ( $P = 0.001$ , Eta-squared = 0.434) and total macular volume reduced from  $11.7 \pm 1.7 \mu\text{l}$  to  $10.5 \pm 1.1 \mu\text{l}$  ( $P = 0.001$ , Eta-squared = 0.413) [Fig. 1]. Twelve eyes (50%) showed complete anatomical response to Aflibercept. A multivariate logistic regression analysis failed to unveil any baseline predictors for complete response. Fig. 2a illustrates the OCT image of an eye with clinically significant macular edema at baseline and Fig. 2b shows a complete anatomical response to Aflibercept at follow-up in the same eye. The diffuse retinal thickening resolved in 37% ( $P = 0.002$ ), the size of intraretinal

cystoid spaces decreased ( $P = 0.029$ ) with complete resolution in five (21%) eyes, and ellipsoid zone disruption improved in half of the eyes ( $P = 0.042$ ). No other changes were observed in the remaining OCT variables.

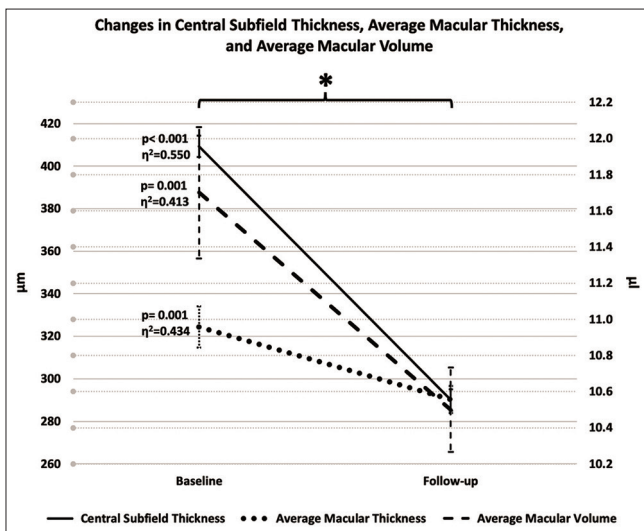
Among the eyes with baseline PDR (all of which had received PRP), the average baseline BCVA was  $0.55 \pm 0.13$  LogMAR and the mean CST was  $405.0 \pm 105.5 \mu\text{m}$ . At 1-year follow-up, BCVA improved by 3.3 letters to  $0.48 \pm 0.12$  LogMAR, and CST decreased by 30% to  $283.5 \pm 75.9 \mu\text{m}$ . Intergroup analysis between those with PDR (and prior PRP) and those with no PDR did not evidence any differences for the primary outcomes, including BCVA ( $P = 0.869$ ), CST ( $P = 0.641$ ), AMT ( $P = 0.095$ ), and AMV ( $P = 0.091$ ). At baseline, four eyes had undergone pars plana vitrectomy for nonclearing vitreous hemorrhage. The average vision at baseline was  $0.47 \pm 0.17$  LogMAR and the mean CST was  $356.0 \pm 74.9 \mu\text{m}$ . At 1-year, BCVA improved by an average of 4.75 letters to  $0.38 \pm 0.05$  LogMAR, and CST decreased by 11% to a mean of  $317.0 \pm 40.3 \mu\text{m}$ . Given the differences in intravitreal drug pharmacokinetics following pars plana vitrectomy, we compared the outcomes



**Table 2: Changes in functional and anatomical characteristics of patients from baseline to follow-up (n=24)**

Variables	Baseline	Follow-up	P	Eta <sup>2</sup>
Best-corrected visual acuity <sup>#</sup> (LogMAR)	0.49±0.13	0.41±0.11	<0.001*	0.479
Intraocular pressure <sup>#</sup> (mmHg)	17.0±3.7	17.5±4.2	0.507	0.021
Central Subfield Thickness <sup>#</sup> (µm)	409.4±85.8	290.0±64.5	<0.001*	0.550
Average Macular Thickness <sup>#</sup> (µm)	324.3±45.6	290.3±29.5	0.001*	0.434
Total Macular Volume <sup>#</sup> (µl)	11.7±1.7	10.5±1.1	0.001*	0.413
Diffuse retinal thickening <sup>§</sup> , n (%)	24 (100%)	15 (63%)	0.002*	
Hyper-reflective dots <sup>§</sup> , n (%)	24 (100%)	23 (96%)	0.500	
Intra-retinal cystoid space size <sup>†</sup> (none: small <250 µm: medium=250-500 µm: large >=500 µm)	0:8:8:8	5:5:9:5	0.029*	
Hard exudates <sup>§</sup> , n (%)	21 (88%)	21 (88%)	1.000	
Cone outer segment tips <sup>†</sup> (Distinct : Discernible: Obscured: Disrupted)	3:1:6:14	3:9:0:12	0.091	
Ellipsoid zone disruption <sup>†</sup> (No : 0-25% : 25-50% : >50%)	8:5:8:3	16:2:4:2	0.042*	
Epi-retinal membrane <sup>§</sup> , n (%)	12 (50%)	12 (50%)	1.000	
External limiting membrane disruption <sup>§</sup> , n (%)	5 (21%)	6 (25%)	0.500	
Vitreomacular adhesion <sup>§</sup> , n (%)	4 (17%)	3 (13%)	0.500	
Sponge-like retinal swelling <sup>§</sup> , n (%)	1 (4%)	1 (4%)	1.000	
Sub-retinal fluid <sup>§</sup> , n (%)	1 (4%)	0 (0%)	0.500	
Vitreomacular traction <sup>§</sup> , n (%)	0 (0%)	0 (0%)	1.000	
Tractional retinal detachment <sup>§</sup> , n (%)	0 (0%)	0 (0%)	1.000	

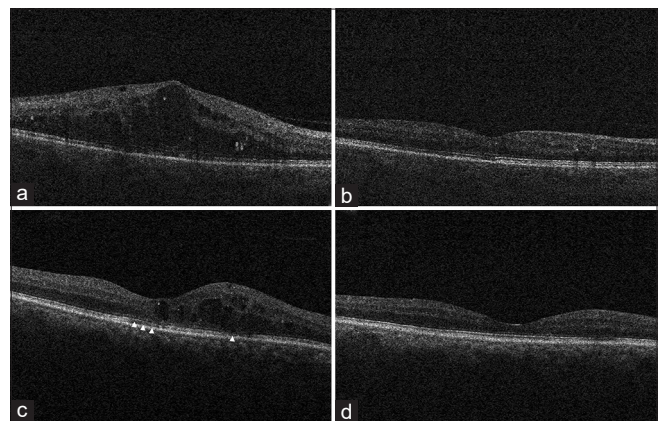
The continuous and discrete data are presented as mean±standard deviation and frequency (percentage), respectively. <sup>#</sup>Based on the repeated measure ANOVA. <sup>§</sup>Based on the McNemar test. <sup>†</sup>Based on the Wilcoxon test. \*Denotes statistical significance at P<0.05



**Figure 1:** Changes in the central subfield thickness (CST), average macular thickness (AMT), and average macular volume (AMV) from pre-Aflibercept switching to follow-up. The solid and dotted lines represent the CST and AMT, respectively (left axis), and the dashed line represents AMV (right axis). The vertical bars show the standard error of the mean. \* denotes statistical significance at P < 0.05. η<sup>2</sup>, effect size. There was a significant decrease in CST (P < 0.001), AMT (P = 0.001), and AMV (P = 0.001)

of vitrectomized and nonvitrectomized eyes, which failed to evidence any time-group interaction for the primary outcomes, including BCVA (P = 0.266), CST (P = 0.216), AMT (P = 0.108), and AMV (P = 0.109).

Our sample included 7 patients whose both eyes met the inclusion criteria and an additional 10 patients whose only



**Figure 2:** (a) OCT showing clinically significant macular edema with central subfield thickness of 659 µm at baseline. (b) OCT showing complete anatomical response to Aflibercept and improved central subfield thickness of 271 µm at follow-up. (c) OCT showing disrupted cone outer segment tip (arrowheads). (d) OCT showing significant improvements in cone outer segment tip (COST) with a discernible COST line

one eye did. A sub-analysis of the contralateral eyes of these 10 patients was performed: Four eyes without CI-DME were receiving Bevacizumab and were switched to Aflibercept at the same time as their contralateral eye. These four nonstudy eyes did similarly to their contralateral study eye, in terms of both BCVA changes (P = 0.417) and CST reductions (P = 0.420). Three eyes had no history of prior anti-VEGF therapy but developed CI-DME and were started on Aflibercept at the same time as switching their contralateral eye. These three eyes did similarly to their contralateral study eye in terms of BCVA (P = 0.821) while a trend for larger CST reductions was observed for the study eyes (P = 0.059). Lastly, three eyes had no CI-DME,

were not receiving any intravitreal injections, and remained dry and free of anti-VEGF therapy throughout the follow-up. These eyes did similarly to their contralateral study eye in terms of BCVA ( $P = 0.154$ ); however, the study eye experienced a significant CST reduction of 50% while the nonstudy eye remained stable with a baseline CST of  $250.6 \pm 42.14 \mu\text{m}$  and a follow-up CST of  $244.7 \pm 37.1 \mu\text{m}$  (2.5% reduction,  $P = 0.238$ ).

Another sub-analysis included the seven patients whose bilateral eyes were included and compared the behavior of each eye to its contralateral eye with regards to the primary outcomes. Our analysis found that bilateral eyes responded similarly to the switch in terms of both BCVA ( $P = 0.325$ ) and CST ( $P = 0.832$ ).

### Baseline predictors of response

Linear regression analyses were performed to investigate possible predictors of vision and anatomical response, accounting for age, sex, diabetes duration, glycemic control represented by HbA1C, presence of PDR, the total number of Bevacizumab injections received prior to switching, presence of epiretinal membrane, history of vitrectomy, modified grid laser or panretinal photocoagulation, baseline BCVA, and CST.

The model for predictors of vision response accounted for 75% of variations in BCVA ( $R^2 = 0.749$ , adjusted  $R^2 = 0.541$ ,  $P = 0.009$ ) and is presented in Table 3. Poorer vision at baseline was associated with greater vision improvements ( $\beta = 0.742$ ,  $P = 0.001$ ), and those with baseline BCVA worse than 0.48 LogMAR (~20/60) improved significantly more ( $P = 0.005$ ). In addition, higher baseline CST was associated with greater vision improvements ( $\beta = 0.439$ ,  $P = 0.035$ ).

The regression model for predictors of anatomical improvement accounted for 81% of the variations in CST ( $R^2 = 0.809$ , adjusted  $R^2 = 0.700$ ,  $P = 0.001$ , Table 3). Larger baseline CST ( $\beta = 0.667$ ,  $P = 0.001$ ) and lower HbA1C ( $\beta = 0.395$ ,  $P = 0.039$ ) were associated with greater anatomical improvements.

Vision improvement was associated with improved intra-retinal cystoid space ( $P = 0.038$ ) such that vision improved in 80% of those with improved intra-retinal cystoid space at follow-up compared to 33% in those without. Similarly, vision improved in 80% of those with COST improvement at follow-up compared to 33% of those without, highlighting an association between vision improvement and decreased COST disruption ( $P = 0.038$ ). Fig. 2c illustrates an example of disrupted COST at baseline and Fig. 2d shows COST improvements in the same eye with a discernible COST line.

### Safety and adverse events

No systemic or ocular adverse events including endophthalmitis, ocular hypertension, retinal detachment, or rapid progression of cataracts were evidenced in our population.

## Discussion

The common treatment options for DME include laser photocoagulation, corticosteroids, and intravitreal anti-VEGF agents. Traditionally, laser photocoagulation has been the mainstay of treatment for DME; however, this technique is associated with limitations such as atrophic creep, scotoma due to heat-induced damage to the retinal tissue, and restricted efficacy in maintaining visual acuity.<sup>[17]</sup> Corticosteroids have been shown to be effective in reducing macular edema by

inhibiting the expression of VEGF. Evidence from randomized control trials highlighted the superiority of corticosteroids over laser photocoagulation at four-month follow-up, noninferiority at 1 year, and inferiority at 2-year follow-up.<sup>[18]</sup> Concern regarding the long-term efficacy and the safety of corticosteroids such as cataract formation and intraocular pressure spikes<sup>[19]</sup> has limited their use to mainly adjuvant therapy in anti-VEGF nonresponders, and more particularly pseudophakic patients. Evidence from clinical trials highlighting the superiority of anti-VEGFs over laser photocoagulation in CI-DME has shifted the paradigm of therapy for DME.<sup>[5,20]</sup>

Up to 56.7% of DME eyes treated with Bevacizumab and 40% of those treated with Ranibizumab are reported as nonresponders, shown by persistent macular edema despite 24 months of anti-VEGF therapy.<sup>[21,22]</sup> In cases of poor response, switching to a different therapy, such as corticosteroids<sup>[3]</sup> or an alternative anti-VEGF agent is usually a viable step.<sup>[4]</sup> A few have investigated the response to switching to Aflibercept in a chronic DME population refractory to longer-term Bevacizumab therapy<sup>[6-14]</sup>; however, the number of pre-switch Bevacizumab therapy and the post-switch follow-up duration was limited in the majority of these studies and only a few investigated the morphometric features and the predictors of response to the switch.

Prior to the approval and public drug coverage for Aflibercept, many Canadian DME patients received bevacizumab for extended periods of time. Our sample consisted of a cohort of DME patients with poor response to bevacizumab that got the opportunity of switching to Aflibercept following its approval and drug coverage by the provincial drug insurance. The results of this study show that switching to Aflibercept in a chronic CI-DME refractory to Bevacizumab, leads to substantial anatomical improvements, as evidenced by a decrease in foveal and macular thickness, diffuse retinal thickness, intra-retinal cystoid spaces, as well as ellipsoid zone disruption. In addition, vision improved in more than half of our population, and on average, our patients gained four letters of acuity. Our findings are in line with a few similar studies.<sup>[10,12,13]</sup> Vision gain in our population was well within the 3.9 to 4.5 letters range previously reported<sup>[10,12,13]</sup> and the 29% decrease in CST is comparable to the 12.6 to 26.2% range reported in the literature. A previous study investigating the early outcomes of switching to Aflibercept reported complete anatomical response among 24% of the patients following an average of 2.2 Aflibercept injections (2.4 months follow-up).<sup>[10]</sup> In our cohort, complete anatomical response was evidenced in half of the eyes. We hypothesize that a larger number of Aflibercept injections and longer follow-up has likely allowed complete anatomical response among a greater proportion of patients. Our regression analysis failed to identify any baseline predictors of complete response, which we relate to the limited sample size and statistical power of our study. Future studies with larger samples should further investigate the characteristics of the eyes with and without complete response to switching to Aflibercept.

The effect of vitreoretinal abnormalities on the efficacy of intravitreal anti-VEGFs was assessed in a previous study,<sup>[23]</sup> which did not evidence any differences in CST reduction between eyes with no intravitreal abnormalities and those with eccentric ERM. While 50% of the eyes in our cohort had ERM, none were severe or involved the macular center that

**Table 3: Linear regression models for baseline predictors of response to switching to Aflibercept (n=24)**

Best Corrected Visual Acuity, ( $R^2=0.749$ , adjusted $R^2=0.541$ , $P=0.009$ )						
Independent Variable	B	$\beta$	t	P	95% CI	
Age	-0.001	0.104	0.579	0.574	-0.004	0.006
Sex	-0.054	-0.215	-1.214	0.248	-0.150	0.043
Hemoglobin A1C (%)	-0.011	-0.136	-0.698	0.499	-0.046	0.024
Duration of Diabetes	0.000	-0.037	-0.146	0.887	-0.006	0.005
Number of Bevacizumab injections	0.002	0.123	0.513	0.617	-0.006	0.010
Vitrectomy pre-switching	-0.056	-0.178	-0.819	0.429	-0.204	0.093
Proliferative diabetic retinopathy/ history of pan retinal photocoagulation	0.089	0.376	1.460	0.170	-0.044	0.223
Epiretinal membrane	-0.030	-0.125	-0.673	0.511	-0.125	0.065
Macular laser pre-switching	0.091	0.367	1.657	0.123	-0.029	0.212
Baseline BCVA	-0.651	-0.742	-4.350	0.001*	-0.976	-0.325
Baseline CST	0.001	-0.439	-2.382	0.035*	-0.006	-0.001
Central Subfield Thickness, ( $R^2=0.809$ , adjusted $R^2=0.700$ , $P=0.001$ )						
Independent Variable	B	$\beta$	t	P	95% CI	
Age	-0.866	-0.079	-0.505	0.623	-4.604	2.873
Sex	-10.944	-0.049	-0.318	0.756	-86.360	64.371
Hemoglobin A1C (%)	28.956	0.395	2.321	0.039*	1.774	56.138
Duration of Diabetes	-1.092	-0.116	-0.517	0.615	-5.697	3.513
Number of Bevacizumab injections	4.520	0.339	1.625	0.130	-1.541	10.518
Vitrectomy pre-switching	-23.117	-0.082	-0.432	0.673	-139.628	93.394
Proliferative diabetic retinopathy/ history of pan retinal photocoagulation	-3.836	-0.018	-0.080	0.938	-108.489	100.816
Epiretinal membrane	-35.739	-0.166	-1.223	0.240	-98.008	26.531
Macular laser pre-switching	-79.963	-0.356	-1.848	0.089	-174.260	14.334
Baseline BCVA	-72.145	-0.091	-0.615	0.550	-327.736	183.446
Baseline CST	-0.820	-0.667	-4.148	0.001*	-1.251	-0.390

$\beta$ , standardized coefficient beta; B, regression coefficient; BCVA, best-corrected visual acuity; CI, confidence interval; CST, central subfield thickness. \*Denotes statistical significance at  $P<0.05$

required Vitrectomy. In line with the findings of Kulikov and colleagues,<sup>[23]</sup> we did not evidence any difference between the functional and anatomical outcomes of the eyes with eccentric ERM and those without ERM.

Anatomical improvements following Aflibercept were predicted by larger baseline CST, which is in agreement with the results of the previous studies including the ETDRS study.<sup>[24,25]</sup> We hypothesize that this phenomenon can be explained by the fact that eyes with larger CST at baseline have a larger room for improvement. In addition, larger vision improvements in those with higher baseline CST could be secondary to greater anatomical improvements observed in this sub-population. Data on the association between glycemic control and response to anti-VEGFs is mixed.<sup>[26,27]</sup> In line with the findings of a few other studies,<sup>[26]</sup> our results highlighted an association between better glycemic control and greater anatomical response to Aflibercept; however, failed to evidence an association for the functional response. We hypothesis that this lack of association could be related to the chronicity of DME, as other studies in chronic DME patients also failed to report this association.<sup>[26]</sup>

The significant role of COST in photoreceptor function has been well documented, and COST disruption has been linked to photoreceptor dysfunction.<sup>[16]</sup> In our sample, those with COST

improvement experienced greater vision gains compared to the ones without. Despite the individual-level improvements, COST only showed a trend for improvement ( $P = 0.091$ ) at follow-up. We postulate that the absence of significant improvements in COST could have potentially limited greater vision gains in our population. Future studies with a larger sample shall further assess the improvements in COST and its association with vision in this challenging population. The ellipsoid zone corresponds to a portion of the photoreceptors' inner segment, and its integrity has been associated with visual function.<sup>[28]</sup> Similar to Bahrami's findings,<sup>[29]</sup> ellipsoid zone disruption did not predict functional vision improvements. We hypothesize that this lack of association could be due to irreversible damage to the neural retina secondary to the chronicity of DME,<sup>[30,31]</sup> which in turn might have limited visual gains. Anti-VEGF agents have rarely been associated with certain ocular and systemic adverse events.<sup>[12,29]</sup> None of our patients experienced any adverse events.

It has been reported that the improved vision associated with Aflibercept leads to modest improvements in quality-of-life; however, it is not cost-effective compared to Bevacizumab.<sup>[32]</sup> It is important to note that the focus of these studies was not the DME patients refractory to Bevacizumab, and the cost-effectiveness of Aflibercept in this therapeutically



challenging group remains unclear. Our results highlight statistically significant anatomical and vision improvements associated with switching to Aflibercept. While it can be argued that these improvements might not be clinically significant, it is important to consider these improvements while keeping in mind the possibility of deterioration among these eyes, had switching not occurred. In the absence of strong evidence about the cost-effectiveness of switching to Aflibercept among DME patients with poor response to Bevacizumab, we encourage future works to study this area.

Our study is limited by its retrospective nature, lack of control arm, small sample size, and geographical restriction, and the results of this study should be interpreted in light of its limitations., in light of limited evidence on outcomes related to switching to Aflibercept in DME patients with refractory edema and insufficient data for predictors of response,<sup>[10,12,13]</sup> our real-world results and predictive analyses further add to the existing literature with the hope of helping ophthalmologists with individualized decision making while also encouraging future studies to further assess different treatment regimens for managing the challenging cases of refractory DME.

## Conclusion

Chronic and recalcitrant DME remains a challenge in ophthalmology, responsible for visual disability and substandard quality of life among many patients worldwide. Our results suggest that switching this population to Aflibercept leads to functional vision improvements, more so in those with poorer baseline vision while also improving the macular edema.

## Financial support and sponsorship

Nil.

## Conflicts of interest

There are no conflicts of interest.

## References

- Canadian Ophthalmological Society Diabetic Retinopathy Clinical Practice Guideline Expert C, Hooper P, Boucher MC, Cruess A, Dawson KG, Delpero W, *et al.* Canadian Ophthalmological Society evidence-based clinical practice guidelines for the management of diabetic retinopathy-executive summary. *Can J Ophthalmol* 2012;47:91-6.
- Diabetic Retinopathy Clinical Research N, Scott IU, Edwards AR, Beck RW, Bressler NM, Chan CK, *et al.* A phase II randomized clinical trial of intravitreal bevacizumab for diabetic macular edema. *Ophthalmology* 2007;114:1860-7.
- Busch C, Zur D, Fraser-Bell S, Lains I, Santos AR, Lupidi M, *et al.* Shall we stay, or shall we switch? Continued anti-VEGF therapy versus early switch to dexamethasone implant in refractory diabetic macular edema. *Acta Diabetol* 2018;55:789-96.
- Takamura Y, Ohkoshi K, Murata T. New strategies for treatment of diabetic macular edema. *J Ophthalmol* 2018;2018:4292154. doi: 10.1155/2018/4292154.
- Korobelnik JF, Do DV, Schmidt-Erfurth U, Boyer DS, Holz FG, Heier JS, *et al.* Intravitreal aflibercept for diabetic macular edema. *Ophthalmology* 2014;121:2247-54.
- Wood EH, Karth PA, Moshfeghi DM, Leng T. Short-term outcomes of aflibercept therapy for diabetic macular edema in patients with incomplete response to ranibizumab and/or bevacizumab. *Ophthalmic Surg Lasers Imaging Retina* 2015;46:950-4.
- Shah CP, Heier JS. Aflibercept for diabetic macular edema in eyes previously treated with ranibizumab and/or bevacizumab may further improve macular thickness. *Ophthalmic Surg Lasers Imaging Retina* 2016;47:836-9.
- Rahimy E, Shahlaee A, Khan MA, Ying GS, Maguire JI, Ho AC, *et al.* Conversion to aflibercept after prior anti-VEGF therapy for persistent diabetic macular edema. *Am J Ophthalmol* 2016;164:118-27.e2.
- Lim LS, Ng WY, Mathur R, Wong D, Wong EY, Yeo I, *et al.* Conversion to aflibercept for diabetic macular edema unresponsive to ranibizumab or bevacizumab. *Clin Ophthalmol* 2015;9:1715-8.
- Laiginhas R, Silva MI, Rosas V, Penas S, Fernandes VA, Rocha-Sousa A, *et al.* Aflibercept in diabetic macular edema refractory to previous bevacizumab: Outcomes and predictors of success. *Graefes Arch Clin Exp Ophthalmol* 2018;256:83-9.
- Klein KA, Cleary TS, Reichel E. Effect of intravitreal aflibercept on recalcitrant diabetic macular edema. *Int J Retina Vitreous* 2017;3:16. doi: 10.1186/s40942-017-0064-0.
- Bahrami B, Hong T, Schlub TE, Chang AA. Aflibercept for persistent diabetic macular edema: Forty-eight-week outcomes. *Retina* 2019;39:61-8.
- Ashraf M, Souka AA, ElKayal H. Short-term effects of early switching to ranibizumab or aflibercept in diabetic macular edema cases with non-response to bevacizumab. *Ophthalmic Surg Lasers Imaging Retina* 2017;48:230-6.
- Chen YY, Chang PY, Wang JK. Intravitreal aflibercept for patients with diabetic macular edema refractory to bevacizumab or ranibizumab: Analysis of response to aflibercept. *Asia Pac J Ophthalmol (Phila)* 2017;6:250-5.
- Rayat JS, Grewal PS, Whelan J, Tennant MT, Choudhry N. Canadian preference and trends survey results for anti-VEGF treatment of macular edema. *Can J Ophthalmol* 2016;51:233-7.
- Ooto S, Hangai M, Sakamoto A, Tsujikawa A, Yamashiro K, Ojima Y, *et al.* High-resolution imaging of resolved central serous chorioretinopathy using adaptive optics scanning laser ophthalmoscopy. *Ophthalmology* 2010;117:1800-9. 9.e1-2.
- Yadav NK, Jayadev C, Rajendran A, Nagpal M. Recent developments in retinal lasers and delivery systems. *Indian J Ophthalmol* 2014;62:50-4.
- Diabetic Retinopathy Clinical Research N. A randomized trial comparing intravitreal triamcinolone acetonide and focal/grid photocoagulation for diabetic macular edema. *Ophthalmology* 2008;115:1447-9. 9 e1-10.
- Gillies MC, Simpson JM, Gaston C, Hunt G, Ali H, Zhu M, *et al.* Five-year results of a randomized trial with open-label extension of triamcinolone acetonide for refractory diabetic macular edema. *Ophthalmology* 2009;116:2182-7.
- Do DV, Nguyen QD, Boyer D, Schmidt-Erfurth U, Brown DM, Vitti R, *et al.* One-year outcomes of the da Vinci Study of VEGF Trap-eye in eyes with diabetic macular edema. *Ophthalmology* 2012;119:1658-65.
- Sivaprasad S, Crosby-Nwaobi R, Heng LZ, Peto T, Michaelides M, Hykin P. Injection frequency and response to bevacizumab monotherapy for diabetic macular oedema (BOLT Report 5). *Br J Ophthalmol* 2013;97:1177-80.
- Aiello LP, Edwards AR, Beck RW, Bressler NM, Davis MD, Ferris F, *et al.* Factors associated with improvement and worsening of visual acuity 2 years after focal/grid photocoagulation for diabetic macular edema. *Ophthalmology* 2010;117:946-53.
- Kulikov AN, Sosnovskii SV, Berezin RD, Maltsev DS, Oskanov DH, Gribanov NA. Vitreoretinal interface abnormalities in diabetic macular edema and effectiveness of anti-VEGF therapy: An optical coherence tomography study. *Clin Ophthalmol* 2017;11:1995-2002.
- Chen YP, Wu AL, Chuang CC, Chen SN. Factors influencing

- clinical outcomes in patients with diabetic macular edema treated with intravitreal ranibizumab: Comparison between responder and non-responder cases. *Sci Rep* 2019;9:10952. doi: 10.1038/s41598-019-47241-1.
25. Bressler SB, Qin H, Beck RW, Chalam KV, Kim JE, Melia M, *et al.* Factors associated with changes in visual acuity and central subfield thickness at 1 year after treatment for diabetic macular edema with ranibizumab. *Arch Ophthalmol* 2012;130:1153-61.
  26. Ozturk BT, Kerimoglu H, Adam M, Gunduz K, Okudan S. Glucose regulation influences treatment outcome in ranibizumab treatment for diabetic macular edema. *J Diabetes Complications* 2011;25:298-302.
  27. Bansal AS, Khurana RN, Wieland MR, Wang PW, Van Everen SA, Tuomi L. Influence of glycosylated hemoglobin on the efficacy of ranibizumab for diabetic macular edema: A post hoc analysis of the RIDE/RISE trials. *Ophthalmology* 2015;122:1573-9.
  28. Spaide RF, Curcio CA. Anatomical correlates to the bands seen in the outer retina by optical coherence tomography: Literature review and model. *Retina* 2011;31:1609-19.
  29. Bahrami B, Hong T, Zhu M, Schlub TE, Chang A. Switching therapy from bevacizumab to aflibercept for the management of persistent diabetic macular edema. *Graefes Arch Clin Exp Ophthalmol* 2017;255:1133-40.
  30. Brown DM, Nguyen QD, Marcus DM, Boyer DS, Patel S, Feiner L, *et al.* Long-term outcomes of ranibizumab therapy for diabetic macular edema: The 36-month results from two phase III trials: RISE and RIDE. *Ophthalmology* 2013;120:2013-22.
  31. Heier JS, Korobelnik JF, Brown DM, Schmidt-Erfurth U, Do DV, Midena E, *et al.* Intravitreal aflibercept for diabetic macular edema: 148-week results from the VISTA and VIVID studies. *Ophthalmology* 2016;123:2376-85.
  32. Ross EL, Hutton DW, Stein JD, Bressler NM, Jampol LM, Glassman AR, *et al.* Cost-effectiveness of aflibercept, bevacizumab, and ranibizumab for diabetic macular edema treatment: Analysis from the diabetic retinopathy clinical research network comparative effectiveness trial. *JAMA Ophthalmol* 2016;134:888-96.