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

Ali Salimi1, Natalia Vila1, Milad Modabber2, Michael Kapusta1,2

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 ≥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 ± 10.7 years, an average of 16.8 ± 8.5 Bevacizumab injections prior to switching to Aflibercept, and mean follow-up duration of 11.8 ± 1.7 months following switching to Aflibercept. Best-corrected visual acuity (BCVA) improved significantly from 0.49 ± 0.13 to 0.41 ± 0.11 logMAR (P < 0.001), and central subfield thickness (CST) decreased by 119.4 µm from 409.4 ± 85.8 µm to 290.0 ± 64.5 µm (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 photoocoagulation for those with center-involved DME (CI-DME).1,2 Off-label use of Bevacizumab (Avastin®) has shown to be effective in treating DME;3 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 corticosteroids4 or an alternative anti-VEGF agent is usually a viable step.5

Aflibercept (Eylea®) 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.6 A few studies have investigated the outcomes related to switching to Aflibercept in DME patients refractory to Bevacizumab therapy7–9; 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.10 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.
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) ≥300 µm[10] 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 ≤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 µm and decreased intra-retinal reflectivity, hyper-reflective dots, hard exudes, 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 µm, medium: 250-500 µm, and large: >=500 µm). Cone outer segment tip (COST) status – an early marker of photoreceptor damage[16] – 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 >=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: \( \text{VAR} = 100 \times \log(\text{LogMAR}) \).

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 µm at follow-up with a reduction greater than 10% compared to baseline in the absence of sub-retinal fluid.[10]

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 ± 10.7 years, mean diabetes duration was 20.4 ± 11.7 years, and the average number of Bevacizumab injections prior to switching to Aflibercept was16.8 ± 8.5 (the last six of which were administered monthly). At baseline, the average BCVA was 0.49 ± 0.13 LogMAR, mean CST was 409.4 ± 85.8 µm, AMT was 324.3 ± 45.6 µm, and AMV was 11.7 ± 1.7 µl. 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 ± 1.2 weeks and a mean follow-up duration of 11.8 ± 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...
improved from 0.49 ± 0.13 LogMAR to 0.41 ± 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 µm (29% reduction), from 409.4 ± 85.8 µm to 290.0 ± 64.5 µm (P < 0.001, Eta-squared = 0.550) and 71% of eyes experienced a reduction greater than 50 µm. In addition, the overall edema in macula improved, as the AMT decreased by 10% from 324.3 ± 45.6 µm to 290.3 ± 29.5 µm (P = 0.001, Eta-squared = 0.434) and total macular volume reduced from 11.7 ± 1.7 µl to 10.5 ± 1.1 µl (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 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 ± 0.13 LogMAR and the mean CST was 405.0 ± 105.5 µm. At 1-year follow-up, BCVA improved by 3.3 letters to 0.48 ± 0.12 LogMAR, and CST decreased by 30% to 283.5 ± 75.9 µm. 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 ± 0.17 LogMAR and the mean CST was 356.0 ± 74.9 µm. At 1-year, BCVA improved by an average of 4.75 letters to 0.38 ± 0.05 LogMAR, and CST decreased by 11% to a mean of 317.0 ± 40.3 µm. Given the differences in intravitreal drug pharmacokinetics following pars plana vitrectomy, we compared the outcomes

| 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 |
| Epiretinal 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
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
two eyes (four right eyes and six left eyes) failed to meet the
inclusion criteria. Therefore, a total of 24 eyes were
included in our study. The demographic and clinical
characteristics of the included patients are listed in Table 1.

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

| Variables                                      | Baseline   | Follow-up | P     | Eta² |
|------------------------------------------------|------------|-----------|-------|------|
| Best-corrected visual acuity (LogMAR)          | 0.49±0.13  | 0.41±0.11 | <0.001* | 0.479 |
| Intraocular pressure (mmHg)                    | 17.0±3.7   | 17.5±4.2  | 0.507  | 0.021 |
| Central Subfield Thickness (µm)                | 409.4±85.8 | 290.0±64.5 | <0.001* | 0.550 |
| Average Macular Thickness (µm)                 | 324.3±45.6 | 290.3±29.5 | 0.001* | 0.434 |
| Total Macular Volumer (µl)                     | 11.7±1.7   | 10.5±1.1  | 0.001* | 0.413 |
| Diffuse retinal thickening, n (%)              | 24 (100%)  | 15 (63%)  | 0.002* |      |
| Hyper-reflective dots, n (%)                   | 24 (100%)  | 23 (96%)  | 0.500  |      |
| Intra-retinal cystoid space size (none: small <250 µm; medium=250-500 µm: large >=500 µm) | 0:8:8:8 | 5:5:9:5 | 0.029* |      |
| Hard exudates, n (%)                           | 21 (88%)   | 21 (88%)  | 1.000  |      |
| Cone outer segment tips (Distinct : Discernible: Obscured: Disrupted) | 3:1:6:14 | 3:9:0:12 | 0.091  |      |
| Ellipsoid zone disruption (No: 0-25% : 25-50% : >50%) | 8:5:8:3 | 16:2:4:2 | 0.042* |      |
| Epiretinal membrane, n (%)                     | 12 (50%)   | 12 (50%)  | 1.000  |      |
| External limiting membrane disruption, n (%)   | 5 (21%)    | 6 (25%)   | 0.500  |      |
| Vitreomacular adhesion, n (%)                  | 4 (17%)    | 3 (13%)   | 0.500  |      |
| Sponge-like retinal swelling, n (%)            | 1 (4%)     | 1 (4%)    | 1.000  |      |
| Sub-retinal fluid, n (%)                       | 1 (4%)     | 0 (0%)    | 0.500  |      |
| Vitreomacular traction, n (%)                  | 0 (0%)     | 0 (0%)    | 1.000  |      |
| Tractional retinal detachment, n (%)           | 0 (0%)     | 0 (0%)    | 1.000  |      |

The continuous and discrete data are presented as mean±standard deviation and frequency (percentage), respectively. *Based on the repeated measure ANOVA. †Based on the McNemar test. ‡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. η², effect size. There was a significant decrease in CST (P < 0.001), AMT (P = 0.001), and AMV (P = 0.001)

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
ten 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 ± 42.14 μm and a follow-up CST of 244.7 ± 37.1 μm (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 ($β = 0.742$, $P = 0.001$), 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 ($β = 0.439$, $P = 0.035$).

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 ($β = 0.667$, $P = 0.001$) and lower HbA1C ($β = 0.395$, $P = 0.039$) 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 mainstream 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.[23] 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.[19] Concern regarding the long-term efficacy and the safety of corticosteroids such as cataract formation and intraocular pressure spikes[20] 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.[5,20]

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.[21,22] In cases of poor response, switching to a different therapy, such as corticosteroids[21] or an alternative anti-VEGF agent is usually a viable step.[41] A few have investigated the response to switching to Aflibercept in a chronic DME population refractory to longer-term Bevacizumab therapy[6‑14]; 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.[10,12,13] Vision gain in our population was well within the 3.9 to 4.5 letters range previously reported[10,12,13] 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).[10] 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,[23] 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
required Vitrectomy. In line with the findings of Kulikov and colleagues,[23] 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.[24,25] 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.[26,27] In line with the findings of a few other studies,[28] 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.[29]

The significant role of COST in photoreceptor function has been well documented, and COST disruption has been linked to photoreceptor dysfunction.[30] 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.[28] Similar to Bahrami’s findings,[29] 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,[30,31] which in turn might have limited visual gains. Anti-VEGF agents have rarely been associated with certain ocular and systemic adverse events.[12,29] 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.[32] 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

### 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 | 0.242 |
| 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 $P<0.05$. 

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 Afibercept. 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 Afibercept 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 Afibercept in DME patients with refractory edema and insufficient data for predictors of response[10,12,13] 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 Afibercept 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**

1. 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.

2. 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.

3. 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.

4. Takamura Y, Ohkoshi K, Murata T. New strategies for treatment of diabetic macular edema. J Ophthalmol 2018;2018:4292154. doi: 10.1155/2018/4292154.

5. Korobelnik JF, Do DV, Schmidt-Erfurth U, Boyer DS, Holz FG, Heier JS, et al. Intravitreal afibercept for diabetic macular edema. Ophthalmology 2014;121:2247-54.

6. Wood EH, Kauth PA, Moshfeghi DM, Leng T. Short-term outcomes of afibercept therapy for diabetic macular edema in patients with incomplete response to ranibizumab and/or bevacizumab. Ophthalmic Surg Lasers Imaging Retina 2015;46:950-4.

7. Shah CP, Heier JS. Afibercept 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.

8. Rahimy E, Shahlaee A, Khan MA, Ying GS, Maguire MJ, Ho AC, et al. Conversion to afibercept after prior anti-VEGF therapy for persistent diabetic macular edema. Am J Ophthalmol 2016;164:118-27.e2.

9. Lim LS, Ng WY, Mathur R, Wong D, Wong EY, Yeo I, et al. Conversion to afibercept for diabetic macular edema unresponsive to ranibizumab or bevacizumab. Clin Ophthalmol 2015;9:1715-8.

10. Laiginhas R, Silva ML, Rosas V, Penas S, Fernandes VA, Rocha-Sousa A, et al. Afibercept in diabetic macular edema refractory to previous bevacizumab: Outcomes and predictors of success. Graefes Arch Clin Exp Ophthalmol 2018;256:83-9.

11. Klein KA, Cleary TS, Reichel E. Effect of intravitreal afibercept on recalcitrant diabetic macular edema. Int J Retina Vitreous 2017;3:16. doi: 10.1186/s40942-017-0046-0.

12. Bahrami B, Hong T, Schulte TE, Chang AA. Afibercept for persistent diabetic macular edema: Forty-eight-week outcomes. Retina 2019;39:61-8.

13. Ashraf M, Souka AA, ElKayal H. Short-term effects of early switching to ranibizumab or afibercept in diabetic macular edema cases with non-response to bevacizumab. Ophthalmic Surg Lasers Imaging Retina 2017;48:230-6.

14. Chen YY, Chang PY, Wang JK. Intravitreal afibercept for patients with diabetic macular edema refractory to bevacizumab or ranibizumab: Analysis of response to afibercept. Asia Pac J Ophthalmol (Philia) 2017;6:250-5.

15. 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.

16. 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, e1-e2.

17. Yadav NK, Jayadev C, Rajendran A, Naggal M. Recent developments in retinal lasers and delivery systems. Indian J Ophthalmol 2014;62:50-4.

18. 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, e9-110.

19. 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.

20. 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.

21. Sivaprasad S, Crosby-Nwaoibi R, Heng LZ, Peto T, Michaelides M, Hykin P. Injection frequency and response to bevacizumab monotherapy for diabetic macular oedema (BOLT Report S). Br J Ophthalmol 2013;97:1177-80.

22. 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.

23. Kulikov AN, Sosnovskiy SV, Berezin RD, Maltese DS, Oskanov DH, Gribov AO. Vitreoretinal interface abnormalities in diabetic macular edema and effectiveness of anti-VEGF therapy: An optical coherence tomography study. Clin Ophthalmol 2017;11:1995-2002.

24. 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.