Conversion to Aflibercept After Prior Anti-VEGF Therapy for Persistent Diabetic Macular Edema

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• PURPOSE: To evaluate the short-term functional and anatomic outcomes of patients with persistent diabetic macular edema (DME) who were converted from bevacizumab and/or ranibizumab to aflibercept.

• DESIGN: Retrospective, interventional, noncomparative, consecutive case series.

• METHODS: Only eyes treated with at least 4 consecutive injections of ranibizumab/bevacizumab spaced 4–6 weeks apart prior to conversion and with at least 2 aflibercept injections afterward were considered for inclusion. Pertinent patient demographic, examination, and treatment data were extracted from clinical charts and tabulated for analysis.

• RESULTS: Fifty eyes of 37 patients were included. Eyes received a mean of 13.7 bevacizumab/ranibizumab injections prior to conversion, followed by 4.1 aflibercept injections over 4.6 months of subsequent follow-up. The mean logMAR visual acuity at the pre-switch visit was 0.60 ± 0.43 (Snellen equivalent, 20/80). This improved to 0.55 ± 0.48 (Snellen equivalent, 20/70) by the second visit after conversion, corresponding to a mean logMAR change of −0.05 ± 0.22 ($P = .12$). The average central macular thickness from the pre-switch spectral-domain optical coherence tomography scan was 459.2 ± 139.2 μm. This significantly improved to 348.7 ± 107.8 μm by the second visit following conversion, reflecting a mean decrease of 112 ± 141 μm ($P < .0001$). The mean intraocular pressure (IOP) recorded at the pre-switch visit was 15.1 ± 3.3 mm Hg. At the second follow-up after converting to aflibercept, the IOP averaged 14.9 ± 3.2 mm Hg, with a mean decrease of 0.2 ± 3.0 mm Hg ($P = .63$).

• CONCLUSIONS: Conversion to aflibercept for persistent DME resulted in significant anatomic improvements. While trends towards improved visual acuity and reduction in IOP were observed, these were not statistically significant. (Am J Ophthalmol 2016;164:118–127.

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DIABETIC MACULAR EDEMA (DME) IS THE LEADING cause of visual impairment in patients with diabetic retinopathy.[1] In 2010, approximately 20.6 million out of a projected 92.6 million adults with diabetic retinopathy worldwide were estimated to have concurrent DME.[2] This global healthcare burden will likely continue to increase at alarming rates, as some models estimate the number of diabetics will double by the year 2030.[3]

With the Early Treatment Diabetic Retinopathy Study (ETDRS) in the 1980s,[4] macular laser photocoagulation became the mainstay of DME management, and it remained the standard of care in the decades that followed. The advent of intravitreal pharmacotherapy agents, primarily driven by the class of vascular endothelial growth factor (VEGF) inhibitors, has since revolutionized how this condition is treated. Validated through the RISE and RIDE phase 3 clinical trials,[5] ranibizumab (Lucentis; Genentech, South San Francisco, California, USA) became the first VEGF inhibitor approved by the Food & Drug Administration (FDA) for this indication in 2012. While off-label, bevacizumab (Avastin; Genentech) has been evaluated through smaller trials, such as the BOLT study.[6] Most recently, aflibercept (Eylea; Regeneron, Tarrytown, New York) gained FDA approval to treat DME in July 2014 with the VIVID and VISTA phase 3 clinical trials.[7,8]

While there is ample evidence supporting the safety and efficacy of the 3 anti-VEGF agents in the management of DME, a head-to-head comparison only recently became available when the Diabetic Retinopathy Clinical Research Network (DRCR) published the 1-year outcomes of its Comparative Effectiveness Study of Intravitreal Aflibercept, Bevacizumab, and Ranibizumab for DME (Protocol T).[9] The results demonstrated that when baseline visual acuity (VA) loss was mild (≥20/40), there was no clinical difference between the 3 medications. However, when the initial acuity loss was more severe (≤20/50), a greater visual benefit was derived from aflibercept.[9]

Since the FDA approval of aflibercept for DME, and in light of Protocol T's findings, many retinal specialists are converting eyes from ranibizumab or bevacizumab to aflibercept with the goal of optimizing treatment outcomes, particularly in cases of refractory DME. In the current study, we evaluated the short-term functional and

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anatomic responses of patients with persistent DME after multiple previous anti-VEGF injections that were converted to aflibercept therapy.

METHODS

FOLLOWING APPROVAL FROM THE INSTITUTIONAL REVIEW Board at Wills Eye Hospital, a retrospective, interventional, noncomparative, consecutive case series of patients treated for DME at the Retina Service of Wills Eye Hospital and the outpatient offices of Mid Atlantic Retina was performed. Research adhered to the tenets of the Declaration of Helsinki and was conducted in accordance with regulations set forth by the Health Insurance Portability and Accountability Act.

Electronic billing records of all patients with DME (International Classification of Diseases, 9th revision code 362.07) seen between August 1, 2014 and March 31, 2015 were evaluated to identify eyes previously treated with ranibizumab (0.3 mg) and/or bevacizumab (1.25 mg) that were subsequently converted to aflibercept (2.0 mg) therapy. Eligible participants were aged 18 years or older with a history of diabetes mellitus (type 1 or type 2), baseline evidence of clinically significant macular edema as defined by the ETDRS,[4] and commensurate center-involving DME (central macular thickness [CMT] ≥300 μm) by spectral-domain optical coherence tomography (SD OCT) imaging. Indications for transitioning to aflibercept included persistent exudative fluid on examination and/or SD OCT as determined by the treating physician. Persistent DME was defined as no reduction, incomplete resolution, or an increase in central subfield thickening by SD OCT, necessitating additional anti-VEGF therapy at the time of conversion. Only eyes treated with at least 4 consecutive injections of ranibizumab/bevacizumab performed at the exact same interval (eg, every 4, 5, or 6 weeks) prior to conversion and with at least 2 aflibercept injections afterward at that same interval were considered for study inclusion.

Patients were excluded if they had any of the following treatments during the 6-month period prior to anti-VEGF conversion or after: intravitreal or sub-Tenon injections of corticosteroids, corticosteroid implants, focal/grid macular laser photocoagulation, panretinal photocoagulation, cataract surgery, or pars plana vitrectomy. Additionally, individuals were excluded if they had any of the following concomitant ocular diseases aside from nonproliferative diabetic retinopathy in the treated eye: age-related macular degeneration, central/branch retinal vein occlusion, choroidal neovascularization, history of ocular trauma, or any other history of prior intraocular surgery (with the exception of cataract surgery >6 months prior to conversion). Treatment schedules as well as injection methods were at the discretion of the supervising retinal specialist. However, in order to mitigate any confounding effect from injection frequency, only eyes maintained on the same treatment interval after switching were included in this series. The pre-switch visit was defined as the date when conversion to aflibercept occurred.

Pertinent patient demographic, examination, and treatment data were extracted from clinical charts and tabulated for analysis. Snellen VA measurements were collected from patients using their most up-to-date distance correction or best pinhole correction. Intraocular pressure (IOP) recordings were performed using the handheld Tono-Pen XL (Medtronic Solan, Jacksonville, Florida, USA) prior to dilation and injection at each visit. Ancillary SD OCT scans obtained using the Heidelberg Spectralis (Heidelberg Engineering, Heidelberg, Germany) were reviewed at each visit to document the presence/absence of intraretinal/subretinal fluid and associated vitreoretinal interface abnormalities (vitreomacular adhesion [VMA], vitreomacular traction [VMT], or epiretinal membrane [ERM]). SD OCT images were interpreted independently by 2 experienced reviewers (E.R., A.S.). CMT values were obtained using the integrated software.

• **STATISTICAL ANALYSIS:** Snellen VA was converted into logarithm of the minimal angle of resolution (logMAR) scores for statistical analysis. For evaluating the effect of switching to aflibercept on VA, CMT, and IOP, we performed the comparison of these outcomes at the pre-switch visit vs post-switch visits using generalized linear models. The intereye correlation was accounted for using generalized estimating equations.[10] Similarly, we also performed the comparison of VA change from the pre-switch visit between eyes with VA ≥20/40 vs ≤20/50, and between eyes with vs without concurrent ERM present at the time of conversion. The outcomes at each visit were summarized as mean ± standard deviation. Statistical significance was set at $P < .05$. All analyses were performed using SAS v9.4 (SAS Institute Inc, Cary, North Carolina, USA).

RESULTS

SIXTY-FIVE EYES WERE TRANSITIONED FROM BEVACIZUMAB, ranibizumab, or both to aflibercept between August 1, 2014 and March 31, 2015. A total of 15 eyes were excluded from the study for the following reasons: 9 eyes had an irregular treatment interval and follow-up schedule after conversion to aflibercept and 6 eyes reverted back to ranibizumab or bevacizumab therapy at some point after converting to aflibercept. Ultimately, a total of 50 eyes from 37 consecutive individuals with DME meeting inclusion criteria for the study were evaluated. The mean patient age ± standard deviation was 69.9 ± 9.4 years (range, 44–88 years). Baseline

TABLE 1. Demographics and Clinical Characteristics of Patients With Diabetic Macular Edema Converted From Prior Anti–Vascular Endothelial Growth Factor Therapy to Aflibercept (N = 50 Eyes, 37 Patients)

Age (y)	
Mean (SD)	69.6 (9.4)
Median (min, max)	71 (44, 88)
Sex	
Male	19 (51.4%)
Female	18 (48.6%)
Duration of known diabetes (y)	
Mean (SD)	20.4 (10.3)
Median (min, max)	21 (1, 43)
Hemoglobin A1c level	
Mean (SD)	7.0 (0.9)
Median (min, max)	7.1 (5.6, 9.5)
Hypertension	
No	9 (24.3%)
Yes	28 (75.7%)
Lens status	
IOL	29 (58.0%)
Phakic	21 (42.0%)
Number of anti-VEGF injections pre-switch	
Mean (SD)	13.7 (6.1)
Median (min, max)	13 (4, 30)
Anti-VEGF regimen pre-switch	
Ranibizumab only	36 (72.0%)
Bevacizumab only	2 (4.0%)
Both	12 (24.0%)
Other prior treatments (>6 months from conversion)	
Panretinal photocoagulation	14 (28%)
Focal macular laser	22 (44%)
Intravitreal triamcinolone	4 (8%)
Pars plana vitrectomy	3 (6%)

IOL = intraocular lens; SD = standard deviation; VEGF = vascular endothelial growth factor.

demographics and ocular characteristics are outlined in Table 1.

• **TREATMENT CHARACTERISTICS:** The average number of anti-VEGF injections the cohort received before transitioning to aflibercept was 13.7 ± 6.1 (median, 13; range, 4–30 injections). Thirty-six eyes (72%) had been treated with ranibizumab exclusively, 2 eyes (4%) were treated only with bevacizumab, and the remaining 12 eyes (24%) received some combination of both intravitreal agents. After conversion, a mean number of 4.1 ± 1.7 aflibercept injections (median, 4; range, 2–9 injections) were then performed over an average follow-up period of 4.6 ± 1.7 months (median, 4.5; range, 2–9 months). Clinical follow-up was available for all eyes through the second visit following aflibercept conversion, which averaged 2.5 ± 0.5 months (median, 2.3; range, 2–3 months). As such, this time point was used for primary outcome analysis. Beyond this visit, 29 eyes (58%) had 3 or more post-switch follow-ups, 22 (44%) had at least 4 follow-ups, and 10 (20%) had at least 5 follow-ups.

• **VISUAL OUTCOMES AFTER SWITCHING TO AFLIBERCEPT:** The mean logMAR VA of the affected eye at the pre-switch visit was 0.60 ± 0.43 (Snellen equivalent, 20/80). This improved to 0.55 ± 0.48 (Snellen equivalent, 20/70) by the second visit following conversion, corresponding to a mean logMAR change of −0.05 ± 0.22 ($P = .12$). Notably, after 2 injections of aflibercept, 25 eyes (50%) had gained ≥1 line of vision, of which 11 (11/50; 22%) gained ≥2 lines and 6 (6/50; 12%) gained ≥3 lines. Consecutive VA measurements at subsequent visits are outlined in Table 2 and Figure 1. While there was a trend toward improved mean VA during the course of treatment, this was not statistically significant overall. However, of note, the cohort that completed at least 4 post-switch visits (22 eyes, 44%) did experience a significant improvement in vision from a mean logMAR VA of 0.80 ± 0.52 at the pre-switch visit to 0.65 ± 0.46 at the fourth visit following conversion ($P = .003$, Figure 2).

Subgroup analysis was conducted to determine the impact of the pre-switch VA—separated into VA ≥20/40 (16 eyes) or ≤20/50 (34 eyes)—on the visual response to change in therapy (Table 3). After 2 aflibercept injections had been administered, no significant difference in VA change was observed between both groups. Further analysis was then performed to determine the effect of macular ERM on the visual response after conversion (Table 3). Similarly, no significant difference was noted in either baseline pre-switch VA or the visual outcomes after 2 injections based on presence (18 eyes, 36%) or absence (32 eyes, 64%) of concurrent ERM on SD OCT.

• **ANATOMIC OUTCOMES AFTER SWITCHING TO AFLIBERCEPT:** The average CMT from the pre-switch SD OCT scan was 459.2 ± 139.2 μm (median, 411; range, 382–549 μm). This significantly improved to 348.7 ± 107.8 μm (median, 351; range, 282–387 μm) by the second visit following conversion, reflecting a mean decrease of 112 ± 141 μm ($P < .0001$). Central macular thickness measurements at consecutive visits are outlined in Table 4 and Figure 1. At each subsequent visit after the initial conversion to aflibercept, a statistically significant improvement in CMT compared to the pre-switch value was measured. Altogether, 28 eyes (56%) demonstrated improvement of DME on SD OCT at their most recent follow-up, defined as both a reduction in CMT and decrease in retinal thickness, intraretinal cysts, and/or subretinal fluid as determined by the interpreters (E.R., A.S.); 12 eyes (24%) had complete resolution of fluid; while 10 eyes (20%) remained unchanged (Figure 3). The number of eyes with vitreoretinal interface

TABLE 2. Visual Acuity Over Time Before and After Conversion to Aflibercept for Diabetic Macular Edema

	1 Visit Pre-switch	Pre-switch Visit	First Visit Post-switch	Second Visit Post-switch	Third Visit Post-switch	Fourth Visit Post-switch
Eyes with data	50	50	50	50	29	22
VA levels, n (%)						
20/25	4 (8.0)	3 (6.0)	3 (6.0)	6 (12.0)	1 (3.5)	2 (9.1)
20/30	9 (18.0)	4 (8.0)	11 (22.0)	7 (14.0)	3 (10.3)	3 (13.6)
20/40	7 (14.0)	9 (18.0)	2 (4.0)	7 (14.0)	5 (17.2)	1 (4.6)
20/50	4 (8.0)	6 (12.0)	7 (14.0)	6 (12.0)	2 (6.9)	2 (9.1)
20/60	5 (10.0)	4 (8.0)	9 (18.0)	6 (12.0)	4 (13.8)	3 (13.6)
20/70	2 (4.0)	3 (6.0)	1 (2.0)	2 (4.0)	1 (3.5)	1 (4.6)
20/80	0	4 (8.0)	4 (8.0)	3 (6.0)	3 (10.3)	2 (9.1)
20/100	6 (12.0)	5 (10.0)	1 (2.0)	3 (6.0)	2 (6.9)	0
20/200	8 (16.0)	9 (18.0)	8 (16.0)	7 (14.0)	5 (17.2)	6 (27.3)
20/300	0	0	0	0	1 (3.5)	0
20/350	1 (2.0)	0	0	0	0	0
20/400	1 (2.0)	1 (2.0)	1 (2.0)	0	1 (3.5)	1 (4.6)
CF	3 (6.0)	2 (4.0)	3 (6.0)	3 (6.0)	1 (3.5)	1 (4.6)
Mean (SD) logMAR VA	0.60 (0.48)	0.60 (0.43)	0.59 (0.47)	0.55 (0.48)		
Median (Q1, Q3) logMAR VA	0.5 (0.2, 1.0)	0.5 (0.3, 0.7)	0.5 (0.2, 0.7)	0.4 (0.2, 0.7)		
VA change from pre-switch visit						
Mean (SD)			−0.01 (0.2)	−0.05 (0.22)	−0.06 (0.20)	−0.14 (0.23)
P value from paired *t* test for comparison of mean			.63	.12	.09	.003
≥3 lines gain, n (%)			4 (8.0)	6 (12.0)	4 (13.8)	4 (18.2)
1–2 lines gain, n (%)			15 (30.0)	19 (38.0)	5 (17.2)	7 (31.8)
Within 1 line change, n (%)			21 (42.0)	16 (32.0)	14 (48.3)	10 (45.5)
1–2 lines loss, n (%)			5 (10.0)	7 (14.0)	6 (20.7)	1 (4.6)
≥3 lines loss, n (%)			5 (10.0)	2 (4.0)	0 (0)	0 (0)

Q1 = quartile 1; Q3 = quartile 3; SD = standard deviation; VA = visual acuity.

abnormalities (VMA, VMT, and ERM) remained stable during the course of therapy (Table 4).

• **INTRAOCULAR PRESSURE AFTER SWITCHING TO AFLIBERCEPT:** The mean IOP recorded at the pre-switch visit was 15.1 ± 3.3 mm Hg (median, 15; range, 13–17 mm Hg). At the second follow-up after conversion, the IOP averaged 14.9 ± 3.2 mm Hg (median, 14; range, 11–16 mm Hg), with a mean decrease of 0.2 ± 3.0 mm Hg ($P = .63$). Sequential IOP measurements at each visit are outlined in Table 5 and Figure 1. Notably, while IOP remained relatively stable during the treatment course early on, a decline of 1.5 mm Hg was observed in the 22 eyes with follow-up through the fourth visit after conversion ($P = .04$, Figure 2).

• **ADVERSE EVENTS:** After anti-VEGF conversion, 204 aflibercept injections were administered in this study. No ocular adverse events, including endophthalmitis, uveitis, retinal detachment, retinal pigment epithelial tears, submacular hemorrhage, or sustained elevated intraocular pressure requiring topical ocular hypertensive drops, were observed. Furthermore, no systemic thromboembolic adverse events (eg, myocardial infarction, transient ischemic attack, or cerebrovascular accident) occurred during the study period.

DISCUSSION

WHILE THERE IS EXTENSIVE LITERATURE ON OUTCOMES OF aflibercept conversion in the treatment of neovascular age-related macular degeneration (AMD),[11–13] this study, to our knowledge, represents one of the first "real-world" assessments of aflibercept for treating DME in a cohort of eyes having previously received chronic anti-VEGF therapy. A similar, but smaller study of 14 eyes corroborated the anatomic improvements we observed in our series after conversion to aflibercept in the setting of DME with incomplete response to ranibizumab and/or bevacizumab.[14] In comparison, Protocol T excluded eyes with a history of anti-VEGF injections within the previous 12 months prior to study participation, resulting in a vast majority of study

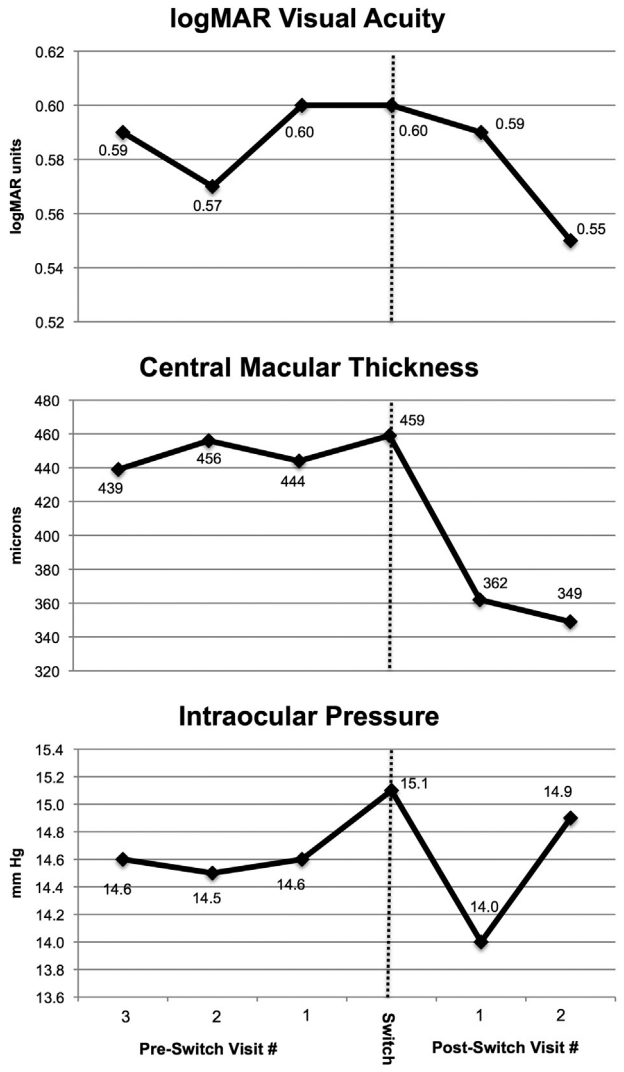

FIGURE 1. Comparison of visual acuity, central macular thickness, and intraocular pressure before and after conversion to aflibercept for diabetic macular edema through first 2 post-switch visits (n = 50 eyes). Dashed line indicates visit where switch to aflibercept occurred.

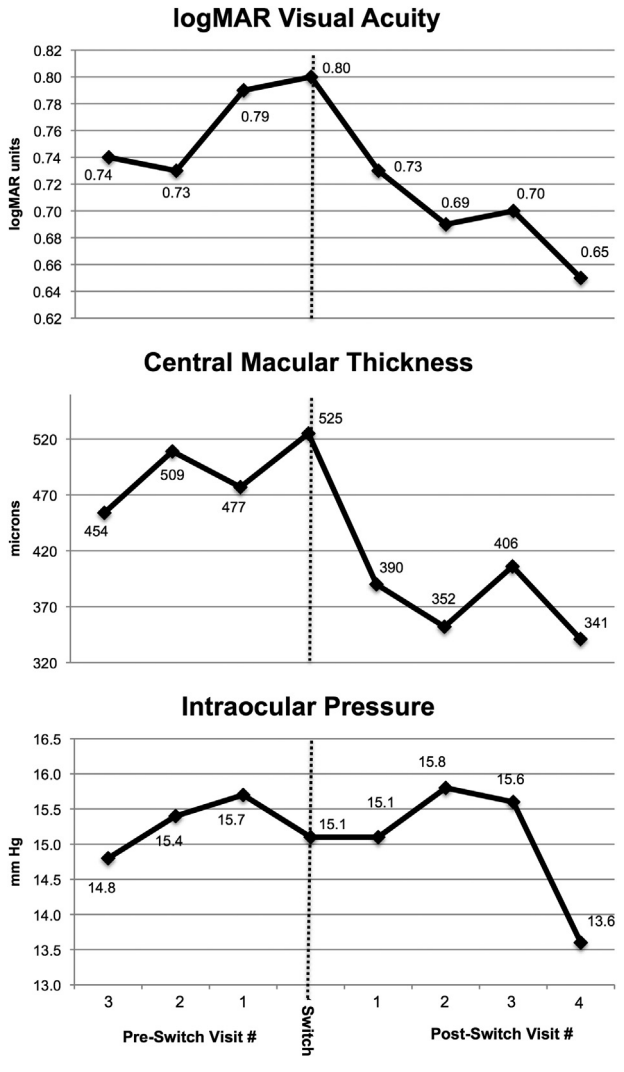

FIGURE 2. Comparison of visual acuity, central macular thickness, and intraocular pressure before and after conversion to aflibercept for diabetic macular edema through first 4 post-switch visits (n = 22 eyes). Dashed line indicates visit where switch to aflibercept occurred.

participants being treatment-naïve (576 of 660 eyes, 87.3%).[9] Meanwhile, VIVID and VISTA excluded those having received anti-VEGF therapy in the study eye (VISTA) or in either eye (VIVID) within a shorter 3-month period prior to enrollment. As a result, 93.5% of eyes in VIVID and 57.1% of eyes in VISTA were treatment-naïve.[7] The results of our study address a challenging scenario clinicians are encountering on an increasingly frequent basis regarding the optimal management of patients with persistent DME. Based on the significant, rapid anatomic improvement we observed, the option to switch these patients to aflibercept therapy may be an appealing initial alternative to continuing ranibizumab/bevacizumab injections or trying intravitreal/periocular steroids.

The considerable anatomic improvement demonstrated after converting to aflibercept may be explained by several factors. First, aflibercept has been shown to bind VEGF-A with over 100-fold greater affinity than either ranibizumab or bevacizumab.[15,16] Increased levels of VEGF-A are known to result in VEGF receptor 2–mediated breakdown of the internal/inner blood-retinal barrier (eg, vascular endothelium), leading to DME formation.[17] The superior binding affinity of aflibercept may theoretically lead to a more sustained VEGF-A inhibition, especially in the setting of ischemic retinovascular diseases like diabetic retinopathy, where the VEGF load is high.[18,19] Second, the pharmacodynamic properties between aflibercept and ranibizumab/bevacizumab invariably differ from one another. Unlike ranibizumab or bevacizumab, aflibercept

TABLE 3. Overall Visual Response in the First 2 Visits After Conversion to Aflibercept for Diabetic Macular Edema, and by Subgroups of Epiretinal Membrane and Baseline Visual Acuity

	ERM Pre-switch			Baseline VA Pre-switch		
	No (n = 32)	Yes (n = 18)	*P* Value[a]	≥20/40 (n = 16)	≤20/50 (n = 34)	*P* Value[a]
VA at Pre-switch Visit						
Mean (SD) logMAR VA	0.50 (0.49)	0.62 (0.31)	.78	0.24 (0.06)	0.77 (0.42)	<.0001
VA change from pre-switch to first visit post-switch						
Mean (SD)	0.01 (0.22)	−0.06 (0.15)	.16	−0.01 (0.12)	−0.02 (0.23)	.80
≥3 lines gain, n (%)	2 (6.3)	2 (11.1)		0 (0.0)	4 (11.8)	
2 lines gain, n (%)	4 (12.5)	2 (11.1)		2 (12.5)	4 (11.8)	
1 line gain, n (%)	6 (18.8)	3 (16.7)		4 (25.0)	5 (14.7)	
<1 line change, n (%)	11 (34.4)	10 (55.6)		5 (31.3)	16 (47.1)	
1 line loss, n (%)	3 (9.4)	0 (0.0)		3 (18.8)	0 (0.0)	
2 lines loss, n (%)	2 (6.3)	0 (0.0)		2 (12.5)	0 (0.0)	
≥3 lines loss, n (%)	4 (12.5)	1 (5.6)		0 (0.0)	5 (14.7)	
VA change from pre-switch to second visit post-switch						
Mean (SD)	−0.04 (0.24)	−0.07 (0.17)	.58	−0.03 (0.11)	−0.06 (0.25)	.47
≥3 lines gain, n (%)	3 (9.4)	3 (16.7)		0 (0.0)	6 (17.7)	
2 lines gain, n (%)	2 (6.3)	3 (16.7)		2 (12.5)	3 (8.8)	
1 line gain, n (%)	12 (37.5)	2 (11.1)		4 (25.0)	10 (29.4)	
<1 line change, n (%)	10 (31.3)	6 (33.3)		7 (43.8)	9 (26.5)	
1 line loss, n (%)	2 (6.3)	3 (16.7)		2 (12.5)	3 (8.8)	
2 lines loss, n (%)	2 (6.3)	0 (0.0)		1 (6.3)	1 (2.9)	
≥3 lines loss, n (%)	1 (3.1)	1 (5.6)		0 (0.0)	2 (5.9)	

ERM = epiretinal membrane; VA = visual acuity; SD = standard deviation.
[a]For comparison of mean using paired *t* test for paired data for overall change from baseline or 2-group *t* test for comparison between 2 subgroups.

TABLE 4. Anatomic Outcomes Over Time Before and After Conversion to Aflibercept for Diabetic Macular Edema

	1 Visit Pre-switch	Pre-switch Visit	First Visit Post-switch	Secnd Visit Post-switch	Third Visit Post-switch	Fourth Visit Post-switch
Eyes with data	50	50	50	48	28	22
CMT (μm)						
Mean (SD)	444 (131)	459 (139)	362 (118)	349 (108)		
Median (Q1, Q3)	411 (382, 549)	411 (382, 549)	361 (296, 409)	351 (282, 387)		
Change from pre-switch visit						
Mean (SD)			−95 (130)	−112 (141)	−117 (110)	−184
P value			<.0001	<.0001	<.0001	.0003
ERM, n (%)						
No	32 (64.0)	32 (64.0)	32 (64.0)	28 (58.3)	18 (64.3)	13 (59.1)
Yes	18 (36.0)	18 (36.0)	18 (36.0)	20 (41.7)	10 (35.7)	9 (40.9)
VMT, n (%)						
VMA	10 (20.0)	10 (20.0)	10 (20.0)	4 (8.3)	3 (1.1)	3 (13.6)
VMT	2 (4.0)	2 (4.0)	2 (4.0)	4 (8.3)	1 (0.4)	1 (4.6)

CMT = central macular thickness; ERM = epiretinal membrane; Q1 = quartile 1; Q3 = quartile 3; SD = standard deviation; VMA = vitreomacular adhesion; VMT = vitreomacular traction.

additionally targets VEGF-B and placental growth factor (PlGF).[15,20,21] Patients with diabetic retinopathy have been shown to have high vitreous levels of PlGF,[22] and this compound has been specifically implicated in the pathogenesis of DME.[23–26] By inducing VEGF receptor 1–mediated rupture of the RPE junctions, PlGF is thought to potentiate DME formation by facilitating breakdown of the external/outer blood-retinal barrier.[23]

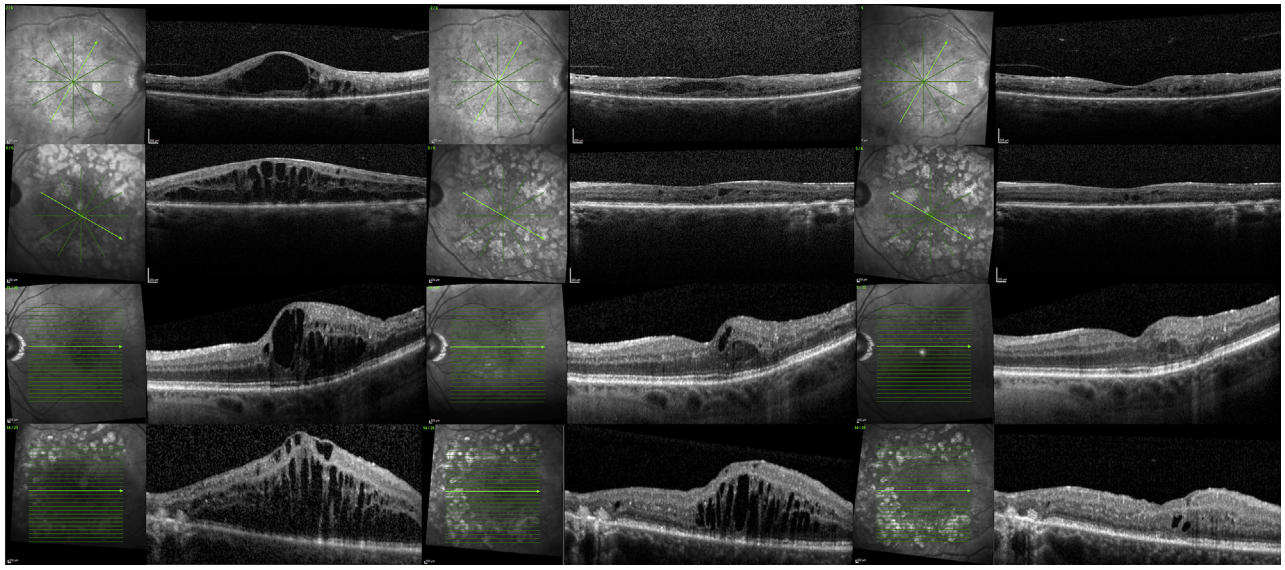

FIGURE 3. Anatomic improvement after conversion to aflibercept for diabetic macular edema. Four representative cases of persistent diabetic macular edema previously receiving chronic anti–vascular endothelial growth factor therapy with corresponding spectral-domain optical coherence tomography images at the pre-switch visit (Left column), first visit following conversion (Middle column), and second visit following conversion (Right column).

TABLE 5. Intraocular Pressure Over Time Before and After Conversion to Aflibercept for Diabetic Macular Edema

	1 Visit Pre-switch	Pre-switch Visit	First Visit Post-switch	Second Visit Post-switch	Third Visit Post-switch	Fourth Visit Post-switch
Eyes with data	50	50	50	50	29	22
IOP (mm Hg)						
Mean (SD)	14.6 (3.0)	15.1 (3.3)	14.0 (3.4)	14.9 (3.2)		
Median (Q1, Q3)	14 (12, 17)	15 (13, 17)	14 (11, 16)	15 (13, 17)		
Change from pre-switch visit						
Mean (SD)			−1.1 (3.7)	−0.2 (3.0)	−0.07 (3.9)	−1.5 (3.3)
Median (Q1, Q3)			−1.0 (−4.0, 1.0)	0 (−2.0, 1.0)	−0.5 (−3.0, 3.0)	−1.5 (−3.0, 0)
P value			.08	.68	.93	.04

IOP = intraocular pressure; Q1 = quartile 1; Q3 = quartile 3; SD = standard deviation.

In addition, PlGF may indirectly activate VEGF receptor 2, further contributing to the disruption of the internal/inner blood-retinal barrier.[26,27]

Lastly, another potential explanation for the anatomic success relates to inherent patient factors rather than properties of aflibercept. Numerous studies have demonstrated that patients treated with repetitive ranibizumab/bevacizumab injections over time may demonstrate tachyphylaxis, or a diminished therapeutic response, to those respective agents.[28,29] The mechanisms underlying this phenomenon are thought to be multifactorial, involving cellular (eg, upregulation of VEGF from local macrophages, altered expression of surface receptors, or activation of alternate angiogenic signaling pathways), metabolic (eg, alterations in pharmacokinetics with changes in drug absorption, distribution, and metabolism), and/or humoral responses.[26,28] After intravitreal injection, a systemic immune reaction to anti-VEGF molecules that have entered the patient's serum, as well as a local response secondary to a compromised blood-retinal barrier, may contribute to the formation of neutralizing antibodies.[28,30] Unlike aflibercept, both ranibizumab and bevacizumab contain murine antibody components, which may theoretically incite the systemic immune response. Switching to aflibercept may overcome any tolerance that had developed to previous anti-VEGF proteins, at least in the short term.

The morphologic improvements we observed, however, did not translate into a significant visual benefit during the short course of follow-up. One plausible explanation for this disparity may be the irreversible functional damage caused by long-standing DME.[31] This is reasonable in the

context of our study, as these eyes were not treatment-naïve and had received, on average, over 13 anti-VEGF injections prior to starting aflibercept. In fact, 35 eyes (70%) had received over 10 injections during at least a 1-year period prior to conversion, of which 11 eyes (11/50; 22%) had received over 20 injections. Furthermore, we cannot rule out a contributing effect from other complications of diabetic retinopathy (eg, macular ischemia) that may limit VA outcomes. Alternatively, it is possible that the short-term follow-up available was not sufficient to uncover a delayed-onset recovery in vision. Indeed, previous investigations have suggested that functional visual improvement may lag behind anatomic resolution of fluid in DME.[32] It is interesting to note that the group of 22 eyes with at least 4 follow-up visits after switching to aflibercept experienced a visually significant improvement in logMAR VA compared to the pre-switch vision ($P = .003$). This suggests that longer-term follow-up after aflibercept conversion is necessary to provide a more accurate assessment of VA outcomes.

With respect to IOP, numerous studies have linked repeated intravitreal injections to both transient and sustained increases in IOP levels.[33,34] An analysis of the VIEW 1 and VIEW 2 trials evaluating aflibercept in neovascular AMD revealed a lower incidence of IOP elevation, and actually a slight decrease in IOP from baseline, among patients in the aflibercept treatment arms compared to those receiving ranibizumab.[35] Most recently, one group examined the IOP effects of switching from ranibizumab/bevacizumab to aflibercept in neovascular AMD and observed a significant reduction in mean IOP from 14.87 mm Hg pre-aflibercept to 14.14 mm Hg during aflibercept treatment, and 13.79 mm Hg at the last available measurement.[36] The authors suggested that aflibercept carries a more favorable IOP safety profile and may be an attractive anti-VEGF option to use in patients with glaucoma or at higher risk for developing it. In the current study, while we did not observe a significant difference in mean IOP when comparing pre-aflibercept measurements to the second visit after conversion, we did find that the group with at least 4 visits post conversion demonstrated a statistically significant drop in IOP ($P = .04$). It is plausible that with longer follow-up, a more favorable IOP effect with aflibercept in DME may be confirmed, as studies in neovascular AMD have demonstrated.

Because of the retrospective nature of the study and the relatively small number of eyes, it is difficult to make direct comparisons of our findings to Protocol T. Most notably, we used Snellen charts to measure VA instead of standardized ETDRS protocol refractions as per the DRCR Network's studies. The lack of refractive data and a uniform visual assessment may result in a different interpretation of VA than Protocol T determined. Furthermore, while 22 eyes (44%) had previous focal laser treatment for DME outside of the study period (>6 months prior to aflibercept conversion), we did not evaluate the effect of additional focal laser therapy on persistent DME, for which eyes in Protocol T were eligible after 24 weeks. Our results, however, are not meant to advise against focal laser therapy, which has a proven role in treating persistent DME. Rather, in order to best assess whether a pure pharmacologic difference existed between these medications, the study was designed to exclude eyes that had other interventions performed around the time of conversion to aflibercept, or afterward during the follow-up period.

There are several additional limitations to our study that warrant discussion. First, the retrospective nature did not allow for inclusion of a comparison/control group with which to directly compare treatment outcomes of eyes converted to aflibercept. Second, while we are reporting results on both ranibizumab and bevacizumab therapy prior to aflibercept conversion, we now know through the year 1 results of Protocol T that the 3 drugs do not have comparable treatment outcomes in cases of DME with initial VA of 20/50 or worse.[9] Post hoc exploratory analyses further suggested that even in eyes with initial VA of better than 20/50 and baseline CMT ≥400 μm, treatment with bevacizumab resulted in worse visual outcomes compared to either ranibizumab or aflibercept.[37] Any effect from which medication was used prior to conversion in our study is likely offset by the fact that only 2 eyes (4%) of the cohort were being treated exclusively with bevacizumab prior to aflibercept conversion, while the remainder either had been treated exclusively with ranibizumab or had been started on bevacizumab and were eventually switched to ranibizumab by the treating physician. Third, in cases of chronic DME, CMT measurements may not be the best surrogate for predicting VA.[38] Rather, the integrity of the external limiting membrane and ellipsoid zones[39] or disorganization of the inner retinal layers,[40] which were not evaluated in the current study, may correlate better to visual outcomes. Future investigations may benefit from assessing these additional components during the SD OCT acquisition. Finally, the limited follow-up interval only allows us to draw short-term conclusions after converting to aflibercept.

Despite the inherent limitations, this study offers potentially useful clinical insight into the initial experience with aflibercept in managing DME in a "real-world" setting where patients have been previously treated with other VEGF inhibitors. A major strength of its design lies in the inclusion of eyes maintained on a consistent injection interval before and after switching to aflibercept, helping limit the impact of treatment frequency on the outcomes measured. Altogether, our results support the notion that converting patients with persistent DME to aflibercept results in improved anatomic outcomes and at least maintenance of vision. Future studies will be needed to determine whether these findings will be sustained or further improve with longer follow-up.

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Biosketch

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Biosketch

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