ORIGINAL RESEARCH

Characteristics and Treatment Patterns of Patients with Diabetic Macular Edema Non-Responsive to Anti-Vascular Endothelial Growth Factor Treatment in Ontario, Canada

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Purpose: To understand the demographics, clinical characteristics, treatment patterns, visual and anatomic responses of patients with diabetic macular edema (DME) initially treated with anti-vascular endothelial growth factor (anti-VEGF) agents in the real-world clinical setting.

Patients and Methods: This retrospective cohort study used electronic health records to identify consecutively presenting patients with DME who received their first documented anti-VEGF injection (index injection) on or after 1 October 2015 and before 30 September 2016 (index period) at 4 clinical sites in Ontario, Canada. Patients receiving anti-VEGF injections in the study eye were followed for ≥18 months. After the first 3 monthly injections, patients were classified as "responder" (≥20% reduction in central retinal thickness [CRT] from index date) or "nonresponder" (<20% reduction in CRT) to anti-VEGF treatment.

Results: At 12 months, change from baseline (CFB) in best visual acuity (BVA) of responders (n = 30) was mean (SD) 12.8 (13.00) letters; CFB in nonresponders (n = 56) was 3.2 (16.3) letters. Sensitivity analyses stratified by initial BVA were supportive. Mean (SD) change in CRT (μm) was −160.4 (111.4) in responders and −62.2 (98.6) in nonresponders. While changes in anti-VEGF therapy were lower in responders versus nonresponders (10.0% vs 23.2%), mean number of injections was similar (8.3 in each cohort).

Conclusion: Despite receiving a substantial number of injections and requiring changes in therapy more frequently, nonresponders showed a lack of clinically meaningful change in BVA and CRT. Nonresponders could be identified after 3 anti-VEGF injections. There remains an unmet need for treatment options in patients with DME who show a nonresponse after 3 months of anti-VEGF treatment.

Keywords: real-world evidence, diabetic macular edema, drug therapy, anti-vascular endothelial growth factor, visual acuity

Introduction

Treatment of diabetic macular edema (DME) with anti-vascular endothelial growth factor (anti-VEGF) agents typically requires monthly injections for an extended period, and a substantial proportion of patients (30–65%) are partial or nonresponders.[1–5] A suboptimal or nonresponse has been defined in clinical studies as patients achieving <5 letter gain in best-corrected visual acuity (BCVA) or <10% or 20% decrease in central retinal thickness (CRT).[1,6–9] A post hoc analysis of the Diabetic Retinopathy Clinical Research Retina Network Protocol I study indicated that approximately 40% of eyes receiving monthly ranibizumab had suboptimal BCVA improvement at 12 weeks. Treatment over 3 years produced only modest improvement with one third of eyes having <5 letter gain.[6] However, data from the Protocol T study comparing aflibercept, bevacizumab, and ranibizumab indicate that suboptimal response (BCVA <5 letters) at 12 weeks following 3

consecutive anti-VEGF injections does not necessarily preclude meaningful vision improvement from occurring in many eyes.[10]

Changes in anti-VEGF agent therapy because of poor response to an original treatment has not been well studied in the real-world clinical setting although data have shown marginal benefits in visual outcomes in nonresponders.[11] Lim et al[12] reported that patients who were refractory to 6 injections of ranibizumab/bevacizumab had improved anatomic and visual outcomes following conversion to aflibercept, while other studies have reported that the subsequent administration of aflibercept after a mean of 13.7 injections was not associated with significant visual acuity (VA) improvements but only anatomic outcomes.[13] The use of another class of drugs such as intravitreal corticosteroids (dexamethasone or fluocinolone) has shown significant improvement in visual and anatomical outcomes in nonresponders to anti-VEGF therapy.[4] In addition, studies have shown that early use of alternative therapy in nonresponders is beneficial.[4,6] Early identification of patients with DME who are poorly or un-responsive to anti-VEGF therapy would enable more timely consideration of potential changes to their treatment regimens.[1] This study reviews the use of anti-VEGF treatment for DME in a Canadian real-world population to better understand the demographics, clinical characteristics, treatment patterns, and vision and anatomic responses of patients with DME initially treated with anti-VEGF agents.

Methods

Study Design and Data Source

This retrospective, noninterventional, observational, cohort study was conducted in 4 clinical sites in Ontario, Canada. Electronic health records (EHRs) were screened to identify consecutively presenting patients with a diagnosis of DME who received their first documented anti-VEGF injection (index event) on or after 1 October 2015 and before 30 September 2016 (index date identification period; Figure 1). The study complied with International Society for Pharmacoepidemiology Good Pharmacoepidemiology Practice guidelines and the tenets of the 2013 Declaration of Helsinki. Approval of the protocol was obtained from a centralized independent institutional review board (Advarra, Columbia, MD). Since the collected data were retrospective and anonymized, written informed patient consent was waived.

Patient Identification

Adult patients, naïve to anti-VEGF therapy, who received ≥1 anti-VEGF injection to treat visual impairment due to DME on or after 1 October 2015 and before 30 September 2016 (index period) and who had follow-up data for ≥18 months were eligible. Patients with unconfirmed DME, and missing data on age, gender, and to assess treatment response within 60 days of the third anti-VEGF injection, and VA or optical coherence tomography (OCT) recorded at baseline (defined
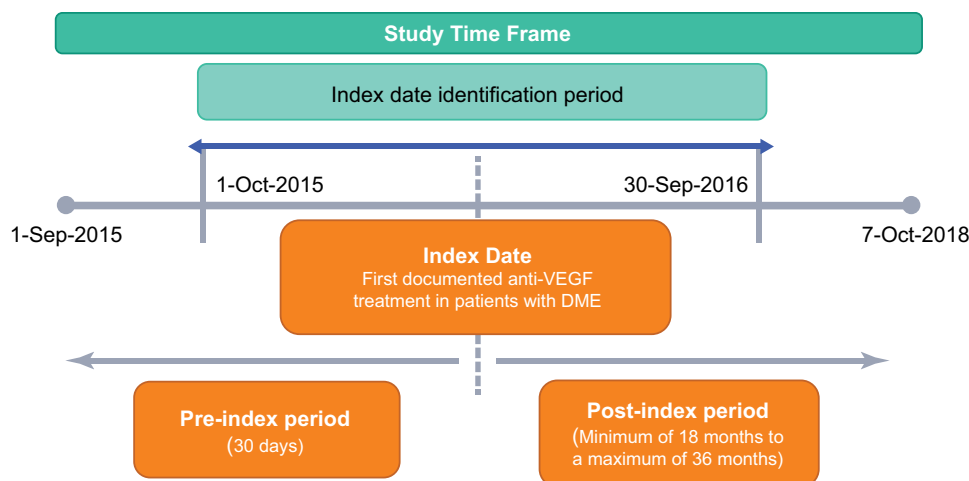

Figure 1 Study design.
Abbreviations: Anti-VEGF, anti-vascular endothelial growth factor; DME, diabetic macular edema.

as no more than 30 days prior to the index date [date of index event] through 7 days after the index date) were excluded as were eyes for which laterality of the anti-VEGF injection was not identified, and eyes with concomitant retinal diagnoses commonly treated with anti-VEGF therapy (retinal vein occlusion and neovascular age-related macular degeneration as identified by International Classification of Diseases codes). If patients received anti-VEGF injection in both eyes, the eye that received the maximum number of injections was deemed the study eye.

Once eligibility was confirmed, patients were stratified into one of the two study cohorts – anti-VEGF responders or anti-VEGF nonresponders. Responders were defined as patients with a ≥20% reduction in CRT from the index date to the first CRT value within 60 days after the third anti-VEGF injection; the 60-day designated window allowed variability in visit times from patient to patient. If the index date CRT was not available, the last pre-index date measurement recorded within 60 days prior to the index date was used. Nonresponders were defined as having a <20% reduction in CRT from the index date to the first OCT value within 60 days after the third injection. If the index date CRT was not available, the last pre-index date measurement measured within 60 days prior to the index date was used.

Data Collection

Retrospective data from EHRs were anonymized and entered in an electronic data capture system by the site personnel. Patient data were collected for at least 18 months to 2 years after the index date or until 7 October 2018 (follow-up period; Figure 1). Baseline patient demographics and characteristics and data on the type, date, and frequency of anti-VEGF injections, and VA and CRT measurements performed at baseline and during the follow-up period were recorded. Snellen VA measurements were converted to approximate Early Treatment Diabetic Retinopathy Study letter scores.

Data Analysis

Outcome variables evaluated included anti-VEGF agent utilization, ie, the number of anti-VEGF injections administered/ year and the use of an alternative agent; anti-VEGF agent effectiveness including change in VA and CRT from the index date to the end of follow-up (at least 18 months to 2 years after the index date); VA at baseline and at 12, 18, and 24 months and stratified by baseline VA; and eyes with ≥15 letter gain. Data were analyzed for the full population and the anti-VEGF responder and nonresponder cohorts (primary analysis).

To corroborate the results from the primary analyses, 3 sensitivity analyses were performed by changing the definitions of responder and nonresponder. In sensitivity analysis 1, in alignment with the Protocol I EARLY analysis,[7,14] responders were defined as patients with a ≥10% reduction in CRT or ≥5 letter gain from baseline (index date) to the first CRT or VA value, within 60 days after the third anti-VEGF injection. For sensitivity analysis 2, patients were assigned to responder vs nonresponder cohorts after 6 anti-VEGF injections using the base case definition of responder (≥20% reduction in CRT). In sensitivity analysis 3, responders were defined as those who had either ≥20% reduction in CRT or ≥5 letter gain based on the first CRT or VA value within 60 days after the third anti-VEGF injection.

Analyses were primarily descriptive. Continuous variables were described by mean, standard deviation (SD), median, extreme values (minimum and maximum), and missing data. Categorical variables were summarized using relative frequency and percentage. Two-sided 95% confidence interval of the mean and percentage was calculated when appropriate. The study was exploratory; no formal sample size calculations were performed. Approximately 120 records were planned for inclusion based on eligible patient numbers. Statistical analyses used SAS software version 9.04.01.

Results

Patient Disposition, Baseline Demographics, and Characteristics

Of the 120 patients identified in the EHR database with a diagnosis of DME, 97 were eligible for inclusion. Eleven patients were later excluded mainly due to receiving <3 anti-VEGF injections during study period (Figure 2). The mean (SD) time to cohort allocation was 75.2 (34.1) days for the responder cohort and 73.2 (22.9) days for the nonresponder cohort. In all, 65.1% of patients (56/86) met the nonresponder to anti-VEGF treatment criteria.

Baseline demographics, medical and general ophthalmic history, and study eye characteristics are presented in Table 1 and Table 2 by cohort. In the overall population, the mean (SD) age at baseline was 64.8 (10.2) years, 55.8% of patients
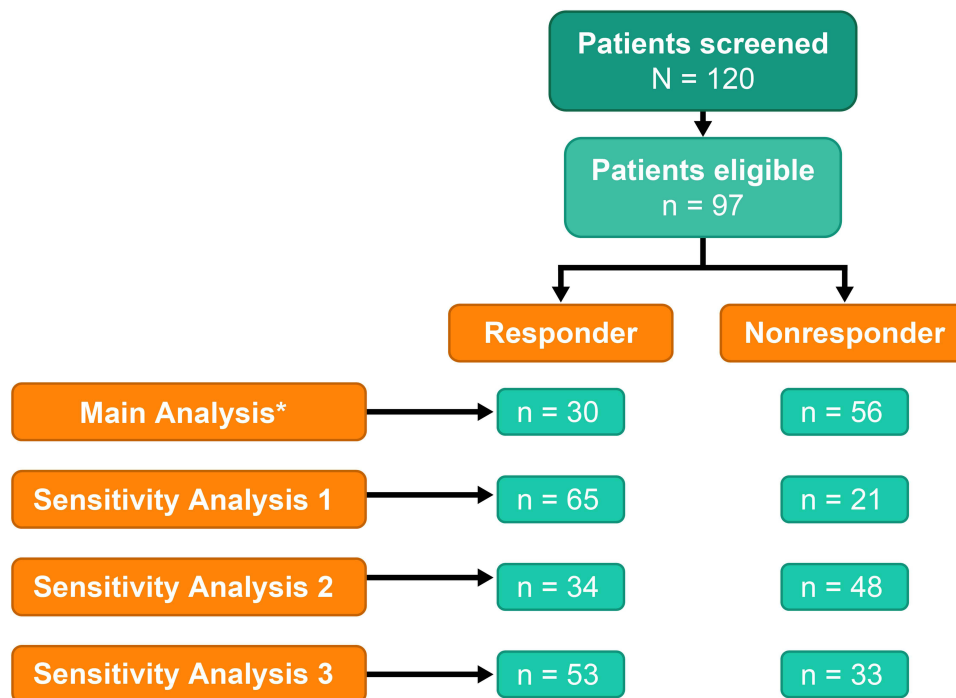
Figure 2 Patient disposition. *11 eligible patients were excluded from the main cohort (1 patient without baseline central retinal thickness [CRT] measurements within 60 days prior to index, 1 patient without baseline CRT date, and 9 patients received <3 injections of anti-vascular endothelial growth factor during study period).

were ≥65 years of age, and 61.6% were male. Of the 40 patients who had reported data, 20.0% and 80.0% had type 1 and type 2 diabetes, respectively, and the overall mean baseline glycosylated hemoglobin (HbA1C) was 7.2. An equal number of right and left eyes were included. Prior to study initiation, 96.5% of study eyes were naïve to corticosteroid therapy with the remainder having no data. Of note, baseline VA was lower and CRT was higher in the responder cohort.

Table 1 Patient Baseline Demographics, and Medical and Ophthalmic History

Parameter	Anti-VEGF		
	Responder N=30	**Nonresponder N=56**	**Overall N=86**
Sex, n (%)			
Male	17 (56.7)	36 (64.3)	53 (61.6)
Age (years)			
Mean (SD)	65.3 (11.0)	64.5 (9.8)	64.8 (10.2)
Min, Max	39, 84	33, 85	33, 85
Age Group (years), n (%)			
≥ 18–34	0 (0.0)	1 (1.8)	1 (1.2)
≥ 35–44	1 (3.3)	0 (0.0)	1 (1.2)
≥ 45–54	5 (16.7)	8 (14.3)	13 (15.1)
≥ 55–64	6 (20.0)	17 (30.4)	23 (26.7)
≥ 65	18 (60.0)	30 (53.6)	48 (55.8)
Drug Coverage Plan, n (%)			
Public - Ontario Drug Plan	17 (56.7)	39 (69.6)	56 (65.1)
Private Drug Plan	13 (43.3)	17 (30.4)	30 (34.9)

(Continued)

Table 1 (Continued).

Parameter	Anti-VEGF		
	Responder N=30	Nonresponder N=56	Overall N=86
Any Medical History	24 (82.8)	29 (54.7)	53 (64.6)
Top 3 chronic conditions, n (%)			
Hypertension	15 (42.9)	25 (35.7)	40 (38.1)
Hypercholesterolemia	16 (45.7)	14 (20.0)	30 (28.6)
Hyperlipidemia	3 (8.6)	3 (4.3)	6 (5.7)
Diabetes Type, n (%)			
Type 1[a]	2 (20.0)	6 (20.0)	8 (20.0)
Type 2[a]	8 (80.0)	24 (80.0)	32 (80.0)
Not Reported	20 (66.7)	26 (46.4)	46 (53.5)
Most Recent HbA1c Results (%)			
Mean (SD)	7.3 (2.07)	7.18 (1.91)	7.21 (1.92)
Median (Q1-Q3)	6.7 (5.90–9.60)	6.5 (5.90–8.00)	6.6 (5.90–8.40)
Min, Max	5, 10.7	5, 12	5, 12
Lens Status, n (%)			
Phakic[a]	14 (50.0)	35 (79.5)	49 (68.0)
Aphakic[a]	14 (50.0)	9 (20.5)	23 (31.9)
Not Reported	2 (6.7)	12 (21.4)	14 (16.3)
Glaucoma Status, n (%)			
Yes[a]	3 (10.7)	4 (7.8)	7 (8.9)
Not Reported	2 (6.7)	5 (8.9)	7 (8.1)
Ocular Hypertension Status, n (%)			
Yes[a]	2 (6.9)	2 (4.0)	4 (5.1)
Not Reported	1 (3.3)	6 (10.7)	7 (8.1)

Note: [a]Percentages based on the number of patients with data.
Abbreviations: anti-VEGF, antivascular endothelial growth factor; HbA1c, glycosylated hemoglobin; Q, quartile; SD, standard deviation.

Anti-VEGF Therapy Administration

In the overall population (n = 86), aflibercept was the most frequently used index treatment in the study eye (61.6%), followed by ranibizumab (26.7%), and bevacizumab (11.6%) (Table 2). Aflibercept was administered in 66.7% of the 30 eyes in the responder cohort and 58.9% of 56 eyes in the nonresponder cohort. Bevacizumab was administered as the index treatment in the nonresponder cohort only. In year 1, the mean number of injections administered to each cohort was similar; in the 18 months to 2-year period, responders received more injections than nonresponders (Table 3).

Some patients required alternate anti-VEGF agents during the study period. Overall, the use of an alternative anti-VEGF treatment was lower in the responder cohort (10% at both 12 and 18 months) versus the nonresponder cohort (23.2% at 12 months; 30.4% at 18 months; Figure 3). The need for an alternative agent was greater in the nonresponder cohort and mean time to switch from the first anti-VEGF agent to the second agent was longer in the responder cohort (Table 4). The majority of first switches were from bevacizumab to aflibercept in 14.3% of nonresponders, aflibercept to ranibizumab in 6.7% of responders, and ranibizumab to either bevacizumab or aflibercept in 5.4% of nonresponders (each).

Visual Acuity Outcomes

At year 1, in the responder cohort, the mean (SD) change in BVA from the index date in the study eye was 12.8 (13.0) letters, whereas in the nonresponder group the change from baseline was 3.2 (16.3) letters. Similar benefit was maintained through 24 months in both groups (Figure 4). More patients in the responder cohort had a ≥15 letter gain than the nonresponder cohort at

Table 2 Patient Baseline Study Eye Characteristics and Index Treatment

Parameter	Anti-VEGF		
	Responder N=30	Nonresponder N=56	Overall N=86
Study eye, n (%)			
Left	12 (40)	31 (55.4)	43 (50)
Visual Acuity (ETDRS Letter Score)			
Mean (SD)	56.45 (16.3)	60.73 (14.4)	59.27 (15.1)
Intraocular Pressure (mm Hg)			
Mean (SD)	15.62 (4.4)	16.48 (4.5)	16.18 (4.5)
Median (Q1-Q3)	15 (12.0–18.0)	15 (14.0–19.0)	15 (13.0–18.0)
Min, Max	9, 26	9, 35	9, 35
Central Retinal Thickness (µm)			
Mean (SD)	441.4 (108.7)	355.7 (97.1)	385.63 (108.7)
Severity of Diabetic Retinopathy, n (%)			
Mild nonproliferative[a]	5 (19.2)	13 (27.7)	18 (24.7)
Moderate nonproliferative[a]	9 (34.6)	12 (25.5)	21 (28.8)
Severe nonproliferative[a]	10 (38.5)	13 (27.7)	23 (31.5)
Proliferative[a]	2 (7.7)	9 (19.1)	11 (15.1)
Not Reported	4 (13.3)	9 (16.1)	13 (15.1)
Index Treatment, n (%)			
Aflibercept	20 (66.7)	33 (58.9)	53 (61.6)
Bevacizumab	0	10 (17.9)	10 (11.6)
Ranibizumab	10 (33.3)	13 (23.2)	23 (26.7)

Note: [a]Percentages based on the number of patients with data.
Abbreviations: anti-VEGF, anti-vascular endothelial growth factor; ETDRS, Early Treatment Diabetic Retinopathy Study; Q, quartile; SD, standard deviation.

Table 3 Number of Anti-VEGF Injections Administered to the Study Eye

Time Frame[a]	Anti-VEGF		
	Responder N=30	Nonresponder N=56	Overall N=86
Year 1, mean (SD)	8.3 (2.2)	8.3 (2.3)	8.3 (2.3)
Min, Max	4, 13	4, 13	4, 13
18 Months, mean (SD)	11.4 (3.4)	10.4 (3.3)	10.7 (3.4)
Min, Max	6, 18	5, 18	5, 18
Year 2, mean (SD)	6.2 (3.1)	4.0 (3.2)	4.7 (3.3)
Min, Max	2, 11	0, 11	0, 11

Note: [a]Year 2 = 13 to 24 months.
Abbreviations: anti-VEGF, anti-vascular endothelial growth factor; SD, standard deviation.

12 months (36.7% vs 15.7%) and 18 months (34.5% vs 14.0%), respectively. The proportion of study eyes achieving BVA of 0.3 LogMAR or better from baseline after 12 and 18 months was 43.3%, and 31.0% in the responder cohort, and 27.5% and 30.0%, respectively, in the nonresponder cohort. The proportion of study eyes achieving a BVA of 20/40-20/200 inclusive after 12 and 18 months in the responder cohort was 46.7% and 58.6%, and in the nonresponder cohort, 58.8% and 54.0%, respectively. When patients with baseline VA were stratified by a baseline letter score of <69 or 78 to 69, mean change from
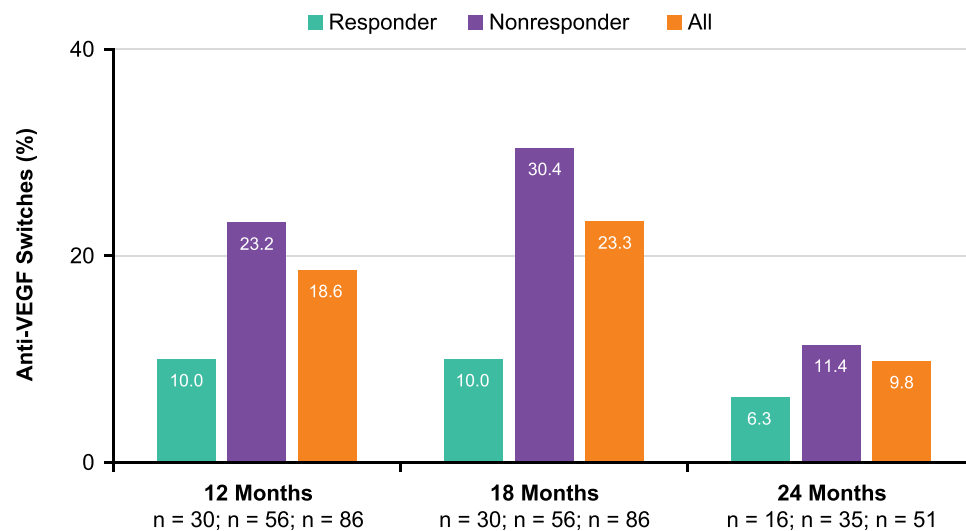
Figure 3 Percentage of patients requiring alternative therapy at 12, 18 and 24 months.
Abbreviation: anti-VEGF, anti-vascular endothelial growth factor.

baseline in letter score at 12 months was greater in the responder versus nonresponder groups. The difference was more pronounced in patients with worse VA (<69 letters) (Table 5).

Anatomic Outcomes

Similar to VA, numerically greater improvements in CRT were observed in responders and were maintained over time. At year 1, the mean (SD) change in CRT from baseline in the study eye in responders was −160.4 (111.4) μm, whereas in the nonresponder group the change was only −62.2 (98.6) μm. Benefit was maintained through 24 months (Figure 5).

Table 4 Patients Requiring Alternate Anti-VEGF Agents in the Study Eye

Time Frame	Anti-VEGF		
	Responder N=30	Nonresponder N=56	Overall N=86
Number of patients requiring use of an alternate therapy[a]			
Year 1, n (%) N	3 (10.0) 30	13 (23.2) 56	16 (18.6) 86
18 Months, n (%) N	3 (10.0) 30	17 (30.4) 56	20 (23.3) 86
Year 2, n (%) N	1 (6.3) 16	4 (11.4) 35	5 (9.8) 51
Time to the need for an alternate therapy, days			
Index to 2nd agent Mean (SD) Min, Max	320.75 (168.01) 194, 550	273.39 (182.37) 70, 698	282 (176.93) 70, 698
2nd to 3rd agent Mean (SD) Min, Max		457.86 (239.15) 172, 829	457.86 (239.15) 172, 829

Note: [a]Only 1 change in therapy was reported during each time frame.
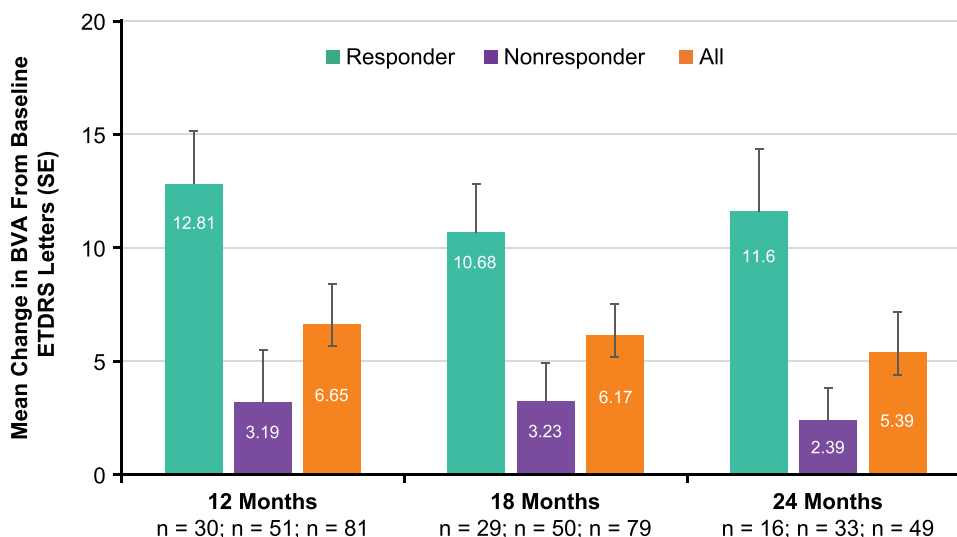**Abbreviations**: anti-VEGF, anti-vascular endothelial growth factor; SD, standard deviation.

Figure 4 Change in best visual acuity (BVA) from index date in responders, nonresponders and the overall population at 12, 18 and 24 months from baseline.
Abbreviations: ETDRS, Early Treatment Diabetic Retinopathy Study; SE, standard error.

Sensitivity Analyses

Patients meeting the definitions for responder and nonresponder for each sensitivity analysis and their VA and CRT findings are summarized in Table 6. Overall, in sensitivity analysis 1, both responders and the nonresponders showed ≥10% reduction in CRT from baseline at almost all time points. Despite this reduction in CRT, the nonresponder group showed only a maximum of 3-letter gain in BVA. In comparison, there was a minimum of 6-letter to a maximum of 17-letter gain in BVA in the responder group.

In sensitivity analyses 2 and 3, CRT thickness decreased (27% to 39%) and BVA letters gained increased (6 to 11) in the responder group. However, in the nonresponder group, at most time points, the reduction in CRT was not ≥20%. In concert with this finding, the gain in BVA was not significant (−1.8 to 3.7). Therefore, sensitivity analyses by definition

Table 5 Visual Acuity (ETDRS Letters) at Baseline and at 12 Months (Stratified by Baseline Visual Acuity)

	Anti-VEGF		Overall
	Responder	**Nonresponder**	
Letter Score of <69 at baseline			
Number of eyes	24	45	69
Visual acuity at baseline			
Mean (SD)	52.17 (15.08)	54.53 (10.97)	53.71 (12.49)
Visual acuity at 12-month follow-up			
Mean (SD)	66.81 (11.39)	61.13 (15.23)	63.11 (14.15)
Change from baseline letter score			
Mean improvement (SD)	18.31 (13.72)	6.63 (11.65)	10.7 (13.49)

(Continued)

Table 5 (Continued).

	Anti-VEGF		Overall
	Responder	**Nonresponder**	
Letter score of 78 to 69 at baseline			
Number of eyes	10	19	29
Visual acuity at baseline			
Mean (SD)	70.6 (1.9)	72.53 (3.04)	71.86 (2.82)
Visual acuity at 12-month follow-up			
Mean (SD)	76.44 (5.96)	73.4 (5.56)	74.84 (5.8)
Change from baseline in letter score			
Mean improvement (SD)	5.78 (5.85)	1 (5.89)	3.26 (6.21)

Abbreviations: anti-VEGF, anti-vascular endothelial growth factor; ETDRS, Early Treatment Diabetic Retinopathy Study; SD, standard deviation.

further supported the results of the primary analysis; anti-VEGF treatment did not result in a clinically meaningful improvement in VA in the nonresponder group.

Discussion

In this retrospective analysis, we identified 86 patients in the clinical practice setting who received their first documented anti-VEGF injection to treat visual impairment for DME and followed their treatment journey for a minimum of 18 months. At Index, of the 86 patients in the total cohort, 11.6% were receiving bevacizumab, 26.7% ranibizumab, and 61.6% aflibercept. When categorized as responders or nonresponders to anti-VEGF therapy based on a ≥20% or <20% reduction in CRT from baseline, respectively, after 3 injections, almost two-thirds of patients were identified as nonresponders (<20% decrease in CRT), a rate higher than typically reported in other studies.[1–5]
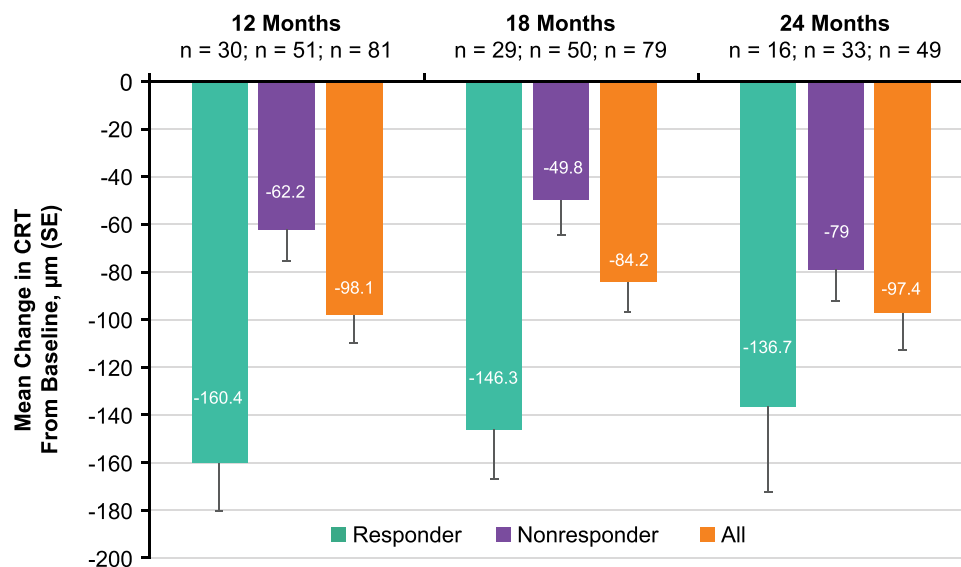

Figure 5 Mean change in central retinal thickness (CRT) from baseline in overall cohort, and in responders and nonresponders.
Abbreviation: SE, standard error.

Table 6 Sensitivity Analyses: Change in Best Visual Acuity (BCA) and Central Retinal Thickness (CRT)

	Responders			Nonresponders		
	BVA (ETDRS Letters)	**CRT (μm)**	**Decrease in CRT (%)**	**BVA (ETDRS Letters)**	**CRT (μm)**	**Decrease in CRT (%)**
Sensitivity Analysis 1: Responder, either ≥10% reduction in CRT OR ≥5-letter gain in VA from baseline after 3 anti-VEGF injections						
	N = 65			**N = 21**		
Baseline (Index)	58.62 (14.8)	401.8 (104.91)	-	61.81 (15.98)	339.19 (108.39)	-
Mean Change from Baseline (SD) at: 12 months 18 months 24 months	8.73 (12.7) 8.19 (11.6) 6.11 (13.5)	−120.19 (108.3) −108.98 (113.9) −104.91 (126.3)	30% 27.12% 26.11%	−0.59 (22.3) −1.93 (12.5) 3.09 (9.8)	−35.72 (103.9) −17.89 (106.5) −77.33 (71.9)	10.53% 5.27% 22.80%
Sensitivity Analysis 2: Responder, ≥20% reduction in CRT after 6 anti-VEGF injections						
	N = 34			**N = 48**		
Baseline (Index)	55.94 (17.6)	456.51 (101.7)	-	62.1 (12.56)	336.81 (84.54)	-
Mean Change from Baseline (SD) at: 12 months 18 months 24 months	10.25 (13.8) 9.06 (12.5) 6.13 (9.9)	−179.74 (90.5) −165.69 (84.9) −172.93 (111.7)	39.37% 36.29% 37.88%	2.98 (16.5) 2.92 (11.8) 3.67 (14.0)	−34.97 (89.4) −18.77 (103.9) −53.96 (98.9)	10.38% 5.57% 16.02%
Sensitivity Analysis 3: Responder, ≥20% reduction in CRT or ≥5-letter gain in VA						
	N = 53			**N = 33**		
Baseline (Index)	56.62 (14.3)	411.33 (108.29)	-	63.85 (15.4)	346.36 (97.61)	-
Mean Change from Baseline (SD) at: 12 months 18 months 24 months	11.13 (12.4) 9.94 (11.2) 9.62 (10.5)	−129.23 (113.4) −116.73 (123.3) −110.12 (123.2)	31.42% 28.40% 26.77%	−1.04 (17.8) −1.16 (11.3) −1.82 (13.1)	−54.34 (97.2) −39.93 (95.4) −79.0 (99.5)	15.70% 11.53% 22.81%

Abbreviations: anti-VEGF, anti-vascular endothelial growth factor; ETDRS, Early Treatment Diabetic Retinopathy Study; SD, standard deviation; VA, visual acuity.

No clinically meaningful differences in baseline demographics or medical and ophthalmic history were apparent between cohorts. The responders had a numerically larger mean (SD) CRT at baseline (441.4 [109.7] μm) than the nonresponders (355.7 [97.1] μm), while baseline VA was slightly lower in responders.

Aflibercept was the most frequently used index treatment in both cohorts followed by ranibizumab and the mean number of anti-VEGF injections administered appeared to be consistent over the 2 years of therapy. The majority of the initial anti-VEGF therapy switches were to aflibercept (from bevacizumab [9.3%] and ranibizumab [4.7%]). At 12 and 18 months, the number of switches was lower in responders (10% each) than in nonresponders (23.2% and 30.4%, respectively). Despite changing therapies, 65% of nonresponders were still nonresponders and did not reap the benefit of anti-VEGF treatment. In fact, other studies indicate that 30–65% of participants are nonresponders to anti-VEGF treatment.[1–5] This higher percentage of nonresponders in our study could be due to small sample size, differences in the standard of care across practices, and differences in care outcomes and response assessment in real-world studies compared with randomized controlled trials.

Despite receiving a similar number of injections and requiring an alternate anti-VEGF agent more frequently than responders, nonresponders showed a lack of clinically meaningful change in BVA and CRT over 24 months. In fact, the

responder cohort had an approximately four times greater change in BVA than the nonresponder group at 12 months and an approximate three times greater change at 18 months. Considering that the base definition of responder/nonresponder centered on CRT only, vision in responders benefited greatly from anti-VEGF therapy, while nonresponders realized only minimal BVA changes. The reduction in CRT in responders was more than twice that of the nonresponders at 12 and 18 months. However, the responders had a higher CRT at baseline, which may partially explain the large difference in the change from baseline.

In sensitivity analysis 1, lowering the CRT to ≥10% yielded a greater number of responders (N = 65) than nonresponders (N = 21), the opposite of the responder to nonresponder ratio with the base definition of ≥20%. Similarly, sensitivity analysis 3 yielded a greater number of responders while sensitivity analysis 2 with a more stringent threshold (responder of ≥20% reduction in CRT after 6 injections) yielded a greater number of nonresponders indicating the stronger influence of CRT change and a much lesser effect of allowing 6 versus 3 injections on outcome. In current practice, generally 6 injections are administered before a decision is made to choose an alternate therapy.[15]

Of note, optical coherence tomography angiography (OCT-A) has more recently been suggested as a promising method of predicting diabetic macular edema refractory to anti-VEGF therapy.[16] Elnahry et al[16] found that, after 3 anti-VEGF injections, eyes with a higher CRT at baseline gained more vision than those eyes that failed to improve, similar to our study. Although starting CRT was the strongest predictor of both anatomic and visual response, OCT-A vascular parameters independently predicted the likelihood that macular edema would improve with anti-VEGF agents indicating that nonresponding eyes may have more macular ischemia at the outset. This may be important because irreversible structural damage may occur with inadequately managed swelling. Although larger studies are needed, OCT-A could assist clinicians in identifying eyes that are unlikely to respond to anti-VEGF therapy and making earlier decisions as to when to switch from anti-VEGF therapies to alternate therapies to treat DME.[16]

A key limitation of this study was its descriptive nature with a sample size of responders and nonresponders too small/underpowered to assess statistical differences between or within groups. Further, real-world studies with adequate sample size and adjustment for confounders are warranted to assess differences in demographics and clinical characteristics among optimal and suboptimal responders. Other study limitations include the lack of data on the type of anti-VEGF regimen administered and the omission of vitreoretinal interface diseases as an exclusion criterion as they can create a serious nonresponse.[17]

Conclusions

Our findings from the real-world sample indicated that more than 50% of the participants are nonresponders to anti-VEGF therapy for DME, despite switching between different anti-VEGF agents. This outcome is not surprising given the complex pathophysiology of DME.[2,18] Further, other studies have shown that targeting pathways other than VEGF, can be beneficial to anti-VEGF nonresponders.[2–4,18–22] Current alternatives to anti-VEGF treatment include the use of corticosteroids, which act by targeting anti-inflammatory pathway along with decreasing VEGF synthesis, focal laser, subthreshold laser therapies, and vitrectomy.[5] Finally, emerging pharmacotherapeutics targeting other mediators such as cytokines/chemokines, adhesion molecules, and multiple growth factors also show promise to anti-VEGF nonresponders.[5,23]

Abbreviations

BVA, best visual acuity; BCVA, best-corrected visual acuity; CADTH, Canadian Agency for Drugs and Technologies in Health; CFB, change from baseline; CRT, central retinal thickness; DME, diabetic macular edema; EHR, electronic health records; ETDRS, Early Treatment Diabetic Retinopathy Study; HbA1c, glycosylated hemoglobin; OCT, optical coherence tomography; SD, standard deviation; VA, visual acuity; VEGF, vascular endothelial growth factor.

Data Sharing Statement

AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized, individual, and trial-level data (analysis data sets), as well as other information (eg, protocols and Clinical Study Reports), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications. These clinical trial data can be requested by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research proposal and Statistical Analysis Plan (SAP) and execution of a Data Sharing Agreement (DSA). Data requests can be submitted at any

time, and the data will be accessible for 12 months, with possible extensions considered. For more information on the process, or to submit a request, visit the following link: https://www.abbvie.com/our-science/clinical-trials/clinical-trials-data -and-information-sharing/data-and-information-sharing-with-qualified-researchers.html.

Ethics Approval and Informed Consent

Approval of the protocol was obtained from a centralized independent institutional review board (Advarra, Columbia, MD). Since the collected data were retrospective and anonymized, written informed patient consent was waived.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agreed to be accountable for all aspects of the work.

Disclosure

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