

THREE-YEAR TREATMENT OUTCOMES OF AFLIBERCEPT VERSUS RANIBIZUMAB FOR DIABETIC MACULAR EDEMA

Data from the Fight Retinal Blindness! Registry

PIERRE-HENRY GABRIELLE, MD, PhD, FEBO,*† VUONG NGUYEN, PhD,*
 CATHERINE CREUZOT-GARCHER, PhD,† JENNIFER J. ARNOLD, MBBS,*‡ HEMAL MEHTA, MD,*§
 MÓNICA ASENSIO DURAN, MD,¶ WALID BOUGAMHA, MSc,** ESTER CARREÑO, PhD,††
 FRANCESCO VIOLA, MD,‡‡ DAVID SQUIRRELL, MBBS,§§ DANIEL BARTHELMES, PhD,*¶¶
 MARK GILLIES, PhD*

Purpose: Compare the 3-year outcomes of ranibizumab versus aflibercept in eyes with diabetic macular edema in daily practice.

Methods: This was a retrospective analysis of naive diabetic macular edema eyes starting intravitreal injections of ranibizumab (0.5 mg) or aflibercept (2 mg) from January 1, 2013 to December 31, 2017 that were collected in the Fight Retinal Blindness! Registry.

Results: We identified 534 eyes (ranibizumab—267 and aflibercept—267) of 402 patients. The adjusted mean (95% confidence interval) visual acuity change of +1.3 (−0.1 to 4.2) letters in the ranibizumab group and +2.4 (−0.2 to 5.1) letters ($P = 0.001$) in the aflibercept group at 3 years was not clinically different. However, the adjusted mean CST change seemed to remain significantly different throughout the 3-year period with higher reductions in favor of aflibercept (−87.8 [−108.3 to −67.4] μm for ranibizumab vs. −114.4 [−134.4 to −94.3] for aflibercept; $P < 0.01$). When baseline visual impairment was moderate (visual acuity ≤ 68 Early Treatment Diabetic Retinopathy Study letters), we found a faster improvement in visual acuity in eyes treated with aflibercept up until 18 months of treatment than eyes treated with ranibizumab, which then stayed similar until 36 months of treatment, whereas there was no apparent difference when baseline visual impairment was mild (visual acuity ≥ 69 Early Treatment Diabetic Retinopathy Study letters). The rate of serious adverse events was low.

Conclusion: Aflibercept and ranibizumab were both effective and safe for diabetic macular edema over 3 years.

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Reported outcomes of diabetic macular edema (DME) treatment in real-world practice have generally been inferior to the excellent outcomes reported in pivotal clinical trials.^{1–7} The Diabetic Retinopathy Clinical Research Network protocol T study, meta-analysis, and real-world data found that aflibercept (Eylea, Bayer, Berlin, Germany) tends to improve vision at 1 year more effectively than ranibizumab (Lucentis, Genentech Inc/Novartis, Basel, Switzerland) in eyes with baseline visual acuity of ≤ 68 letters (Snellen equivalent 20/50), whereas there was no difference in eyes with baseline visual acuity ≥ 69 letters (20/40).^{1,2,4} This difference was no longer seen 2 years after starting treatment in the protocol T study.⁵ The

protocol T extension study recently reported that the 5-years mean visual acuity was still better than baseline in DME eyes treated with vascular endothelial growth factor (VEGF) inhibitors. However, visual acuity tended to worsen without significant change in retinal thickness when eyes exited the 2-years clinical trial and returned to routine clinical care.⁶ Evidence on outcomes of treatment of DME in daily practice for longer than 2 years is limited but necessary to optimize patient outcomes. We compared the 3-years treatment outcomes of ranibizumab versus aflibercept intravitreal injections in eyes with DME in daily practice based on data collected from the Fight Retinal Blindness! (FRB!) Registry.

Methods

Design and Setting

Retrospective analysis of eyes tracked in the prospectively designed FRB! registry.⁷ Treatment-naïve eyes with clinically significant DME (CSME) (defined as DME meeting one of these criteria: edema within 500 μm of the center of the fovea or at least one disc area of swelling, any part of which is within disc diameter of the center of the fovea) that started treatment with

From the *The University of Sydney, Sydney Medical School, Discipline of Ophthalmology, Save Sight Institute, New South Wales, Australia; †Department of Ophthalmology, Dijon University Hospital, Dijon, France; ‡Marsden Eye Specialists, Sydney, Australia; §Department of Ophthalmology, Royal Free London NHS Foundation Trust, London, United Kingdom; ¶Department of Ophthalmology, La Paz University Hospital, Madrid, Spain; **Department of Ophthalmology, University Hospital Nice, University of Nice, France; ††Department of Ophthalmology, Fundacion Jimenez Diaz University Hospital; ‡‡Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, University of Milan, Milan, Italy; §§Department of Ophthalmology, the University of Auckland, Auckland, New Zealand; and ¶¶Department of Ophthalmology, University Hospital Zurich, University of Zurich, Zurich, Switzerland.

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Reprint requests: Pierre-Henry Gabrielle, MD, PhD, FEBO, The Save Sight institute, Sydney Eye Hospital, 8 Macquarie St, Sydney, NSW 2000, Australia; e-mail: pghabrielle@gmail.com

the intravitreal VEGF inhibitors aflibercept (Eylea, Bayer, Berlin, Germany) or ranibizumab (Lucentis, Genentech Inc/Novartis, Basel, Switzerland) in routine clinical practice were included. Participants in this analysis came from Australia, France, Ireland, Italy, New Zealand, Spain, Switzerland, and the United Kingdom. Institutional approval was obtained from the Royal Australian and New Zealand College of Ophthalmologists Human Research Ethics Committee; the Southern Eastern Sydney Local Health District Human Research Ethics Committee; the French Institutional Review Board (IRB) (Société Française d’Ophtalmologie IRB); the Mater Private Hospital IRB; the IRCCS Cà Granda Foundation Maggiore Policlinico Hospital Milan; the Clinical Research Ethics Committee of the Clinic Hospital, Barcelona, Spain; the Cantonal Ethics Committee Zurich; and the Caldicott Guardian at the Royal Free London NHS Foundation Trust. All patients gave their informed consent. Informed consent (“opt-in consent”) was obtained from patients in France, Ireland, Italy, Spain, Switzerland, New Zealand, and the United Kingdom. Ethics committees in Australia approved the use of “opt-out” patient consent. This study adhered to the tenets of the Declaration of Helsinki and followed the STROBE statements for reporting observational studies.⁸

Data Sources and Measurements

The Fight Retinal Blindness! Registry has a module that collects data from eyes being treated for DME.⁷ One or both eyes from the same patient were considered for the present analysis. Data were obtained from each clinical visit, including the number of letters read on a logarithm of the minimum angle of resolution visual acuity chart (best of uncorrected, corrected, or pinhole), type of treatment given, the central subfield thickness (CST [μm]) measured using spectral domain optical coherence tomography, and the presence of CSME and if it involved the fovea. If not completed, DME activity was carried forward from the previous visit. Surgical procedures and adverse events were also collected. Demographic characteristics, duration and types of diabetes, severity grading of diabetic retinopathy, and previous treatments received were recorded at the baseline visit. Treatment decisions, including type of drug, injection frequency, and the number of macular laser sittings, were collected over the follow-up period.

Patient Selection and Groups

All eligible eyes with treatment-naïve CSME from January 1, 2013 to December 31, 2017 were considered for this study, thereby allowing the possibility of having at least 3 years of follow-up after the start of treatment. The eyes with a history of DME treatment, such as intravitreal injection, macular focal laser, or

vitrectomy, were excluded. The 3-years end point was the closest visit to 1,095 days of follow-up ± 90 days. The eyes were grouped into either ranibizumab or aflibercept based on their initial injection. The eyes that completed at least 1,005 days of follow-up were defined as “completers.” The eyes that did not complete 36 months of observations were defined as “noncompleters.” “Switchers” were defined as eyes receiving ≥ 2 injections of the other treatment drug before completion of 3 years from the start of treatment.

Main and Secondary Outcomes

The main outcome was the adjusted mean change in visual acuity from baseline at 3 years between ranibizumab and aflibercept. Secondary outcomes were the change in CST, number of visits, injections, switching rates, adverse event rates, and noncompletion rates.

Statistical Analysis

Descriptive data were summarized using the mean, SD, median, interquartile range, and percentages where appropriate. Outcomes were compared between ranibizumab and aflibercept for the following groups: all eyes, monotherapy completers, and noncompleters + switchers, with all eyes being the primary analysis group. Reporting of raw visual and anatomical outcomes for all eyes used the last-observation-carried-forward for noncompleters. Switchers were censored at the time of switch. Visual outcomes at the time of switch were also reported. Outcomes were also stratified by baseline vision into 2 groups, ≥ 69 letters (20/40) and ≤ 68 letters (20/50).

Adjusted visual acuity and CST changes were calculated using generalized additive mixed models with visits from all eyes, including completers, noncompleters, and switchers. The adjusted visual acuity and CST were analyzed longitudinally, with the interaction between initial injection and time being the main predictor. The adjusted difference in visual acuity and CST was compared over the entire 3-years period to identify specific time points where the difference was significant. Injections and visits were compared using generalized Poisson mixed models with an offset for log days of follow-up. Both the generalized additive mixed models and generalized Poisson models included adjustments for baseline age, baseline visual acuity, baseline CST, and baseline DME activity (fixed effects) and nesting of outcomes within practice and eyes from the same patient (random effects). Time to noncompletion and switching were visualized using Kaplan–Meier survival curves.

All analyses were conducted by using R Statistical Software version 4.0.5 (R Foundation for Statistical Computing, 2021) with the *glmmTMB* package for

generalized Poisson mixed models (V 1.0.2.1), *mgcv* package (V 1.8–35) for generalized additive mixed models, and *survival* package (V 3.2–7) for Kaplan–Meier survival analysis.

Results

Study Participants

There were 534 eligible eyes (267 ranibizumab and 267 aflibercept) from 402 patients for this analysis (see **Figure 1, Supplemental Digital Content 1**, <http://links.lww.com/IAE/B637>), of which 242 eyes (125 ranibizumab and 117 aflibercept) had at least 3 years of follow-up. Most baseline characteristics were similar between both groups, including the visual acuity (64.4 letters vs. 65.0 for ranibizumab and aflibercept, respectively; $P = 0.720$). Baseline characteristics are presented in Table 1.

Visual and Anatomical Outcomes

Visual and anatomical outcomes are summarized in Table 2. The longitudinal adjusted visual acuity change over the 3-years period between ranibizumab and aflibercept using all eyes was significantly different ($P < 0.001$). However, this was likely due to the significantly larger gains in aflibercept in the first 12 months (Figure 1, A and C); the adjusted visual acuity change at 3 years after this initial superiority had diminished was similar {mean (95% confidence interval [CI]) adjusted visual acuity change +1.6 [−0.1 to 4.2] letters for ranibizumab vs. +2.4 [−0.2 to 5.1] letters for aflibercept}. This result was consistent when only the monotherapy completers group was considered, although there were somewhat more eyes receiving aflibercept monotherapy that had ≥ 70 letters at 3 years ($P = 0.050$; see **Table 1, Supplemental Digital Content 2**, <http://links.lww.com/IAE/B639>).

The longitudinal CST change over the 3-years period was also significantly different ($P < 0.001$), although, unlike visual acuity, the adjusted CST change seemed to remain significantly different throughout the entire 3-years period (Figure 1, B and D) with greater reductions in favor of aflibercept (mean [95% CI] adjusted CST change -87.8 [−108.3 to -67.4] μm for ranibizumab vs. -114.4 [−134.4 to -94.3] μm for aflibercept; $P < 0.01$). Again, these trends were similar when considering monotherapy completers (see **Table 1, Supplemental Digital Content 2**, <http://links.lww.com/IAE/B639>). There were also fewer eyes in the aflibercept-treated group with center-involving CSME (44%) compared with ranibizumab (61%) at 3 years ($P < 0.001$).

Table 1. Demographic Characteristics for the Eyes Initiating Treatment With Ranibizumab or Aflibercept

	Ranibizumab	Aflibercept	<i>P</i>
Eyes	267	267	
Patients	202	200	
Females, % patients	38.1%	33%	0.244
Diabetes duration, mean, years (SD)	15.7 (9.1)	15.2 (9.4)	0.537
Diabetes type, n (%)			
Type 1	13 (4.9%)	25 (9.4%)	0.057
Type 2	251 (94%)	235 (88%)	
Unknown	3 (1.1%)	7 (2.6%)	
Diabetic retinopathy grade, n (%)			
Mild NPDR	58 (21.7%)	39 (14.6%)	0.064
Moderate NPDR	112 (41.9%)	107 (40.1%)	
Severe NPDR	73 (27.3%)	79 (29.6%)	
PDR, low risk	15 (5.6%)	24 (9%)	
PDR, high risk	9 (3.4%)	18 (6.7%)	
Age, mean (SD)	65 (12.2)	63.1 (12.1)	0.073
VA, mean (SD)	64.4 (18.3)	65 (17.4)	0.720
≥70 letters, n (%)	126 (47.2%)	139 (52.1%)	0.299
≤35 letters, n (%)	19 (7.1%)	15 (5.6%)	0.595
CST, mean (SD)	424.6 (127.4)	427 (141.6)	0.849
DME activity, n (%)			
Center-involving CSME	243 (91.0%)	240 (89.9%)	0.430
Non-center-involving CSME	22 (8.2%)	21 (7.9%)	
None	2 (0.7%)	6 (2.2%)	
Country, n (%)			
Australia	46 (17.2%)	115 (43.1%)	<0.001
France	55 (20.6%)	66 (24.7%)	
Ireland	6 (2.2%)	2 (0.7%)	
Italy	41 (15.4%)	8 (3%)	
Spain	22 (8.2%)	4 (1.5%)	
Switzerland	59 (22.1%)	34 (12.7%)	
United Kingdom	38 (14.2%)	38 (14.2%)	

Significant *P*-values are shown in bold font.

Injection and Visit Frequency

There was a median (Q1, Q3) of 8 (4, 13) and 12 (6, 17) injections in eyes completing 3 years of monotherapy with ranibizumab and aflibercept, respectively ($P = 0.153$; see **Table 1, Supplemental Digital Content 2**, <http://links.lww.com/IAE/B639>). The combined noncompleters and switchers cohort received a median of 7 ranibizumab and 6 aflibercept injections before being lost to follow-up or switching to an alternative drug (Table 2).

The median (Q1, Q3) number of visits was 21 (16, 26) for monotherapy ranibizumab completers and 23 (17, 27) for monotherapy aflibercept completers ($P = 0.347$; see **Table 1, Supplemental Digital Content 2**, <http://links.lww.com/IAE/B639>). The combined noncompleters and switchers cohort had a median of 20 and 15 visits for ranibizumab and aflibercept, respectively.

The number of visits was substantially higher than the number of injections. More than half (51% ranibizumab and 60% aflibercept) of monotherapy

completers had a period where they did not receive an injection for ≥ 6 months ($P = 0.222$).

Outcomes by Baseline Vision

The eyes were split into 2 groups stratified by baseline vision: visual acuity ≤ 68 letters ($n = 133$ ranibizumab and 124 aflibercept) and visual acuity ≥ 69 ($n = 134$ ranibizumab and 143 aflibercept). The mean change in visual acuity over the 3-years period for eyes starting with ≤ 68 letters was significantly different between ranibizumab and aflibercept ($P < 0.001$) with aflibercept achieving superior gains in the first 18 months (Table 3 and see **Figure 2, Supplemental Digital Content 3**, <http://links.lww.com/IAE/B638>). However, there was no difference between drugs at any point in eyes with starting vision ≥ 69 letters ($P = 0.137$). The reduction in CST was higher for aflibercept for most of the 3-years follow-up period in both baseline visual acuity groups (see **Figure 2, Supplemental Digital Content 3**, <http://links.lww.com/IAE/B638>).

Table 2. Visual and Treatment Outcomes at 3 Years (All Eyes Including Completers, Switchers, and Noncompleters)

	Ranibizumab	Aflibercept	<i>P</i>
Eyes	267	267	
Baseline VA, mean (SD)	64.4 (18.3)	65 (17.4)	0.720
Final VA, mean (SD)*	67.1 (19.1)	68.8 (18.3)	0.300
≥70 letters, n (%)	161 (60.3%)	175 (65.5%)	0.244
≤35 letters, n (%)	25 (9.4%)	17 (6.4%)	0.261
ΔVA, mean (95% CI)*	2.7 (0.5 to 4.9)	3.8 (1.7 to 5.9)	0.463
Gain ≥10 letters, n (%)	70 (26.2%)	89 (33.3%)	0.089
Loss ≥10 letters, n (%)	27 (10.1%)	34 (12.7%)	0.414
Adjusted ΔVA, mean (95% CI)*†	1.6 (−0.1 to 4.2)	2.4 (−0.2 to 5.1)	0.001
Baseline CST, mean (SD)	424.6 (127.4)	427 (141.6)	0.849
Final CST, mean (SD)*	342.6 (103.1)	318.7 (103.6)	0.011
ΔCST, mean (95% CI)*	−82.1 (−99.1 to −65.1)	−108.3 (−125.8 to −90.8)	0.035
Adjusted ΔCST, mean (95% CI)*†	−87.8 (−108.3 to −67.4)	−114.4 (−134.4 to −94.3)	<0.001
Final DME activity, n (%)			
Center-involving CSME	163 (61.0%)	118 (44.2%)	<0.001
Non-center-involving CSME	49 (18.4%)	71 (26.6%)	
None	55 (20.6%)	75 (28.1%)	
Visits, median (Q1–Q3)	20 (13–27)	17 (11–24.5)	0.911
First year	10 (7–13)	10 (8–14)	
Second year	6 (2–8.5)	4 (0–7)	
Third year	4 (1–7)	1 (0–6)	
Injections, median (Q1–Q3)	7 (4–12)	8 (5–13)	0.300
First year	5 (3–7)	6 (4–9)	
Second year	1 (0–3)	0 (0–3)	
Third year	0 (0–1)	0 (0–1)	
≥6 months without injection, n (%)	122 (45.7%)	119 (44.6%)	0.862
Switchers, n (%)	72 (27%)	24 (9%)	<0.001
Additional macular laser, n (%)	24 (9%)	12 (4.5%)	0.058
Cataract surgery, n (%)	31 (11.6%)	44 (16.5%)	0.135

Significant *P*-values are shown in bold font.

*Last observation carried forward for non-completers and data were censored at time of switch for switchers.

†Estimated from longitudinal generalised additive mixed models comparing the trajectory between drugs over the entire 36-months period (Figure 1). Models were adjusted for age, VA, CST and DME activity at baseline, and nesting of outcomes from bilateral patients and within practice.

Switchers and Noncompleters

Switching to another VEGF inhibitor within 3 years was observed in 27% of eyes initiating treatment with ranibizumab (70 eyes to aflibercept and 2 eyes to bevacizumab) and 9% of eyes initiating treatment with aflibercept (21 eyes to ranibizumab and 3 eyes to bevacizumab) ($P < 0.001$; Figure 2B). The mean (SD) visual acuity at the time of switch was 68.3 (17.4) letters for initially ranibizumab eyes and 62.3 (23) letters for initially aflibercept eyes (see **Table 2, Supplemental Digital Content 4**, <http://links.lww.com/IAE/B640>). The mean visual acuity change (95% CI) at the time of the switch was +4.4 (0.9, 7.9) letters and +3.8 (−2.4, 10.1) letters for eyes initiating with ranibizumab and aflibercept, respectively.

The noncompletion rate was 26% for ranibizumab and 47% for aflibercept ($P < 0.001$; Figure 2A). The rate of noncompletion was 23 versus 11% at 12 months, 39 versus 18% at 24 months, and 57 versus 32% at 36 months in aflibercept and ranibizumab

groups, respectively. The mean visual acuity and visual acuity change at the time of dropout were 67.6 (SD 19.2) and +3.2 (95% CI 0.6–5.9) letters for ranibizumab and 68.4 (SD 17.4) and +5.6 (95% CI 2.9–8.2) letters for aflibercept (see **Table 2, Supplemental Digital Content 4**, <http://links.lww.com/IAE/B640>). Reasons for noncompletion were recorded in 27 of the 196 eyes that did not complete 3 years of follow-up and included 14 deceased (5 in the aflibercept group vs. 9 in the ranibizumab group), 1 further treatment futile (in the ranibizumab group), 2 declined further treatment (both in the aflibercept group), and 10 went to another doctor (6 in the aflibercept group vs. 4 in the ranibizumab group).

Adverse Events

A summary of adverse events is presented in Table 4. The most frequent adverse event was preretinal vitreous hemorrhage ($n = 18$ and 20 for ranibizumab and aflibercept, respectively).

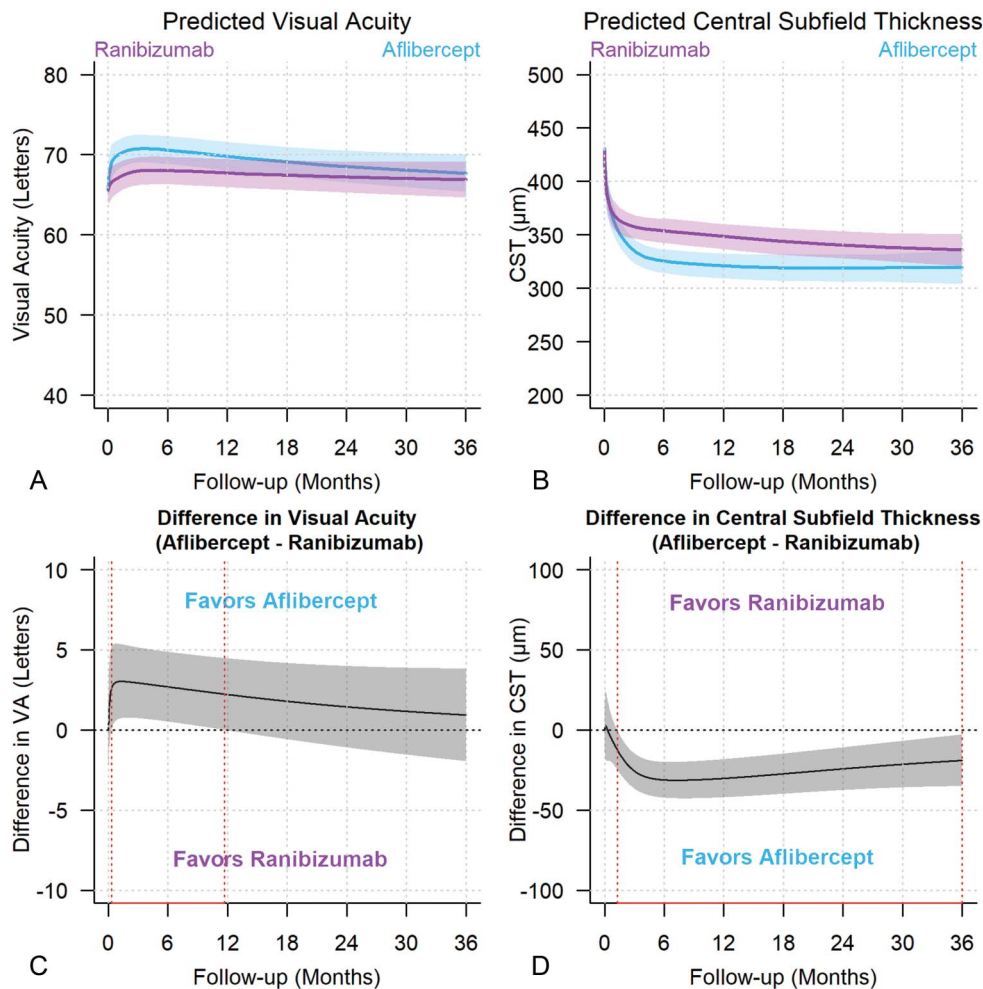


Fig. 1. Predicted (A) visual acuity and (B) CST over time with 95% CIs (shaded) for ranibizumab and aflibercept estimated from generalized additive models using data from all eyes, including completers, non-completers, and switchers. The difference between the drugs is shown in (C) and (D) for visual acuity and CST, respectively. The red dotted lines indicate periods in which the CI for the difference no longer contains 0.

Discussion

We used the FRB! international observational outcomes registry to assess the 3-years outcomes of aflibercept and ranibizumab for DME in daily clinical practice. Both drugs improved visual acuity and reduced CST in DME after 3 years of treatment. We found a significant superior mean visual gain of aflibercept-treated eyes (+5.0 letters) over ranibizumab-treated eyes (+2.9 letters) after the first year of treatment, which then progressively diminished over time to become similar between drugs at 3 years (+2.4 letters for aflibercept vs. +1.6 letters for ranibizumab). Aflibercept-treated eyes (mean CST change: $-114 \mu\text{m}$ at 3 years) had a significantly greater reduction of macular thickness than ranibizumab-treated eyes ($-88 \mu\text{m}$ at 3 years) over 3 years of treatment. When baseline visual impairment was worse (visual acuity ≤ 68 Early Treatment Diabetic Retinopathy Study letters or 20/50), we found a greater and faster improvement in visual acuity in eyes

treated with aflibercept up until 18 months of treatment than eyes treated with ranibizumab, which then stayed similar until 3 years, whereas there was no apparent difference in visual improvement over the 3 years between drugs when baseline visual impairment was mild (visual acuity ≥ 69 Early Treatment Diabetic Retinopathy Study letters or $\geq 20/40$).

Unsurprisingly, visual improvement in our real-world observational study using both drugs was lower than the visual improvement of 7 to 12 letters reported after 3 to 5 years of treatment in pivotal randomized clinical trials (RCTs)^{6,9-11} and similar to previous long-term observational retrospective studies with approximately 3 letters of mean visual acuity gain after 2 to 3 years of treatment.^{12,13} This may be explained by differences in inclusion/exclusion criteria, fewer protocol-driven treatment decisions, and less frequent treatment in routine clinical care.^{6,14} Previous RCTs showed that the mean visual acuity improvement was stabilized in DME eyes treated continuously with VEGF inhibitors within a protocol-defined regimen over the medium term.⁹⁻¹¹

Table 3. Visual and Treatment Outcomes at 3 Years Stratified by Baseline Vision (Completers, Noncompleters, and Switchers Were Included)

	VA ≤68 Letters			VA ≥69 Letters		
	Ranibizumab	Aflibercept	<i>P</i>	Ranibizumab	Aflibercept	<i>P</i>
Eyes	133	124		134	143	
Baseline VA, mean (SD)	52.1 (18.5)	51.7 (17)	0.856	76.6 (5.3)	76.5 (5.6)	0.811
Final VA, mean (SD)*	60.2 (21.1)	62.8 (20.2)	0.303	74 (13.8)	74 (14.8)	0.984
≥70 letters, n (%)	53 (39.8%)	61 (49.2%)	0.167	108 (80.6%)	114 (79.7%)	0.974
≤35 letters, n (%)	20 (15%)	13 (10.5%)	0.366	5 (3.7%)	4 (2.8%)	0.743
ΔVA, mean (95% CI)*	8.1 (4.6 to 11.5)	11.1 (7.9 to 14.3)	0.201	-2.6 (-4.9 to -0.3)	-2.5 (-4.9 to -0.1)	0.941
Gain ≥10 letters, n (%)	62 (46.6%)	74 (59.7%)	0.049	8 (6%)	15 (10.5%)	0.253
Loss ≥10 letters, n (%)	12 (9%)	9 (7.3%)	0.773	15 (11.2%)	25 (17.5%)	0.188
Adjusted ΔVA, mean (95% CI)†	6.5 (2.9 to 10.1)	8.9 (4.8 to 13.0)	<0.001	3.9 (-6.4 to 14.1)	4.1 (-6.2 to 14.5)	0.137
Baseline CST, mean (SD)	476.4 (142.6)	486.9 (166.1)	0.610	380.5 (92.7)	376 (89.9)	0.686
Final CST, mean (SD)*	351.7 (113.4)	329.4 (120.7)	0.156	334.8 (93.3)	309.6 (85.8)	0.024
ΔCST, mean (95% CI)*	-124.7 (-154.3 to -95)	-157.5 (-187 to -128)	0.122	-45.8 (-62.5 to -29)	-66.4 (-84.3 to -48.4)	0.098
Adjusted ΔCST, mean (95% CI)†	-111.0 (-146.8 to -75.2)	-137.1 (-173.5 to -100.7)	0.002	-67.6 (-88.6 to -46.5)	-91.8 (-111.7 to -71.8)	<0.001
Final DME activity, n (%)						
Centre-involving CSME	85 (63.9%)	59 (47.6%)	0.008	78 (58.2%)	62 (43.4%)	0.024
Non-centre-involving CSME	19 (14.3%)	36 (29%)		30 (22.4%)	35 (24.5%)	
None	29 (21.8%)	29 (23.4%)		26 (19.4%)	46 (32.2%)	
Visits, median (Q1, Q3)	22 (15-28)	18 (11-24)	0.982	18 (12-26)	16 (10-25)	0.276
Injections, median (Q1, Q3)	8 (4-14)	8 (5-12.2)	0.734	6.5 (4-10)	8 (5-13)	0.400
≥6 months without injection, n (%)	57 (42.9%)	52 (41.9%)	0.982	65 (48.5%)	67 (46.9%)	0.877
Switchers, n (%)	31 (23.3%)	13 (10.5%)	0.010	41 (30.6%)	11 (7.7%)	<0.001
Additional macular laser, n (%)	10 (7.5%)	6 (4.8%)	0.529	14 (10.4%)	6 (4.2%)	0.076
Cataract surgery, n (%)	20 (15%)	25 (20.2%)	0.360	11 (8.2%)	19 (13.3%)	0.244

Significant *P*-values are shown in bold font.

*Last observation carried forward for non-completers and data were censored at time of switch for switchers.

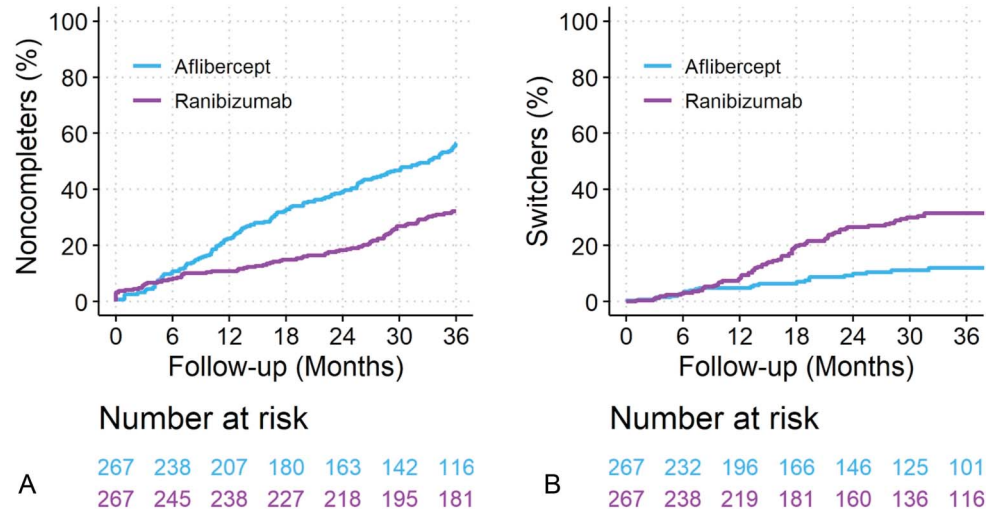
†Estimated from longitudinal generalised additive mixed models comparing the trajectory between drugs over the entire 36-month period (see **Figure 2, Supplemental Digital Content 3**, <http://links.lww.com/IAE/B638>). Models were adjusted for age, VA, CST and DME activity at baseline, and nesting of outcomes from bilateral patients and within practice.

The protocol T extension study recently reported that the mean visual acuity declined from 2 to 5 years when routine clinical care started at the end of the study with fewer visits (median number of 12 from 2 to 5 years vs. 10 in the first 2 years) and treatments (median number of 4 from 2 to 5 years vs. 15 in the first 2 years). Several studies have suggested that there are complex issues around compliance and adherence to the follow-up and treatment in eyes with DME in daily practice related to the follow-up and treatment burden, not only for diabetic retinopathy or DME but also for the other dis-

eases secondary to diabetes in general,¹⁵ that may cause worse visual outcomes.^{16,17} The presenting vision in this study was also high (64.4 letters for ranibizumab and 65.0 letters for aflibercept) which may have resulted in ceiling effects. The visual gains observed in our cohort of eyes starting with visual acuity ≤68 letters (adjusted mean change in visual acuity of +6.5 letters for ranibizumab and +8.9 letters for aflibercept) (Table 3) were closer to that observed in the RCTs.^{5,6}

Randomized clinical trials and meta-analyses have reported that aflibercept 2 mg was superior to both

Fig. 2. Kaplan–Meier survival curves and 95% CIs for time to (A) noncompletion and (B) switching between ranibizumab and aflibercept. Note that 36-months completion only required 1,095 days of follow-up based on the 1,095 ±90-day window, whereas the number at risk of noncompletion at 36 months is for exactly 1,095 days.



ranibizumab 0.3 mg and bevacizumab 1.25 mg at 1 year when starting visual acuity impairment is moderate (visual acuity ≤20/50) in DME eyes.^{1,4} One observational study has confirmed this difference at 1 year when comparing aflibercept 2 mg to ranibizumab 0.5 mg.² However, the superiority of aflibercept 2 mg over ranibizumab 0.3 mg was not observed at 2 years in the DRRCR.net protocol T trial.⁵ The present analysis confirms that the greater and faster visual improvement observed in aflibercept 2 mg–treated eyes than ranibizumab 0.5 mg–treated eyes at 1 year lasts for 2 years with no clinically significant difference at 3 years in a real-world clinical setting. These differences might relate to discrepancies in baseline characteristics and treatment frequency between drugs. Aflibercept-treated eyes tended to receive more injections over 36 months, to be younger, and to have more severe diabetic retinopathy with worse visual acuity and higher CST at baseline than ranibizumab-treated eyes, although these differences were only statistically

significant for baseline DME activity ($P = 0.014$). It has been suggested that some other baseline characteristics could influence outcomes of treatment of DME irrespective of the type of drug.¹⁰ Our analyses were adjusted for age, visual acuity, CST, and DME activity at baseline and nested within practice and patients to control for management variability between practitioners and bilateral cases to compare treatment outcomes between both drugs.¹⁸ Although injection frequency may also affect visual and anatomical outcomes, we found no significant difference in the adjusted number of injections and visits between drugs over 36 months.

Both aflibercept and ranibizumab reduced CST over 3 years with a significantly higher improvement in eyes treated with aflibercept independently of baseline visual impairment. This superiority in the reduction of CST in the aflibercept group did not show a corresponding improvement in visual acuity compared with the ranibizumab group. Previous studies have reported a moderate

Table 4. Summary of Adverse Event Numbers and Rates Per Injection Recorded During the Study Period

	Adverse Events, n (Rate Per Injection)	
	Ranibizumab	Aflibercept
Infectious endophthalmitis	0 (0%)	0 (0%)
Non-infectious endophthalmitis	1 (0.043%)	0 (0%)
Anterior uveitis	0 (0%)	0 (0%)
Occlusive retinal vasculitis	0 (0%)	0 (0%)
Pre-retinal vitreous haemorrhage	18 (0.773%)	20 (0.799%)
Rubeosis	4 (0.172%)	4 (0.16%)
Starts new glaucoma medication	9 (0.386%)	2 (0.08%)
Laser trabeculoplasty	0 (0%)	0 (0%)
Incisional glaucoma surgery	0 (0%)	0 (0%)
Retinal detachment	2 (0.086%)	0 (0%)
Total injections	2,330	2,503

correlation between the change in visual acuity and CST over time in DME.^{19,20} Aflibercept was also more effective in controlling DME anatomically over 3 years with a lower rate of CI-CSME than ranibizumab-treated eyes, although aflibercept-treated eyes started with thicker maculae at baseline. Similarly, a secondary analysis of the DRCR.net protocol T reported that the rate of chronic persistent DME at 2 years tended to be less frequent in the aflibercept group than the ranibizumab group.²¹ Aflibercept-treated eyes in this study tended to have higher CST at baseline and received somewhat more injections than ranibizumab-treated eyes, which may explain the larger mean change in CST.

Comparison of treatment outcomes between drugs may be biased by eyes that are lost to follow-up because of worse outcomes or eventually good response to treatment or switched to another drug because of inadequate response. The noncompletion rate at 3 years was more important in the aflibercept group, whereas the rate of switching was significantly higher from ranibizumab to aflibercept than vice versa. Unfortunately, the true monotherapeutic outcomes of switchers and non-completers cannot be known. However, mixed models are an appropriate method for addressing missing longitudinal data assuming that the data are missing at random.²² That is, we assume that the 36-months outcomes for these eyes can be reasonably inferred based on their available data, and they did not experience an unobserved deviation from their observed trajectory. There is always a degree of lack of adherence to VEGF inhibitors over the long term. We found similar rates of noncompletion as the same FRB 3-year analysis of eyes with neovascular age-related macular degeneration.²³ Nonadherence remains a concern in the treatment of all retinal diseases.²⁴ Reasons for discontinuation and switching did not seem to be related to bad outcomes judging by the mean visual acuity change at drop out or at the time of switch. Our estimated outcomes might be inferior to the real outcomes if patients with good vision tended to discontinue or switch to another drug within 3 years. The treatment outcome trend was also similar when considering the monotherapy completer group.

Real-world observational data are an excellent complement to RCT data to provide evidence on how to get the best outcomes for our patients with DME.²⁵ We recognize several limitations that are frequent in retrospective studies. There was a lack of prospective randomization of drug allocation, although the statistical analysis was adjusted for impactful baseline characteristics such as age, visual acuity, CST, and DME activity and nesting of outcomes within practice and patient. Decision of treatment in daily practice does not rely on the guidance of a study protocol, in contrast to RCTs. The selection of cases and dosing frequency

may also vary among retina specialists. The reasons for switching treatment or selecting a particular VEGF inhibitor type cannot be known from our analysis. The reasons for choosing a particular VEGF inhibitor for each eye and treatment switch cannot be determined from our data. Nonetheless, we have compared both drugs because they are being used in daily practice.

In conclusion, aflibercept and ranibizumab were both safe and effective for DME over 3 years in daily practice, although aflibercept had better anatomical outcomes. The faster and larger visual gains at 1 year observed in eyes treated with aflibercept when the presenting visual impairment was moderate (visual acuity ≤ 68 letters or 20/50) were no longer significant by 18 months as already described in a RCT.⁵ The medium-term real-world treatment outcomes of ranibizumab or aflibercept for DME seemed to be somewhat inferior to those reported in RCTs.

Key words: diabetic macular edema, aflibercept, ranibizumab, clinical outcomes, real-world data, real-world evidence, registry.

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