Three-Year Treatment Outcomes of Aflibercept Versus Ranibizumab for Diabetic Macular Edema: Data from the Fight Retinal Blindness! Registry

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THREE-YEAR TREATMENT OUTCOMES OF AFLIBERCEPT VERSUS RANIBIZUMAB FOR DIABETIC MACULAR EDEMA: DATA FROM THE FIGHT RETINAL BLINDNESS! REGISTRY

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Summary statement (words count = 39/50): Aflibercept and ranibizumab were both effective and safe in DME over 3 years in daily clinical practice, with aflibercept having better anatomical outcomes. Our real-world data confirm previous randomized clinical trial findings, notably from the DRCR.net protocol T study.

Abstract

Purpose Compare the three-year outcomes of ranibizumab *versus* aflibercept in eyes with DME in daily practice.

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

Results We identified 534 eyes (ranibizumab – 267, aflibercept – 267) of 402 patients. The adjusted mean (95% CI) VA change of +1.3 (-0.1, 4.2) letters in the ranibizumab group and +2.4 (-0.2, 5.1) letters ($P = 0.001$) in the aflibercept group at 3 years was not clinically different. However, the adjusted mean CST change appeared to remain significantly different throughout the three-year period with higher reductions in favor of aflibercept (-87.8 [-108.3, -67.4] µm for ranibizumab vs. -114.4 [-134.4, -94.3] for aflibercept; $P < 0.01$). When baseline visual impairment was moderate (VA ≤68 ETDRS letters), we found a faster improvement in VA 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, while there was no apparent difference when baseline visual impairment was mild (VA ≥69 ETDRS letters). The rate of serious adverse events was low.

Conclusions Aflibercept and ranibizumab were both effective and safe for DME over 3 years.

Keywords: Diabetic macular edema, aflibercept, ranibizumab, clinical outcomes, real-world data, real-world evidence, registry.

Introduction

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 (DRCR) Network protocol T study, metanalysis, and real-world data found that aflibercept (Eylea, Bayer, Berlin, Germany) tends to improve vision at one year more effectively than ranibizumab (Lucentis, Genetech Inc/Novartis, Basel, Switzerland) in eyes with baseline visual acuity (VA) of ≤ 68 letters (Snellen equivalent 20/50) while there was no difference in eyes with baseline VA ≥ 69 letters (20/40).[1,2,4] This difference was no longer seen two years after starting treatment in the protocol T study.[5] The protocol T extension study recently reported that five-year mean visual acuity (VA) was still better than baseline in DME eyes treated with vascular endothelial growth factor (VEGF) inhibitors. However, VA tended to worsen without significant change in retinal thickness when eyes exited the 2-year clinical trial and returned to routine clinical care.[6] Evidence on outcomes of treatment of DME in daily practice for longer than two years is limited but necessary to optimize patient outcomes. We compared the three-year 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 the intravitreal VEGF inhibitors aflibercept (Eylea, Bayer, Berlin, Germany) or ranibizumab (Lucentis, Genetech 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 United Kingdom (UK). 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 sought from patients in France, Ireland, Italy, Spain, Switzerland, New Zealand and the UK. 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 logMAR VA

Chart (best of uncorrected, corrected or pinhole), type of treatment given, the central subfield thickness (CST [μm]) measured using spectral-domain optical coherence tomography (OCT) 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 (DR), 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 1 January 2013 to 31 December 2017 were considered for the study, thereby allowing the possibility of having at least three years of follow-up after the start of treatment. Eyes with a history of DME treatment, such as intravitreal injection, macular focal laser or vitrectomy were excluded. The three-year endpoint was the closest visit to 1095 days of follow-up ± 90 days. Eyes were grouped into either ranibizumab or aflibercept based on their initial injection. Eyes that completed at least 1005 days of follow-up were defined as "completers". Eyes that did not complete 36 months of observations were defined as "non-completers". "Switchers" were defined as eyes receiving ≥2 injections of the other treatment drug prior to 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 three years between ranibizumab and aflibercept. Secondary outcomes were the change in central subfield

thickness, number of visits, injections, switching rates, adverse event rates and non-completion rates.

Statistical analysis

Descriptive data were summarized using the mean, standard deviation, median, interquartile range, and percentages where appropriate. Outcomes were compared between ranibizumab and aflibercept for the following groups: all eyes, monotherapy completers and non-completers + 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 non-completers. Switchers were censored at the time of switch. Visual outcomes at time of switch were also reported. Outcomes were also stratified by baseline vision into two groups, ≥69 letters (20/40) and ≤68 letters (20/50).

Adjusted VA and CST changes were calculated using generalized additive mixed models (GAMMs) with visits from all eyes, including completers, non-completers, and switchers. The adjusted VA and CST were analyzed longitudinally, with the interaction between initial injection and time being the main predictor. The adjusted difference in VA and CST were compared over the entire three-year 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 GAMMs and generalized Poisson models included adjustments for baseline age, baseline VA, baseline CST, and baseline DME activity (fixed effects), and nesting of outcomes within practice and eyes from the same patient (random effects). Time to non-completion and switching were visualized using Kaplan-Meier survival curves.

All analyses were conducted 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 GAMMs and *survival* package (V 3.2-7) for Kaplan-Meier survival analysis.

Results

Study participants

There were 534 eligible eyes (267 ranibizumab, 267 aflibercept) from 402 patients for this analysis (**Supplemental Digital Contents:** see Supplemental Figure S1, http://links.lww.com/IAE/B637), of which 242 eyes (125 ranibizumab, 117 aflibercept) had at least 3 years of follow-up. Most baseline characteristics were similar between both groups, including the VA (64.4 letters vs. 65.0 for ranibizumab and aflibercept, respectively; P = 0.720). Baseline characteristics are shown in Table 1.

Visual and Anatomical Outcomes

Visual and anatomical outcomes are summarized in Table 2. The longitudinal adjusted VA change over the three-year 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 (Figures 1A and 1C), the adjusted VA change at three years after this initial superiority had diminished were similar (mean [95% CI] adjusted VA change +1.6 [-0.1, 4.2] letters for ranibizumab vs. +2.4 [-0.2, 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 three years (P = 0.050; **Supplementary Digital Contents:** see Supplemental Table S1, http://links.lww.com/IAE/B639).

The longitudinal CST change over the three-year period was also significantly different (P < 0.001) although, unlike VA, the adjusted CST change appeared to remain significantly

different throughout the entire three-year period (Figures 1B and 1D) with greater reductions in favor of aflibercept (mean [95% CI] adjusted CST change -87.8 [-108.3, -67.4] µm for ranibizumab vs. -114.4 [-134.4, -94.3] µm for aflibercept; $P < 0.01$). Again, these trends were similar when considering monotherapy completers (**Supplementary Digital Contents:** see Supplemental Table S1). There were also fewer eyes in the aflibercept-treated group with centre-involving CSME (44%) compared with ranibizumab (61%) at three years (P < 0.001).

Injection and Visit Frequency

There was a median (Q1, Q3) of 8 (4, 13) and 12 (6, 17) injections in eyes completing three years of monotherapy with ranibizumab and aflibercept, respectively (P = 0.153; **Supplementary Digital Contents:** see Supplemental Table S1). The combined non-completers and switchers cohort received a median of 7 ranibizumab and 6 aflibercept injections prior to 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; **Supplementary Digital Contents:** see Supplemental Table S1). The combined non-completers 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

Eyes were split into two groups stratified by baseline vision: VA ≤68 letters (n = 133 ranibizumab, 124 aflibercept) and VA ≥69 (n = 134 ranibizumab, 143 aflibercept). The mean change in VA over the three-year 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 **Supplemental Digital Contents:** see Supplemental Figure S2, 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 three-year follow-up period in both baseline VA groups (**Supplemental Digital Contents:** see Supplemental Figure S2).

Switchers and Non-completers

Switching to another VEGF inhibitor within three 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) VA at time of switch was 68.3 (17.4) letters for initially ranibizumab eyes and 62.3 (23) letters for initially aflibercept eyes (**Supplemental Digital Contents:** see Supplemental Table S2, http://links.lww.com/IAE/B640). The mean VA 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 non-completion rate was 26% for ranibizumab and 47% for aflibercept (P < 0.001; Figure 2A). The rate of non-completion was 23 vs 11% at 12 months, 39 vs. 18% at 24 months and 57 vs. 32 % at 36 months in aflibercept and ranibizumab groups, respectively. The mean VA and VA change at time of dropout was 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 (**Supplemental Digital Contents:** see Supplemental Table S2). Reasons for non-completion were recorded in 27 of the 196 eyes that did not complete three 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 shown in Table 4. The most frequent adverse event was pre-retinal vitreous haemorrhage (n = 18 and 20 for ranibizumab and aflibercept, respectively).

Discussion

We used the FRB! international observational outcomes registry to assess the 3-year outcomes of aflibercept and ranibizumab for DME in daily clinical practice. Both drugs improved VA and reduced CST in DME after three 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 three years (+2.4 letters for aflibercept *vs.* +1.6 letters for ranibizumab). Aflibercept treated eyes (mean CST change: -114 μm at 3 years) had a significantly greater reduction of macular thickness than ranibizumab treated eyes (-88 μm at 3 years) over 3 years of treatment. When baseline visual impairment was worse (VA ≤68 ETDRS letters or 20/50), we found a greater and faster improvement in VA in eyes treated with aflibercept up until 18 months of

treatment than eyes treated with ranibizumab, which then stayed similar until 3 years, while there was no apparent difference in visual improvement over the 3 years between drugs when baseline visual impairment was mild (VA ≥69 ETDRS letters or ≥ 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 VA 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 VA improvement was stabilized in DME eyes treated continuously with VEGF inhibitors within a protocol-defined regimen over the medium term.[9–11] The protocol T extension study recently reported that mean VA 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 two years) and treatments (median number of 4 from 2 to 5 years vs. 15 in the first two years). Several studies have suggested that there are complex issues around compliance and adherence to follow-up and treatment in eyes with DME in daily practice related to follow-up and treatment burden, not just for DR or DME but also for the other diseases 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 VA≤68 letters (adjusted mean change in VA of +6.5 letters for ranibizumab and +8.9 letters for aflibercept) (Table 3) were closer to that observed in the RCTs.[5,6]

RCTs and metanalyses have reported that aflibercept 2 mg was superior to both ranibizumab 0.3 mg and bevacizumab 1.25 mg at 1 year when starting VA impairment is moderate (VA ≤ 20/50) in DME eyes.[1,4] One observational studies has confirmed this difference at one 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 two years in the DRCR.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 one year lasts for two years with no clinically significant difference at three 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 DR with worse VA and higher CST at baseline than ranibizumab treated eyes, though 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, VA, 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 impact 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 VA compared to the ranibizumab group. Previous studies have reported a

moderate correlation between the change in VA 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 even though aflibercept-treated eyes started with thicker maculae at baseline. Similarly, a secondary analysis of DRCRnet 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 the current 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 due to worse outcomes or eventually good response to treatment or switched to another drug due to inadequate response. The non-completion 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 the data are missing at random.[22] That is, we assume that the 36-month 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 non-completion 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 VA change at drop out or at 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, though the statistical analysis was adjusted for impactful baseline characteristics such as age, VA, CST and DME activity, and nesting of outcomes within practice and patient. Decision of treatment in daily practice do 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 as 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, though aflibercept had better anatomical outcomes. The faster and larger visual gains at one year observed in eyes treated with aflibercept when the presenting visual impairment was moderate (VA ≤ 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.

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Figure captions

Figure 1. Predicted A) visual acuity and B) central subfield thickness over time with 95% confidence intervals (shaded) for ranibizumab and aflibercept estimated from generalised 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 central subfield thickness, respectively. The red dotted lines indicate periods in which the confidence interval for the difference no longer contains 0.

Figure 2. Kaplan-Meier survival curves and 95% confidence intervals for time to A) non-completion and B) switching between ranibizumab and aflibercept. Note that 36-month completion only required 1005 days of follow-up based on the 1095 ± 90-day window whereas the number at risk of non-completion at 36 months is for exactly 1095 days.

Table 1. Demographic characteristics for eyes initiating treatment with ranibizumab or aflibercept			
	Ranibizumab	**Aflibercept**	**P-value**
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 (%)			
Centre-involving CSME	243 (91.0%)	240 (89.9%)	0.430
Non-centre-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%)	

CSME, clinically significant macular edema; CST, central subfield thickness; DME, diabetic macular edema; PDR, proliferative diabetic retinopathy; NPDR, non-proliferative diabetic retinopathy; SD, standard deviation; VA, visual acuity.

Table 2. Visual and treatment outcomes at 3 years (all eyes including completers, switchers, and non-completers)

	Ranibizumab	Aflibercept	P-value
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, 4.9)	3.8 (1.7, 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, 4.2)	2.4 (-0.2, 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, -65.1)	-108.3 (-125.8, -90.8)	**0.035**
Adjusted ΔCST, mean (95% CI) *, †	-87.8 (-108.3, -67.4)	-114.4 (-134.4, -94.3)	**<0.001**
Final DME activity, n (%)			
Centre-involving CSME	163 (61.0%)	118 (44.2%)	**<0.001**
Non-centre-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

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

CI – confidence interval; CSME, clinically significant macular edema; CST, central subfield thickness; DME, diabetic macular edema; SD, standard deviation; VA, visual acuity

Significant p-values are shown in bold font.

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

Table 3. Visual and treatment outcomes at 3 years stratified by baseline vision (completers, non-completers, and switchers were included)

	VA ≤68 letters			VA ≥69 letters		
	Ranibizumab	Aflibercept	P-value	Ranibizumab	Aflibercept	P-value
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, 11.5)	11.1 (7.9, 14.3)	0.201	-2.6 (-4.9, -0.3)	-2.5 (-4.9, -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, 10.1)	8.9 (4.8, 13.0)	**<0.001**	3.9 (-6.4, 14.1)	4.1 (-6.2, 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, -95)	-157.5 (-187, -128)	0.122	-45.8 (-62.5, -29)	-66.4 (-84.3, -48.4)	0.098
Adjusted ΔCST, mean (95% CI) *, †	-111.0 (-146.8, -75.2)	-137.1 (-173.5, -100.7)	**0.002**	-67.6 (-88.6, -46.5)	-91.8 (-111.7, -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

CI – confidence interval; CSME, clinically significant macular edema; CST, central subfield thickness; DME, diabetic macular edema; SD, standard deviation; VA, visual acuity

* 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 (**Supplemental Digital Contents**: see Supplemental Figure S2). Models were adjusted for age, VA, CST and DME activity at baseline, and nesting of outcomes from bilateral patients and within practice.

Significant p-values are shown in bold font.

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	**2330**	**2503**