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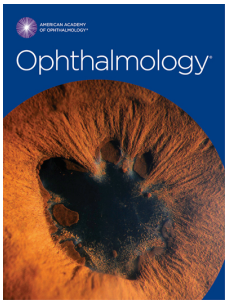

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Ranibizumab or Aflibercept for Diabetic Macular Edema: Comparison of One-Year Outcomes from the Fight Retinal Blindness! Registry

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Conflict of Interest: Gillies and Barthelmes are inventors of the software used to collect the data for this analysis

Running head: Aflibercept or ranibizumab for DME: One-year real-world outcomes

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Abbreviations and Acronyms

CI - Confidence Interval, CST – Central Subfield Thickness, CSME - Clinically Significant Macular Edema, DME – Diabetic Macular Edema, DR – Diabetic Retinopathy, DRCR.net – Diabetic Retinopathy Clinical Research Network, LOESS - Locally Weighted Scatterplot Smoothing, logMAR - logarithm of the minimum angle of resolution, OCT – Optical Coherence Tomography, Q – Quartiles, SD – Standard Deviation, VA – Visual Acuity, VEGF – Vascular Endothelial Growth Factor

Abstract

Purpose: Both ranibizumab and aflibercept improved vision and decreased macular thickness in eyes with diabetic macular edema (DME) in clinical trials. This study compares the 12 month treatment outcomes of each drug in routine clinical practice.

Design: Retrospective analysis of data from a prospectively designed observational outcomes registry: the Fight Retinal Blindness! Project.

Participants: Treatment-naïve eyes starting intravitreal injections of either ranibizumab (0.5mg) or aflibercept (2mg) for DME from 1 December 2013 to 1 June 2018 that were tracked in the registry.

Methods: Visual acuity (VA) was analyzed at 12 months in all eyes (completers, non-completers and eyes that switched treatment).

Main Outcome measures: The primary outcome was the mean change in VA (number of letters read on a logarithm of the minimum angle of resolution chart) from baseline to 12 months.

Results: We identified 383 eyes (Ranibizumab – 166, Aflibercept – 217) of 291 patients. Eyes of patients in the aflibercept group had a lower mean VA (mean difference [MD] -3.1 letters) and a thicker maculae (MD +26μm) than those of ranibizumab at baseline which was not significantly different. Patients on ranibizumab were older (MD +2.7 years). The adjusted MD in VA change and central subfield thickness (CST) reduction were +1 letter (1.4 for aflibercept versus 0.4 for ranibizumab, p = 0.4) and -30 microns (-85 *versus* -55, p<0.01) in eyes with initial VA ≥ 20/40 and +3 letters (10.6 versus 7.6, p<0.01) and -46 microns (-148 *versus* -102, p<0.02) in those presenting with VA ≤ 20/50. Eyes in the aflibercept group received more injections over

12 months, median (Q1, Q3) of 8 (6, 9), than the ranibizumab group, 6 (4, 8), though this difference was not significant (p = 0.13). Treatment switches, albeit low, were more frequent from ranibizumab to aflibercept than *vice versa*. Significantly more eyes in the aflibercept group were lost to follow-up within 12 months (21% *versus* 9% ranibizumab, P<0.01).

Conclusions: Both drugs were beneficial for DME. Aflibercept-treated eyes, which had borderline worse vision and thicker maculae at baseline, had larger reductions in CST after 12 months of treatment. Larger gains in VA was observed with aflibercept treatment when the initial VA was ≤ 20/50.

Introduction

Ranibizumab (Lucentis, Genetech Inc/Novartis) and aflibercept (Eylea, Bayer) are vascular endothelial growth factor (VEGF) inhibitors used first-line in the management of diabetic macular edema (DME).[1-4] The Diabetic Retinopathy Clinical Research (DRCR) Network protocol T study found that aflibercept (2mg) was more effective than ranibizumab (0.3mg) in improving vision at 1 year in eyes presenting with visual acuity (VA) of ≤ 68 letters (Snellen equivalent 20/50) while there was no difference in those presenting with VA ≥ 69 letters (20/40).[5] This difference was not observed two years after starting treatment.[6] A meta-analysis of twenty-four clinical trials of anti-VEGF treatments for DME produced "moderate" evidence that aflibercept had an advantage over ranibizumab one year after starting treatment in terms of VA and reduction in macular edema.[7]

Clinical trials determine the effects of new treatments in controlled conditions for a selected group of patients that may not be representative of the general population with the disease. The validity of results of clinical trials are ideally confirmed in the general population by population-based post-marketing observational studies. Real-world studies have found that ranibizumab and aflibercept treatment significantly improved VA and macular thickness 1 year after starting treatment in eyes with DME.[8, 9] A direct comparison of treatment outcomes of the two VEGF inhibitors for DME in real-world clinical practice has yet to be performed. This study aimed to compare the visual and anatomic outcomes and frequency of treatments of ranibizumab *versus* aflibercept in treatment naïve eyes with DME in routine clinical practice.

Methods

Design and setting

This was a retrospective analysis of data tracked in the prospectively designed observational database – The Fight Retinal Blindness! Registry of real-world treatment outcomes of macular diseases.[10] The registry has modules to collect data in age-related macular degeneration, retinal vein occlusion and DME. The DME module was implemented in Australia, New Zealand and Switzerland in April 2015. This has now expanded to other countries in Europe and Asia. Eyes receiving treatment for clinically significant diabetic macular edema (CSME) in routine clinical practice are eligible in the DME module. Investigators undertook to enter all eyes starting treatment for DME in their practices from when they started data entry. Australian practitioners undertake to track at least 85% of their eligible patients to satisfy the mandatory self-audit requirement for annual registration. This analysis included treatment-naïve eyes that started ranibizumab or aflibercept for DME. Participants in this analysis were patients from practices in Australia, France, Italy, Switzerland and the United Kingdom. Institutional approval was obtained from the Royal Australian and New Zealand College of Ophthalmologists Human Research Ethics Committee, the South Eastern Sydney Local Health District Human Research Ethics Committee, the French Institutional Review Board (Société Française d'Ophtalmologie Institutional Review Board), the Ethics Committee of the University of Milan, the Cantonal Ethics Committee Zurich and the Caldicott Guardian at the Royal Free London NHS Foundation Trust. Informed consent ("opt-in consent") was sought from patients in France, Italy and Switzerland.

Ethics committees in Australia approved the use of "opt-out" patient consent. Data in the registry are anonymized and compliant with the UK Policy Framework for Health and Social Care Research. This study adhered to the tenets of the Declaration of Helsinki.

Data Sources and Measurements

The Fight Retinal Blindness! Registry has a module that collects data from eyes being treated for DME. The data recorded at each clinical visit include the number of letters read on a logarithm of the minimum angle of resolution (logMAR) VA Chart (best of uncorrected, corrected or pinhole), treatment given, the central subfield thickness (CST [μm]) measured using spectral domain optical coherence tomography (OCT), the activity of DME (center-involving clinically significant macular edema [CSME], non-center involving CSME or no CSME), procedures and ocular adverse events.[11] Duration and type of diabetes, grading of diabetic retinopathy (DR) and previous treatment for DME were recorded at the baseline visit. All treatment decisions, including choice of treatment and frequency of visits, were based on VA and OCT at the discretion of the practitioner in consultation with the patient thereby reflecting real-world practice.

Patient selection

Treatment naïve eyes that started DME treatment with either ranibizumab (0.5mg Lucentis, Genetech Inc/Novartis) or aflibercept (2mg Eylea, Bayer) from 1 December 2013 to 1 June 2018 were studied, thereby allowing the possibility of having at least 12 months of observations after the initial treatment. Eyes that did not receive the initial 2 injections of the same drug were excluded from the analysis. Eyes that completed at least 12 months of visits were defined as "completers". Switchers were defined as eyes

that received ≥2 injections of the other drug prior during this time. Visits occurring after the switch to the other drug were censored for analysis. Eyes that did not complete 12 months of observations were defined as “non-completers”.

Outcomes

The main outcome was the mean change in VA in the ranibizumab and the aflibercept treatment groups at 12 months. Secondary outcomes were the mean change in CST, frequency of treatments and visits, the proportions of eyes with VA ≥70 letters (20/40 Snellen equivalent) and ≤35 letters (20/200) and the proportions of eyes that gained ≥10 letters and those that lost ≥10 letters at 12 months. Outcomes were also analyzed in eyes stratified by baseline VA into two groups, ≥69 letters (20/40) and ≤68 letters (20/50), to study the relationship of baseline VA on the VA change. Other outcomes of interest were the proportion of eyes that switched treatment and the rate of non-completion in each of the groups at 12 months.

Statistical analysis

Descriptive data included the mean (standard deviation), median (first and third quartiles) and percentages where appropriate. Eyes were considered to have been observed from the first treatment visit up to their 12 month (365 ± 30 days) visit. T-tests, Wilcoxon rank sum tests, Chi-square tests and Fisher’s exact tests were used as appropriate to compare baseline characteristics between ranibizumab and aflibercept treated eyes. Locally weighted scatterplot smoothing (LOESS) regression curves were used to visualize VA results in eyes throughout the follow-up. Calculation of crude visual

outcomes at 12 months used the last-observation-carried-forward for switchers and non-completers.

We compared VA and CST outcomes between treatments at 12 months using mixed-effects longitudinal generalized additive models with the interaction between initial injection and time as the main predictor variable. Longitudinal models included all visits from completers, switchers (until the time of switch) and non-completers (last observation before the drop-out), and were adjusted for age, baseline VA, baseline CST (fixed-effects), and practice and intra-patient correlation for bilateral cases (random-effects). We used predictions from this model to plot VA and the difference in the mean VA and CST change over 12 months in all eyes. Quasi-Poisson regression models adjusted for age, baseline VA, baseline CST (fixed-effects), and practice and intra-patient correlation (random-effects) with log days of follow-up included as an offset variable were used to compare the number of injections and visits. Cox proportional hazards regression models adjusted for age, VA and CST at baseline (fixed-effects), and practice and intra-patient correlation (random-effects) were used to compare the median time to non-completion and switching over 12 months. Kaplan-Meier survival analysis was used to plot survival curves for time to non-completion and switching.

All analyses were conducted using R version 3.5.3 (http://www.R-project.org/) with the *lme4* package (V1.1-21) for mixed-effects regression analysis, *mgcv* package (V1.8-24) for generalized additive (mixed) model computation, *emmeans* package (V1.3.3) for pairwise comparison of adjusted means, *coxme* package (V2.2-10) to calculate the median time to non-completion and switching *and survival* package (V 2.38) for dropout analysis.[12-17]

Results

Study participants

A total of 383 treatment-naïve eyes (166 ranibizumab and 217 aflibercept), from 291 patients that started DME treatment with either ranibizumab or aflibercept from 1 December 2013 to 1 June 2018, were identified. Table 1 summarizes the baseline characteristics of the eyes in each of the groups. Patients receiving ranibizumab were significantly older than those receiving aflibercept (mean 65.4 *vs.* 62.7 years; P = 0.04) and had diabetes for a longer duration (mean 16 *vs.* 15 years; P = 0.04). Eyes with severe DR grades (severe non-proliferative DR and proliferative DR) were more likely to receive aflibercept. Eyes receiving ranibizumab tended to have better mean vision (67.8 *vs.* 64.7 letters; P = 0.05) and somewhat lower mean CST (407 *vs.* 433 μm; P = 0.05) at baseline. Most eyes had center-involving CSME (92% for both ranibizumab and aflibercept; Table 1).

Visual outcomes at 12 months

The crude mean (95% confidence interval) VA change at 12 months for all eyes, using the last observation carried forward for switchers and dropouts, was higher for aflibercept (6.1 [4.5, 7.7] *versus* 3.3 [1.6, 5.1] letters for ranibizumab; p = 0.02) (Supplementary Table 1). The mean (95% CI) adjusted VA change, using longitudinal models adjusted for age, baseline VA and baseline CST, was also greater in the aflibercept group (5.4 [4.1, 6.7] *vs.* 3.3 [1.9, 4.7] letters for ranibizumab [p<0.01] (Supplementary Table 1). The adjusted mean VA over 12 months for all eyes is shown in Figure 1A. The adjusted mean difference in the VA change was significantly in favor

of aflibercept for most of the 12 months after starting treatment (Figure 1B). The proportion of all eyes with VA ≥ 70 letters and those with VA ≤ 35 letters at 12 months in both the groups were similar. More eyes in the aflibercept group gained ≥ 10 letters at 12 months while similar proportions of each group lost ≥ 10 letters.

We divided the cohort into two groups according to the VA at baseline, eyes with VA ≥ 69 letters (191 eyes [53%]) and those with VA ≤ 68 letters (192 eyes [47%]), to study the relationship of initial vision on VA gain with treatments. The mean VA change at 12 months of treament in eyes with good vision at baseline (VA ≥ 69 letters) was similar for both aflibercept and ranibzumab though more eyes on aflibercept gained ≥ 10 letters at 12 months (19% vs 4%; p<0.01; Supplementary Table 2). However, the mean (95% CI) VA gain at 12 months in eyes with initial vision ≤ 68 letters was significantly higher in eyes on aflibercept, 10.6 (7.9, 13.2) letters, than in those on ranibizumab, 7.6 (4.4, 10.8; p = 0.01) letters.

Figure 2 shows the mean VA over 12 months of three hundred and three eyes (79%) that completed 12 months on monotherapy (aflibercept – 167 [77%], ranibizumab – 136 [82%]) (Supplementary Table 1). The mean (SD) VA of these eyes in the ranibizumab and the aflibercept groups at baseline and 12 months were similar. The crude mean VA change was similar for the two groups at 12 months, but the adjusted mean VA change was significantly higher for the aflibercept group (Supplementary Table 1). The proportion of eyes with VA ≥ 70 letters and those with VA ≤ 35 letters at 12 months was similar in both groups as was the proportion of eyes that gained ≥ 10 letters and those that lost ≥ 10 letters at 12 months.

220 **Macular thickness**

221 Both drugs were effective in reducing macular thickness (Figure 1). Eyes in the
222 aflibercept group had a significantly greater reduction in mean (95% CI) adjusted CST
223 at 12 months than those in the ranibizumab group (-126 [-144, -98] *vs.* -89 [-109, -69]
224 μm; p<0.01) (Supplementary Table 1). The difference in the mean CST change
225 between the two anti-VEGFs at 12 months significantly favored aflibercept (Figure 1C).
226 The advantage of aflibercept over ranibizumab in reducing macular thickness was
227 observed irrespective of whether the initial VA was ≥ 69 letters or ≤ 68 letters
228 (Supplementary Table 2). Figure 2 illustrates the mean CST over 12 months in eyes
229 that completed 12 months in both groups.

230 **Treatments and visits**

231 The median (Q1, Q3) number of anti-VEGF injections and visits in eyes that completed
232 12 months of continuous treatment in the two groups were: 8 (6, 9) for aflibercept *vs.* 6
233 (4, 8; p = 0.13) injections for ranibizumab; 10 (8, 12) visits *vs.* 10 (7, 12) [p = 0.11],
234 (Supplementary Table 1). The number of additional treatments, macular laser and
235 intravitreal steroid injections (triamcinolone and Ozurdex®), in each of the groups during
236 the 12 months were also similar (Supplementary Table 1). There was no difference in
237 the median number of treatments (including additional macular laser and steroids) and
238 visits between ranibizumab and aflibercept groups when eyes were stratified based on
239 the initial VA (Supplementary Table 2).

240 **Treatment switch**

Treatment switches occuring within 12 months were uncommon (19 eyes [5%]) and were more frequent from ranibizumab to aflibercept than *vice versa* (9% vs 2%; p<0.01; Figure 3A). The median (Q1, Q3) times to switch from ranibuzumab to aflibercept was 231 (117, 296) days, and from aflibercept to ranibizumab was 196 (113, 264) days. The mean VA in eyes at baseline and at the time of switch in each of the groups that switched treatment, the mean changes in VA and CST from the start of treatment to the switch and the number of anti-VEGF injections and visits from the start of treatment to the time of switching are shown in supplementary table 1.

Non-completion rate at 12 months

Sixty-one eyes (16%) discontinued treatment before completing 12 months of follow-up. The non-completion rate was higher in the aflibercept group (21% *vs.* 9% in eyes receiving ranibizumab; p<0.01; Figure 3B). The median (Q1, Q3) time to dropout was 223 (121.5, 278) days for aflibercept and 196 (112.5, 264) days for ranibizumab. Eyes that discontinued treatment in both groups had similar mean VA at baseline and at their last visit before they discontinued treatment. The mean (95%CI) VA change, was +7.7 (4.8, 10.7) letters for aflibercept and 3.0 (-1.2, 7.2) letters for ranibizumab (p = 0.06) from the start of treatment to their last visit (Supplementary Table 1). The maculae of the aflibercept group were significantly thicker than eyes in the ranibizumab group when they started treatment. The mean drop in CST at the time treatment was discontinued was also significantly greater in eyes on aflibercept treatment than those on ranibizumab. The median (Q1, Q3) number of anti-VEGF injections, 6 (3, 7) aflibercept *vs.* 4 (3, 5.5; p = 0.51) ranibizumab, and visits, 7 (4.2, 8) *vs.* 5 (3, 7.5; p = 0.22), in the two groups from the start of treatment to their last visit were similar.

The reasons for treatment discontinuation were tracked in 25 of the 61 eyes (41%). The main reason was tranferred care to another physician (52%, ranibizumab – 6 eyes, aflibercept – 7 eyes). Other reasons were patient declined further treatment (24%, ranibizumab – 0 eyes, aflibercept – 6 eyes), patient death (16%, ranibizumab – 3, aflibercept – 1), lack of response to treatment (4%, ranibizumab – 1, aflibercept – 0) and successful treatment (4%, ranibizumab – 1, aflibercept – 0).

Discussion

This analysis in real-world clinical practice from a prospectively designed observational registry found that both aflibercept and ranibizumab improved vision and reduced macular thickness in eyes with DME after one year of treament. Changes in VA for the two treatment groups, +1.4 letters for aflibercept *versus* 0.4 letters for ranibizumab (p = 0.4), was similar (adjusted mean difference of 1 letter) in eyes with initial VA ≥ 69 letters (20/40) and that the greater improvement with aflibercept, 10.6 *versus* 7.6 letters (p<0.01), was observed in eyes with initial VA ≤ 68 letters (20/50). Aflibercept-treated eyes had significantly greater reductions in macular thickness (mean CST change: -128 µm *vs.* -80 µm, p<0.01). Some of this difference might be related to differences in baseline characteristics and injection numbers. Eyes in the aflibercept group received more injections over 12 months, median (Q1, Q3) of 8 (6, 9), than the ranibizumab group, 6 (4, 8), though this difference was not significant (p = 0.13). A few treatment switches occurred during the12 months, more from ranibizumab to aflibercept than *vice versa* but the drop-out rate was higher in the aflibercept group. Eyes that dropped-out in both groups had similar treatment frequencies and visits from the start of treatment to their last visit.

Eyes receiving aflibercept tended to have more advanced disease with somewhat lower mean VA and thicker maculae when they started treatment. Patients on ranibizumab treatment were on average 2 years older than those on aflibercept, which is consistent with a previous observation in eyes on anti-VEGF treatment for neovascular age-related macular degeneration.[18] This could have resulted from the physicians' concerns on the

risk of stroke with aflibercept treatment in older patients which was mentioned in a report from Europe.[19] We compared treatment outcomes between the two groups after adjusting for age, baseline VA and CST and nesting within practices and patients for bilateral cases.[20]

Consistent with pivotal clinical trials and a recent Cochrane meta-analysis, aflibercept and ranibizumab both improved vision in eyes with DME in clinical practice.[1, 2, 5, 7] We found eyes in the aflibercept group had larger vision gains than those in the ranibizumab group at 12 months from the start of treatment, although baseline characeristics were not ideally matched. A Cochrane meta-analysis identified a visual advantage of aflibercept over ranibizumab 0.3mg one year after starting treatment.[7] Here we have found that aflibercept also appears to be more effective than 0.5 mg ranibizumab in improving vision at one year in eyes with VA ≤ 68 letters at the start of treatment, as was reported by The DRCR.net Protocol T for 0.3mg ranibizumab.[5] The visual gains in both the treatment groups were similar in eyes with initial VA≥ 69 letters, perhaps due to the ceiling effect when treating patients with good vision at baseline.

Vision improvements in the present study in both groups were lower than the mean VA gains of 6.8 to 13.1 letters reported after 1 year of treatment in the major clinical trials of anti-VEGF for DME.[5, 21-23] VA improvements in observational studies have usually been lower than those reported by clinical trials.[8, 9, 24] This may be because of different inclusion/exclusion criteria and/or because they receive inadequate treatment.[25] Eyes in the present study received a median of 6 ranibizumab or 8 aflibercept injections over 12 months compared with 10 ranibizumab (50% eyes received additional laser) or 9 aflibercept (35% eyes received additional macular laser) injections in the DRCR.net

study.[5] However, the mean final visual acuity of around 71 letters observed one year after the start of treatment was similar to those reported in the DRCR.net study, suggesting the lower gains in the present study may be partly due to the better starting visual acuity.[5] The mean VA change in the present study was about 9 letters worse in eyes with intial vision ≤ 68 letters and 4 letters better in eyes with initial VA ≥ 69 letters than those of the DRCR.net study.

Both ranibizumab and aflibercept also reduced macular thickness to an extent similar to that reported by Wells et al., with a significantly greater mean reduction in eyes receiving aflibercept which was observed in both strata of VA at the initiation of treatment. [5] Eyes in the aflibercept group in the present study had somewhat thicker maculae at presentation and received somewhat more treatments than eyes in the ranibizumab group, both of which could have contributed for the higher mean drop in macular thickness.

Studies that evaluate treatment outcomes may be biased by eyes that switch treatment or are lost to follow-up since these events may be related to a poor outcome. The rate of switching, though low in the present study (5%), was significantly higher from ranibizumab to aflibercept than *vice versa*. The non-completion rate at 12 months in the present study was higher in the aflibercept group. The primary outcome of the present study included data from all eyes, irrespective of whether they completed, switched or discontinued treatment, to address the potential bias that could arise from asymmetric switching or loss to follow-up. However, the true 12-month outcomes of monotherapy in switchers and non-completers cannot be known and our comparison relies on the assumptions of the model, most notably that the data are missing at random. Thus, we

assume the 12-month outcomes for these eyes can be reasonably inferred based on their observed response and they did not experience an unobserved deviation from their observed trajectory.

A discontinuation or switching rate of 21% as we found after 12 months is typical of observational studies. Reasons for discontinuation, which were recorded in 41% of eyes that did so, were unrelated to poor outcomes in most cases and included transfers to another physician and death (72% of all that discontinued). The remainder were likely related to poor outcomes, including “further treatment considered futile”.

This study has limitations that are inherent in real-world studies. Treatment decisions in routine clinical practice, in contrast to the randomized clinical trials, are made without reference from a reading center or guided by study protocols. Selection of cases and treatment regimen may also differ from clinical trials and among physicians. The data presented here do not provide reasons for the choice of a particular VEGF inhibitor for each eye or for any treatment switch. Nevertheless, we have compared the two VEGF inhibitors for DME treatment as they are actually being used in routine clinical practice. A carefully designed observational study, such as the present study, is unlikely to overestimate the therapeutic effectiveness of an agent.[26] There was a lack of prospective randomization to treatment groups but we have partially offset this with statistical analysis that was adjusted for potentially impactful baseline factors such as VA, age, CST and nesting of outcomes within practice.

The apparent stronger effect of aflibercept over ranibizumab for DME contrasts with similar observational and clinical studies which have reported no discernible difference

360 in the efficacy of the 2 drugs when they are used for neovascular age-related macular
361 degeneration.[27, 28] Perhaps this is because greater levels of aflibercept, which is a much
362 larger molecule than ranibizumab, reach the retinal circulation rather than the subretinal
363 space due to barriers to diffusion of the larger molecule, including the outer limiting
364 membrane and the retinal pigment epithelium for type 1 neovascularization.[29]

365 This study found that both aflibercept and ranibizumab were effective for DME over 12
366 months, with aflibercept having somewhat better anatomic outcomes. Larger VA gains
367 were observed in eyes on aflibercept treatment when the initial VA was ≤ 68 letters
368 (20/50). Longer-term observational studies of intravitreal therapy for DME are warranted
369 to ensure that our patients continue to get the best possible outcomes.

370

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Legends

Figure 1. Line graphs showing (A) the mean predicted visual acuity (VA, solid lines) in logMAR letters (y-axis) and central subfield thickness (CST, dashed lines) in microns (z-axis); (B) the difference in the mean change in VA and (C) CST between ranibizumab (purple) and aflibercept (blue) treated eyes over 12 months in all eyes irrespective of whether they completed, switched (visits at the time of switch) or did not complete 12 months of observations from starting treatment. The grey shaded area in figures B and C represents the 95% confidence interval. Red dashed lines in B and C indicate areas where the 95% confidence interval does not intersect with 0. Predictions were made from a generalized additive model considering adjustments for age, VA and central subfield thickness at baseline (fixed-effects) and the practice and intra-patient correlation for bilateral cases (random-effects).

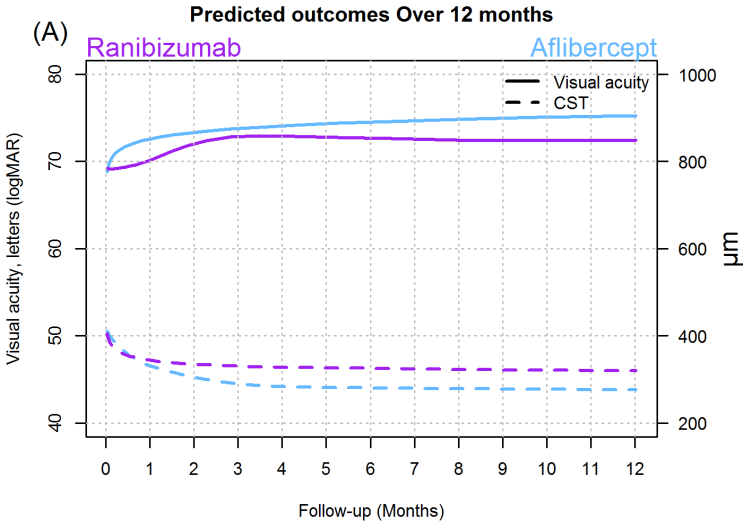
Figure 2. Locally weighted scatterplot smoothing (LOESS) regression curves showing the mean visual acuity (solid lines) in logMAR letters (y-axis) and central subfield thickness (dashed lines) in microns (z-axis) in ranibizumab (purple) and aflibercept (blue) treated eyes completing 12 months of observations from the start of treatment (x-axis).

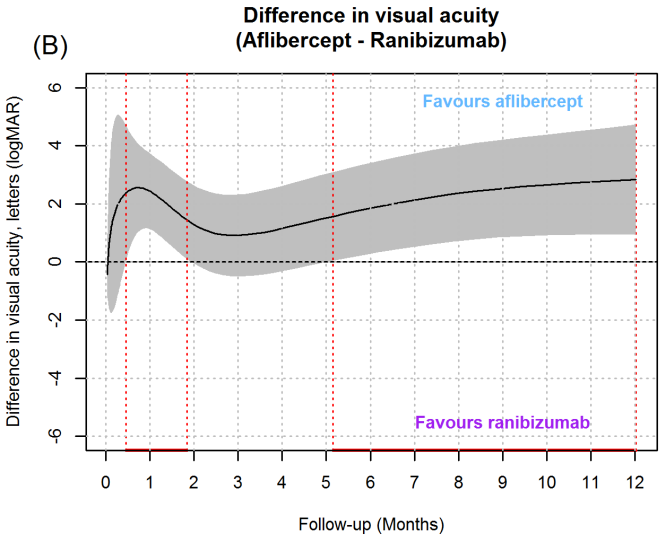
Figure 3. Kaplan-Meier plots for time from starting treatment to (A) treatment switch and (B) dropout in eyes treated with ranibizumab (purple) and aflibercept (blue) treated eyes over 12 months.

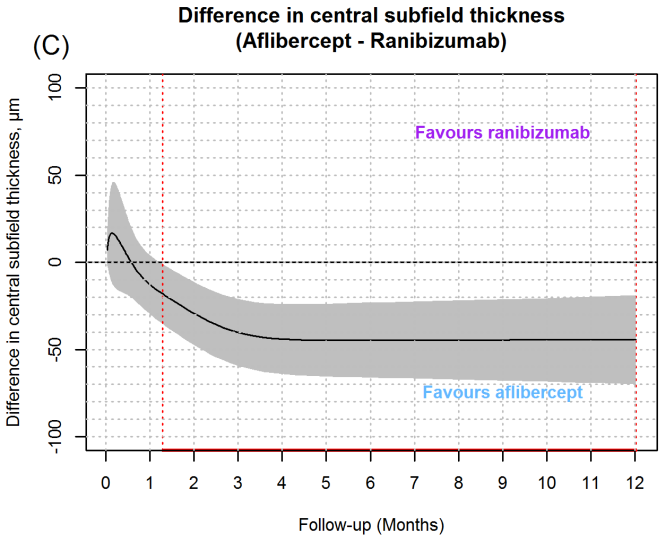
Table 1. Baseline characteristics of eyes treated with Ranibizumab and Aflibercept

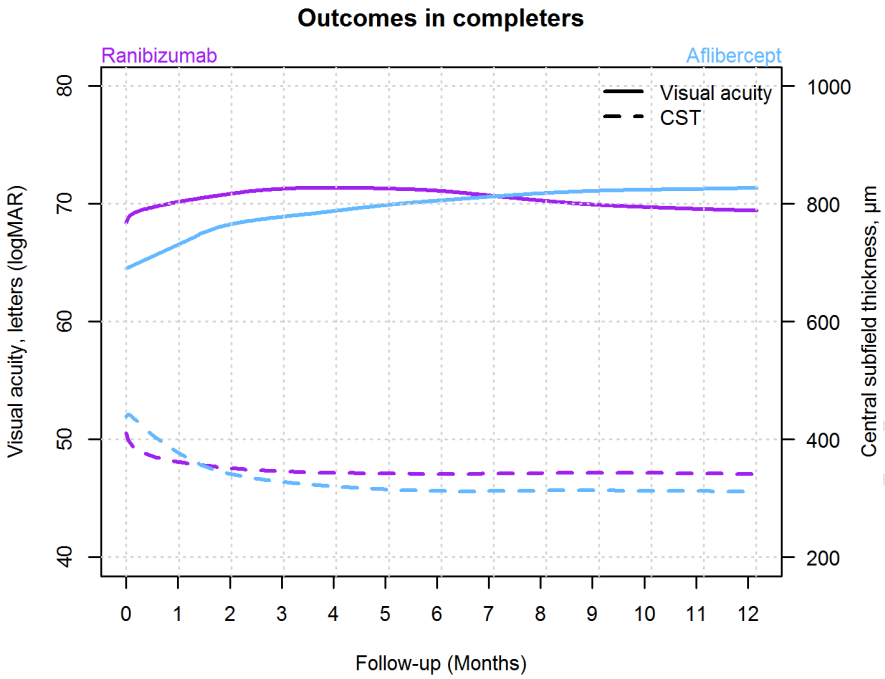
	Ranibizumab	Aflibercept	P value
Eyes, n	166	217	
Patients, n	134	158	
Female, n (%)	55 (41)	58 (37)	0.39
Diabetes duration years, mean (SD)	16 (18)	15 (19)	0.04
Diabetes type, % Type 1, Type 2	 7 93	 9 91	 0.56
Diabetic Retinopathy grades, % Mild NPDR Moderate NPDR Severe NPDR PDR – Low Risk PDR – High Risk	 19 44 28 5 4	 8 41 32 9 10	 <0.01
Baseline age years, mean (SD)	65.4 (12.4)	62.7 (12.3)	0.04
Baseline VA letters, mean (SD)	67.8 (14.3)	64.7 (16)	0.05
VA ≥ 70 letters, %	51	49	0.72
VA ≤ 35 letters, %	3	5	0.46
CST µm, mean (SD)	407 (108)	433 (138)	0.05
DME activity, % Centre involving CSME Non-center involving CSME No CSME	 92 8 0	 92 7 2	 0.22

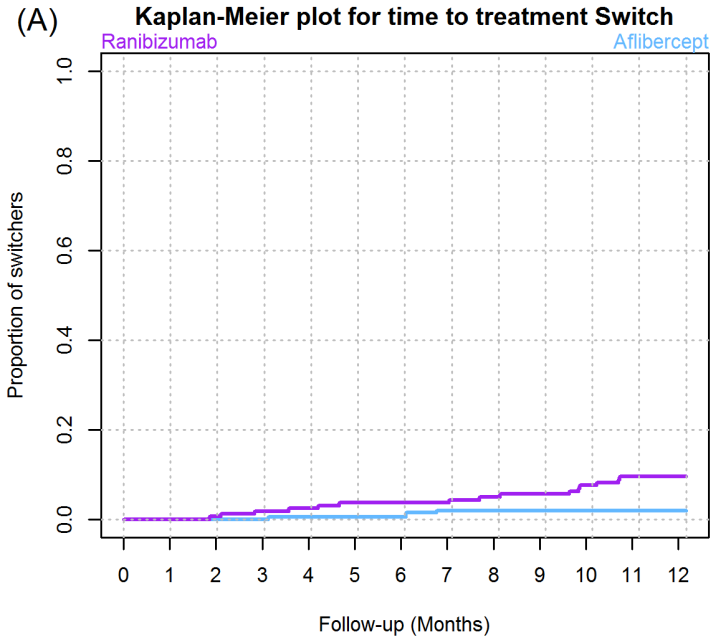
n - Number, SD – Standard Deviation, NPDR – Non-Proliferative Diabetic Retinopathy, PDR – Proliferative Diabetic Retinopathy, VA – Visual Acuity (logMAR letters), CST – Central Subfield Thickness, DME – Diabetic Macular Edema, CSME – Clinically Significant Macular Edema

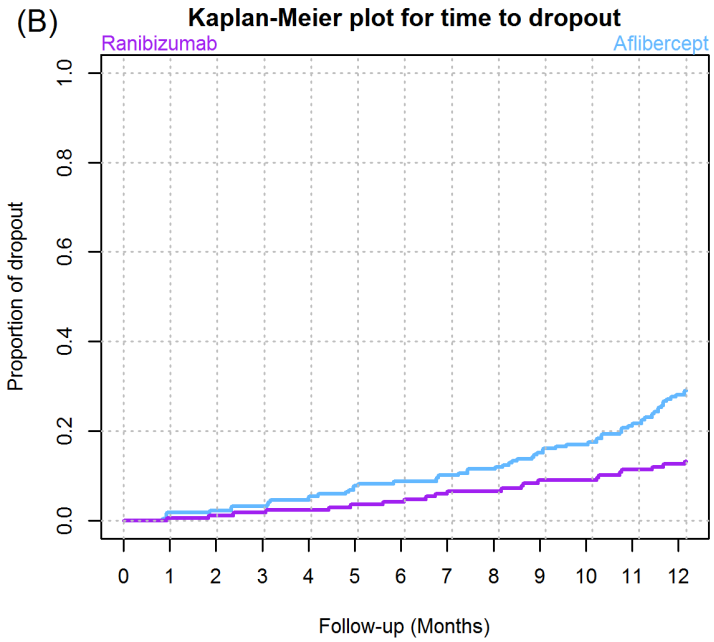

(A)
Predicted outcomes Over 12 months
Ranibizumab
Aflibercept
Visual acuity
CST
Visual acuity, letters (logMAR)
µm
Follow-up (Months)


(B)
Difference in visual acuity
(Aflibercept - Ranibizumab)
Favours aflibercept
Favours ranibizumab
Difference in visual acuity, letters (logMAR)
Follow-up (Months)


(C)
Difference in central subfield thickness
(Aflibercept - Ranibizumab)
Favours ranibizumab
Favours aflibercept
Difference in central subfield thickness, µm
Follow-up (Months)




(A)
Kaplan-Meier plot for time to treatment Switch
Ranibizumab
Aflibercept
Proportion of switchers
0.0
0.2
0.4
0.6
0.8
1.0
0 1 2 3 4 5 6 7 8 9 10 11 12
Follow-up (Months)


(B)
Kaplan-Meier plot for time to dropout
Ranibizumab
Aflibercept
Proportion of dropout
0.0
0.2
0.4
0.6
0.8
1.0
0 1 2 3 4 5 6 7 8 9 10 11 12
Follow-up (Months)

Aflibercept (2mg) and ranibizumab (0.5mg) both were beneficial for diabetic macular edema treatment. Aflibercept resulted in larger reductions in macular thickness over 12 months, but vision improvement was found when initial visual acuity was ≤20/50.