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Treatment Outcomes of Ranibizumab versus Aflibercept for Neovascular Age-Related Macular Degeneration

Data from the Fight Retinal Blindness! Registry

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Purpose: Ranibizumab and aflibercept are both approved for the treatment of neovascular age-related macular degeneration (nAMD). Herein, we compare the 3-year treatment outcomes of the 2 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 nAMD treatment from December 1, 2013 through December 31, 2015, with either ranibizumab or aflibercept that were tracked in the registry.

Methods: Visual acuity (VA) was analyzed annually in completers (those who completed 3 years of treatment) and in all eyes (completers, noncompleters, and those who switched treatment).

Main Outcome Measures: The primary outcome was mean change in VA (number of letters read on a logarithm of the minimum angle of resolution chart).

Results: A total of 965 eyes of 897 patients (ranibizumab, 499 eyes [469 patients]; aflibercept, 466 eyes [432 patients) were identified. The mean VA and the type of the choroidal neovascularization (CNV) at the start of treatment were similar between the 2 groups. The group receiving ranibizumab was older. The crude mean VA change of +1.5 letters (95% confidence interval [CI], 0−3.1 letters) in the ranibizumab group and of +1.6 letters (95% CI, −0.2 to 3.3 letters; $P = 0.97$) in the aflibercept group at 3 years in all eyes was similar, as was the adjusted mean VA change, +0.3 letters (95% CI, −1.5 to 2.0 letters) versus +1.0 letters (95% CI, −0.7 to 2.8 letters; $P = 0.66$). Both treatment groups received a median of 18 injections from a median of 21 clinical visits. The adjusted proportion of clinical visits when the CNV was graded active over 3 years was similar between ranibizumab (43%) and aflibercept (51%; $P = 0.9$). More switches from ranibizumab to aflibercept ($P < 0.001$) took place than vice versa. The proportion of eyes that did not complete 3 years of treatment in each of the group was similar ($P = 0.21$).

Conclusions: Neither ranibizumab nor aflibercept was superior to the other in terms of VA outcomes and treatment frequency at 3 years for nAMD. *Ophthalmology 2019;■:1−8 © 2019 by the American Academy of Ophthalmology*

Ranibizumab (Lucentis; Genentech, Inc., CA/Novartis, Basel Switzerland) and aflibercept (Eylea; Regeneron Pharmaceuticals Inc, NY/Bayer, Leverkusen, Germany) are both approved for the treatment of neovascular age-related macular degeneration (nAMD).[1,2] Alternative regimens, for example pro re nata and treat and extend, were developed to lower the treatment burden when possible by avoiding the monthly injections that were stipulated in the pivotal studies of ranibizumab.[3−6] The reports of outcomes of treatment using these regimens in real-world clinical practice have been variable.[7−11]

Aflibercept first was compared with ranibizumab directly in the VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD Studies.[12] These phase 3 clinical trials reported that the 12-month visual outcomes of aflibercept injections every 2 months (after 3 initial monthly injections) were noninferior to monthly injections of ranibizumab or, indeed, aflibercept. Both drugs were reported to maintain visual acuity (VA) during the second year of treatment under a variable dosing regimen.[13] There was no meaningful difference in the mean number of injections of the 2 drugs during the second year. A clinical trial of ranibizumab versus aflibercept using the treat-and-extend protocol found similar numbers of injections and VA improvements over 12 months of treatment.[14]

Observational studies that compared ranibizumab and aflibercept also reported similar VA outcomes and treatment frequencies over 12 months in real-world clinical

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practice.[15,16] No real-world studies have compared these outcomes after 2 or more years of treatment. We compared the 3-year treatment outcomes after ranibizumab versus aflibercept intravitreal injections in eyes with nAMD in routine clinical practice based on data tracked in an observational database, the Fight Retinal Blindness! (FRB!) Registry.

Methods

Design and Setting

We conducted an observational study from the beginning of treatment with intravitreal injections of vascular endothelial growth factor (VEGF) inhibitors for eyes with nAMD tracked in the prospectively designed web-based FRB! Registry. We previously described details of the FRB! Registry data tracking system.[17] Any physician who is interested in the registry can gain access the system and voluntarily contribute data after a short training session. These data are encrypted, transmitted, and stored in a secure server at the University of Sydney, Sydney, Australia. The registry has implemented modules to collect data in eyes with nAMD, diabetic macular edema, and retinal vein occlusion. In the present analysis, we included data on treatment outcomes from the FRB! nAMD module. Mandatory fields at each visit include the number of letters read on a logarithm of the minimum angle of resolution chart (best of uncorrected, corrected, or pinhole), activity of the choroidal neovascularization (CNV), treatments given, and ocular adverse events. The system has an inbuilt validation process to check whether the mandatory fields are complete, all the numerical data fall within the prespecified ranges, and data from a single visit are not duplicated. Lesion type and history of prior treatment are additional data recorded at the baseline visit. OCT scans were performed routinely during clinical visits, whereas fundus angiography was performed only if deemed necessary by the treating physician. Treatment decisions, drug choice, and visit schedule were determined by the physician in consultation with the patient. This study used data from 38, 2, and 1 practices in Australia, New Zealand, and Switzerland, respectively. Clinical data for this paper were sourced from a transnational research project, which was reviewed and approved by the ethics committees of the South Eastern Sydney Local Health District Human Research Ethics Committee, the Royal Australian and New Zealand College of Ophthalmologists Human Research Ethics Committee, and the Cantonal Ethics Committee Zurich. Ethics committees in Australia and New Zealand approved the use of opt-out patient consent. This research adhered to the tenets of the declaration of Helsinki.

Patient Selection and Variables

We included treatment-naive eyes with nAMD that began treatment with either ranibizumab or aflibercept from December 1, 2013, through December 31, 2015, allowing the possibility of having at least 3 years of treatment. Eyes could have received bevacizumab for their first injection only. We excluded those that had received fewer than 3 injections in the first year.

Eyes were grouped according to which treatment they received first or second in the case of those who started with 1 injection of bevacizumab. Eyes of participants who completed at least 3 years of clinical follow-up and had the same agent injected at every treatment visit were defined as completers. Switchers were defined as eyes that received 2 or more injections of the other drug during this time. Visits occurring after the switch to the other drug were censored for analysis. Eyes that did not complete 3 years of observations were defined as noncompleters.

Age, gender, VA (logarithm of the minimum angle of resolution letters), and lesion type were recorded at the first treatment (baseline) visit. Visual acuity, CNV activity, treatments administered, and adverse events were recorded at each visit. The treating physician graded the lesion activity based on funduscopy, OCT, or fluorescein angiography results, alone or in combination. Lesions were graded as active if there were features such as subretinal or intraretinal fluid or hemorrhages.

Outcomes

The main outcome measure was the mean change in VA in the ranibizumab- and aflibercept-treated eyes 3 years after starting treatment. Secondary outcomes included the frequency of injections and visits. The proportion of eyes with VA of 70 letters or more (Snellen equivalent, 20/40 [driving vision]) and VA of 35 letters or fewer (Snellen equivalent, 20/200 [legally blind]) at 3 years and those that gained 10 letters or more or lost 10 letters or more also were compared. We also evaluated the proportion of eyes that switched treatment, noncompletion rates, and the proportion of visits in which the CNV lesion was graded as active in each of the groups over the 3-year period.

Statistical Analysis

Descriptive data included the mean (standard deviation [SD]), median (first quartile [Q1] and third quartile [Q3]), and percentages where appropriate. Eyes were considered to have been observed from the first treatment visit up to the 3-year visit or the last visit completed for noncompleters. The Student *t* tests, Wilcoxon signed-rank test, chi-square test, and Fisher exact test were used as appropriate to compare baseline characteristics between ranibizumab- and aflibercept-treated eyes. Line graphs were used to display VA results in eyes of patients who completed 3 years of monotherapy. Reporting of crude visual outcomes at 3 years used the last observation carried forward method for switchers and noncompleters.

Visual acuity outcomes between treatments at 3 years were assessed with 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 (up until the time of switch), and noncompleters and were adjusted for age, baseline VA, lesion type (fixed effects), and practice and intrapatient correlation for bilateral cases (random effects). Predictions from this model were used to plot VA and the difference in the mean VA change over 3 years for all eyes. A quasi-Poisson regression model adjusted for age, baseline VA, lesion type, and practice with log days of follow-up included as an offset variable compared the number of injections and visits. A logistic regression model that included age, baseline VA, and lesion type was used to assess the overall proportion of CNV inactivation. Cox proportional hazards regression analysis adjusted for age, baseline VA, and lesion type was used to compare the rate of noncompletion and switching over 3 years. The Kaplan-Meier survival method was used to describe time to treatment noncompletion and switching between treatments.

All analyses were conducted using R software version 3.5.3 (R Project for Statistical Computing, Vienna, Austria; R Foundation for Statistical Computing; 2019, Available at: https://cran.r-project.org) with the lme4 package (version 1.1-21) for mixed-effects regression analysis, the mgcv package (version 1.8-24) for generalized additive (mixed) model computation, the emmeans package (version 1.3.3) for pairwise comparison of adjusted means, the

coxme package (version 2.2−10) to calculate the median time to noncompletion and switching, and the survival package (version 2.42-4) for noncompletion analysis.[18−22]

Results

Study Participants

A total of 1258 eyes of 1149 patients from Australia (1034 eyes [952 patients]), New Zealand (153 eyes [137 patients]), and Switzerland (71 eyes [60 patients]) started intravitreal injections of VEGF inhibitors for nAMD between December 1, 2013, and December 31, 2015. Of these, 293 eyes (23%) were excluded, leaving 965 eyes (499 ranibizumab and 466 aflibercept) of 897 patients available for analysis. Excluded eyes included 95 that did not receive at least 3 VEGF inhibitor injections (43, 27, and 25 started with aflibercept, bevacizumab, and ranibizumab, respectively) and 198 eyes that had more than an initial injection of bevacizumab in the first year. Data from both eyes of 68 patients were analyzed, including 4 patients with 1 eye in each group. The baseline characteristics of the treatment groups are summarized in Table 1. The mean VA at baseline in the ranibizumab and aflibercept groups was similar as was the proportion of eyes with VA of 70 letters or more and VA of 35 letters or fewer. Distribution of CNV lesion type also was similar between the 2 groups. Ranibizumab-treated patients tended to be older (mean ± SD, 82±8 years vs. 79±8 years for the aflibercept group; $P < 0.001$) and were more likely to be female (66% vs. 57%; $P < 0.001$).

Visual Acuity Outcomes at 3 Years

Of the 965 eyes, 359 eyes (37%) completed 3 years of taking the same drug (ranibizumab, 155 eyes [31%]; aflibercept, 204 eyes [44%]; Table 2). The mean VA of these eyes over the 3 years is shown in Figure 1. The crude mean VA change after 3 years of continuous treatment was 2.4 letters (95% confidence interval [CI], −0.6 to 5.3 letters) in the ranibizumab and 1.6 letters (95% CI, −1.1 to 4.3 letters) in the aflibercept group ($P = 0.46$; Table 2). The crude mean VA change at 2 years, for which data are available for comparison from most of the pivotal trials, was +4.6 letters (95% CI, 2.7−6.5 letters) in the ranibizumab and 4.5 letters (95% CI, 2.2−6.8 letters) in the aflibercept group ($P = 0.95$).

Figure 2A shows the predicted mean VA from longitudinal models that included data from all eyes (completers, switchers, and noncompleters). The last observation was carried forward from the time of switch or noncompletion, when appropriate. We found no difference in the crude mean VA change over 3 years between ranibizumab (1.5 letters [95% CI, 0−3.1 letters]) and aflibercept (1.6 letters [95% CI, −0.2 to 3.3 letters]; $P = 0.97$) when all eyes were considered. The adjusted mean change in VA, which considered longitudinal visits from all eyes, was slightly in favor of aflibercept (0.3 letters [95% CI, −1.5 to 2 letters] for ranibizumab vs. 1.0 letters [95% CI, −0.7 to 2.8 letters] for aflibercept; $P = 0.66$; Table 2). The difference in adjusted mean VA change over 3 years showed a small difference (fewer than 1 letter at all follow-up times) that favored aflibercept, but this difference was not clinically important (Fig 2B).

Table 1. Baseline Characteristics of Eyes Treated with Ranibizumab and Aflibercept

	Ranibizumab	Aflibercept	*P* Value
Eyes, no.	499	466	
Patients, no.	469	432	
Women, no. (%)	310 (66)	246 (57)	<0.001
Baseline age (yrs), mean (SD)	82 (8)	79 (8)	<0.001
Baseline VA letters, mean (SD)	59.9 (19)	58.2 (20.2)	0.19
VA (%)			
≥70 letters	38	37	0.52
≤35 letters	11	15	0.08
Lesion type (%)			
Occult	54	58	0.49
Minimally classic	9	8	
Predominantly classic	28	25	
Other	7	6	
Unclassified	2	4	

SD = standard deviation; VA = visual acuity.

Injections and Visits

The median number of intravitreal injections and visits in eyes of participants who completed 3 years of continuous treatment was similar: 18 injections (Q1−Q3, 16−22 injections) for ranibizumab versus 18 injections (Q1−Q3, 15−21 injections; $P = 0.1$) for aflibercept (mean ± SD, 18.6±18.6 injections vs. 18.8±18.8 injections; 21 visits [Q1−Q3, 17−25 visits] vs. 21 visits [Q1−Q3, 17−26 visits; $P = 0.25$; Table 2). The median number of injections was 9 injections (Q1−Q3, 8−9 injections) for ranibizumab versus 8 injections (Q1−Q3, 7−9 injections) for aflibercept in the first year, 5 injections (Q1−Q3, 4−7 injections) versus 4 injections (Q1−Q3, 4−7 injections) in the second year, and 5 injections (Q1−Q3, 4−6 injections) versus 5 injections (Q1−Q3, 4−6 injections) in the third year.

Activity of Lesions

The proportion of visits graded as active over 3 years in eyes completing 3 years of treatment (41% vs. 47%; $P = 0.40$) and in all eyes (43% vs. 51%; $P = 0.9$) for ranibizumab versus aflibercept, respectively, was similar. Three hundred forty-one eyes (185 [37%] ranibizumab and 154 [35%] aflibercept; $P = 0.25$) were considered to have active lesions at their final study visit.

Treatment Switch

One hundred forty-eight eyes (15%) underwent a treatment switch during the 3 years studied. Switching from ranibizumab to aflibercept was more frequent than vice versa (25% vs. 4%, respectively; $P < 0.001$; Fig 3A). The median time to switch was similar (252 days [Q1−Q3, 140−440 days]) for eyes switching from aflibercept to ranibizumab and 270 days (Q1−Q3, 161−519 days]) in eyes switching from ranibizumab to aflibercept. Eyes initially treated with ranibizumab that switched treatment had lower mean VA at baseline than eyes initially treated with aflibercept: 60.2 letters (SD, 18.5 letters) versus 67.1 letters (SD, 9.6 letters; $P = 0.01$). The mean change in VA at the time of switch, however, was similar: 3.4 letters (95% CI, 0.8−6 letters) for ranibizumab and 0.4 letters (95% CI, −7.5 to 8.2 letters) for aflibercept ($P = 0.45$; Table 2). The median number of injections before the switch was also similar (ranibizumab, 8 injections [Q1−Q3, 6−13 injections] vs. aflibercept, 8 injections [Q1−Q3, 5−11 injections]; $P = 0.56$; mean, 9.6 injections [SD, 9.6 injections] vs. 9.3 injections [SD, 9.3 injections]). The mean VA change in the 127 eyes receiving ranibizumab that switched to aflibercept was −3.6 letters (95% CI, −6.7 to −0.5 letters) from

Table 2. Outcomes of Eyes Completing 3 Years of Treatment

	All Eyes*			Completers†			Switchers‡			Noncompleters§		
	Ranibizumab	*Aflibercept*	P *Value*	*Ranibizumab*	*Aflibercept*	P *Value*	*Initially Ranibizumab*	*Initially Aflibercept*	P *Value*	*Ranibizumab*	*Aflibercept*	P *Value*
Eyes (no.)	499	466		155	204		127	21		217	241	
Patients (no.)	469	432		146	194		119	20		206	224	
Baseline VA letters, mean (SD)	59.9 (19)	58.2 (20.2)	0.19	61.7 (16.9)	60.6 (18.2)	0.78	60.2 (18.5)	67.1 (9.6)	0.01	58.4 (20.7)	55.5 (21.9)	0.14
Final VA letters, mean (SD)	61.4 (23.2)	59.8 (24)	0.29	64.1 (20.7)	62.1 (22.8)	0.38	63.6 (20.5)	67.5 (16)	0.33	58.1 (25.8)	57.1 (25.2)	0.67
Crude change in VA letters, mean (95% CI)‖	1.5 (0–3.1)	1.6 (−0.2 to 3.3)	0.97	2.4 (−0.6 to 5.3)	1.6 (−1.1 to 4.3)	0.46	3.4 (0.8–6)	0.4 (−7.5 to 8.2)	0.45	−0.2 (−2.7 to 2.2)	1.6 (−0.7 to 4)	0.28
Adjusted VA change in letters, mean (95% CI)#	0.3 (−1.5 to 2.0)	1.0 (−0.7 to 2.8)	0.66	3.1 (−0.8 to 5.5)	2.5 (0–5)	0.43	—	—		—	—	
Gain ≥10 letters (%)‖	30	33	0.47	34	36	0.48	27	29	1	30	31	0.93
Lost ≥10 letters (%)‖	18	19	0.92	20	20	1	14	14	0.71	19	19	0.92
VA ≥70 letters (%), baseline/final‖	39/54	37/51	0.44	41/58	37/58	1	40/56	57/57	1	37/49	34/44	0.39
VA ≤35 letters (%), baseline/final‖	11/17	15/17	0.94	8/13	11/15	0.48	9/12	0/5	0.47	14/24	20/21	0.55
Active CNV visits (%)	43	51	0.9	41	47	0.40	51	43	0.9	45	57	0.01
Injections, median (Q1–Q3)	11 (7–17)	14 (8–19)	0.04	18 (16–22)	18 (15–21)	0.10	8 (5.5–13)	8 (5–11)	0.56	9 (6–13)	9 (6–14)	0.91
Visits, median (Q1–Q3)	13 (8–20)	15 (10–22)	0.13	21 (17–25)	21 (17–26)	0.25	8 (6–15)	8 (6–11)	0.49	10 (7–14)	11 (6–16)	0.73

CI = confidence interval; CNV = choroidal neovascularization; Q1 = first quantile; Q3 = third quantile; SD = standard deviation; VA = visual acuity; — = not calculated.
*Includes completers, switchers, and noncompleters.
†Eyes with 3 years of observation from the start of treatment.
‡Eyes receiving ≥2 injections of the other treatment drug before completion of 3 years from the start of treatment. Only the observations from the visit before the switch occurred were included in the analysis.
§Eyes not completing 3 years of observations from the start of treatment.
‖Last observation carried forward for switchers and noncompleters.
#Calculated from longitudinal models adjusting for age, baseline VA, lesion type (fixed effects), and practice and intrapatient correlation for bilateral cases (random effects).

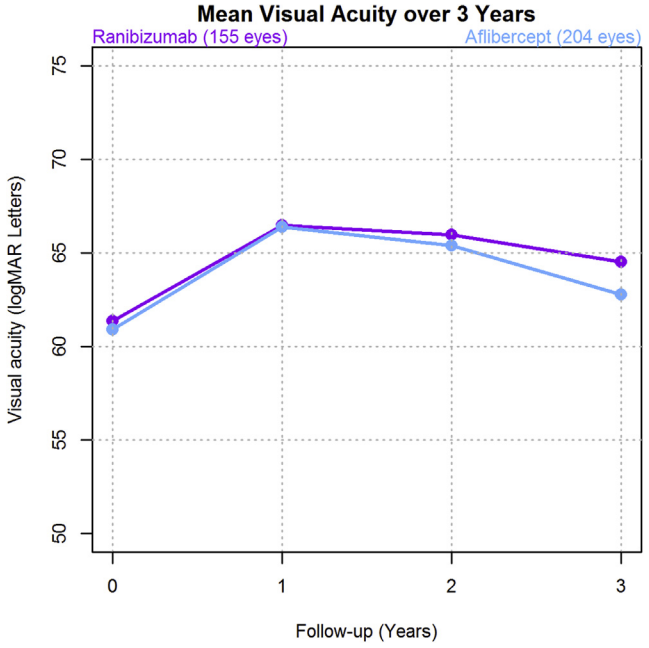

Figure 1. Graph showing mean visual acuity score (logarithm of the minimum angle of resolution [logMAR] chart) for eyes treated consistently with ranibizumab (purple) and aflibercept (blue) with 3 years of follow-up data.

the treatment switch to the 3-year visit compared with −3.0 letters (95% CI, −8.0 to 1.9 letters) for the 21 eyes receiving aflibercept that switched to ranibizumab.

Noncompletion Rate at 3 Years

The noncompletion rates over 3 years between ranibizumab and aflibercept were similar (43% vs. 51%; $P = 0.21$; Fig 3B). The median time to dropout for ranibizumab was 517 days (Q1−Q3, 297−807 days) and 552 days (Q1−Q3, 267−756 days) for aflibercept. The mean change in vision from baseline to the time of dropout was 0.2 letters (95% CI, −2.7 to 2.2 letters) in the ranibizumab group and 1.6 letters (95% CI, −0.7 to 4 letters) in the aflibercept group ($P = 0.28$; Table 2). The median number of injections received before noncompletion was similar: 9 injections [Q1−Q3, 6−13 injections] in the ranibizumab group versus 9 injections [Q1−Q3, 6−14 injections] in the aflibercept group ($P = 0.91$; mean, 9.8 injections [SD, 9.8 injections] vs. 10.4 injections [SD, 10.4 injections]). The CNV lesion was graded as active less often in the ranibizumab group that switched treatments than the aflibercept group (45% vs. 57% of visits; $P = 0.01$).

The reasons for patients discontinuing treatment were tracked in 144 eyes (31%). Common reasons were as follows: transferred to another physician, 27% (ranibizumab, 22 eyes; aflibercept, 17 eyes); death, 24% (ranibizumab, 28 eyes; aflibercept, 6 eyes); further treatment considered futile, 23% (ranibizumab, 15 eyes; aflibercept, 18 eyes); and patient declined treatment, 16% (ranibizumab, 9 eyes; aflibercept, 14 eyes). Other less common reasons were as follows: treatment successful, 7% (ranibizumab, 4 eyes; aflibercept, 6 eyes) and medical contraindication, 3% (ranibizumab, 0 eyes; aflibercept, 5 eyes).

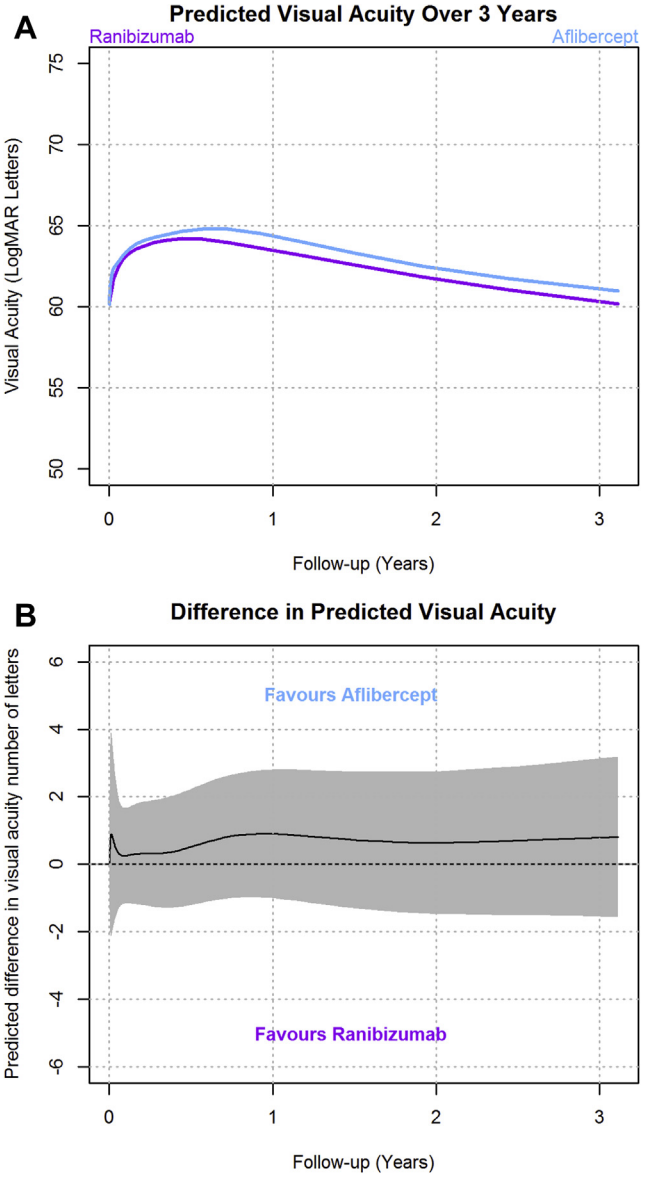

Figure 2. Line graphs showing (**A**) the predicted mean visual acuity (VA) and (**B**) the difference in the mean change in VA between ranibizumab-treated eyes (purple) and aflibercept-treated eyes (blue) over 3 years in all eyes regardless of whether they completed treatment, switched agents (visits at the time of switch), or did not complete 3 years of observations from starting treatment. The grey shaded area in (**B**) represents the 95% confidence interval. Predictions were made from a generalized additive model that adjusted for age, baseline VA, lesion type (fixed effects), and practice and intrapatient correlation for bilateral cases (random effects). logMAR = logarithm of the minimum angle of resolution.

Discussion

We found no significant difference between ranibizumab and aflibercept in mean change in VA (0.3 vs. 1.0 letters; $P = 0.66$) after 3 years of treatment of nAMD in this retrospective analysis from a prospectively designed outcomes registry. Nor did we find any differences in the proportion of eyes with VA of 70 letters or more and those

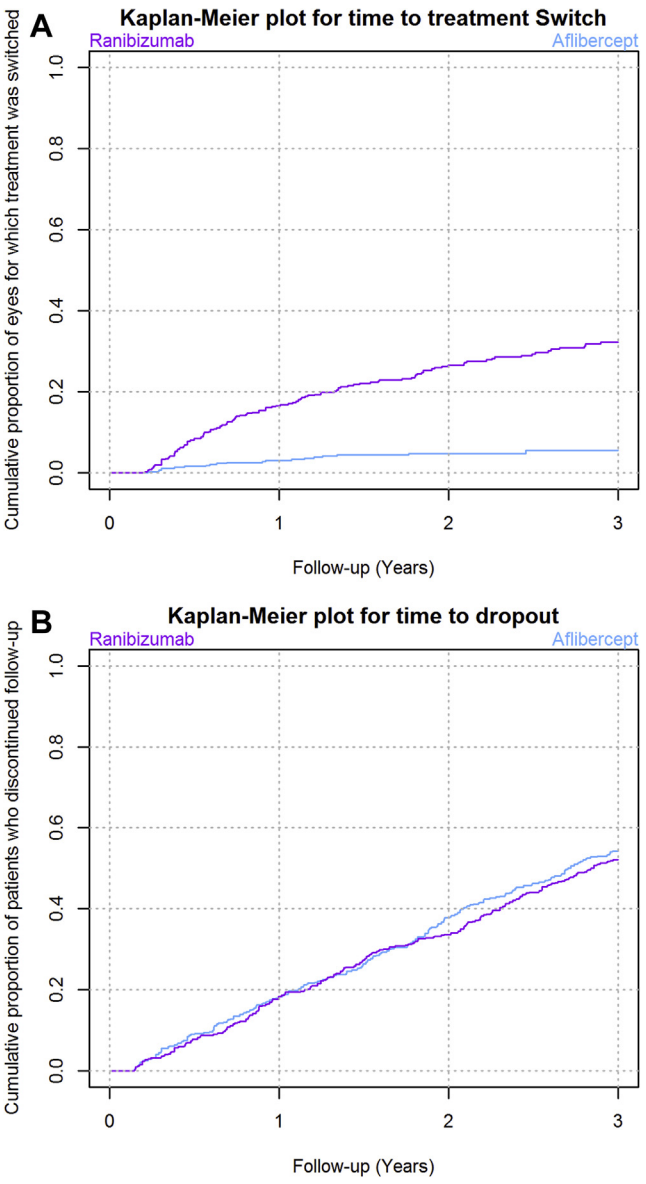

Figure 3. Line graphs showing time from start of intravitreal injections to (**A**) treatment switch and (**B**) last visit completed by patients whose eyes were treated with ranibizumab (purple) and aflibercept (blue) over 3 years.

with VA of 35 letters of fewer at 3 years or in the proportions of eyes that gained 10 letters or more and those that lost 10 letters or more during the same period. There were no differences between the 2 treatment groups in the treatment frequency, patient visits, or the proportion of visits at which the neovascular lesion was judged to be active. More eyes were receiving ranibizumab than were receiving aflibercept, as expected for a new drug. Noncompleters in each group showed similar mean VA when they dropped out. Our study extends to 3 years previous reports that visual outcomes of aflibercept and ranibizumab for nAMD are similar in routine clinical practice after 1 and 2 years of treatment.[12,13,15,16]

Eyes in the 2 groups were comparable at baseline, with similar mean VA and type of CNV lesion. Patients receiving ranibizumab treatment were older than those receiving aflibercept, consistent with a previous report.[23] This could have resulted from physicians' concerns about the possible risk of stroke with aflibercept in patients older than 85 years, which was mentioned in a report from Europe.[24] We compared outcomes between the 2 treatment groups using appropriate adjusted statistical analyses that included adjustments for age, baseline VA, lesion type, and nesting within practices and patients for bilateral cases.[25]

Data from registrational trials on 3-year outcomes of VEGF inhibitor treatment for nAMD are limited, but many studies have published 2-year gains, which, it should be noted, depend heavily on the starting VA level. Eyes receiving ranibizumab in the Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration, which had similar mean VA at baseline as the eyes in the present study, gained a mean of 6.5 to 8.8 letters at 2 years from the baseline.[3] Eyes in the VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD Studies, which had a lower mean VA at baseline (approximately 54 letters) than those in the present study, gained a mean of 6.6 to 7.9 letters after 2 years of treatment.[13] The present study observed a mean gain of 4.6 and 4.5 letters in the ranibizumab and aflibercept groups, respectively, at 2 years, which was lower than those in the registration trials, most likely because they received fewer treatments: 12 to 14 injections over 2 years compared with 24 injections in the Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration and 11.2 (with double dose) to 16.5 injections in the VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD Studies over 2 years, which could have resulted in the difference.[3,13]

The pivotal clinical trial of aflibercept for nAMD reported similar visual outcomes as ranibizumab from fewer injections per a fixed injection study protocol.[12,13] However, real-world studies have found similar numbers of injections over the first 12 months of treatment for both drugs.[14–16] We found eyes in the present study that both treatment groups had undergone the same number of treatments and visits over the 3-year period. Eyes in the present study received injections during 85% of their visits, suggesting that treatment was administered predominantly using a treat-and-extend regimen.

Clinicians switch treatment from one VEGF inhibitor to another hoping for a better outcome. We found more switches from ranibizumab, the older agent, to aflibercept than vice versa. Eyes that switched treatment in the ranibizumab group showed significantly lower mean VA at baseline than those in the aflibercept group. However, the mean change in VA from baseline to the switch was similar in the 2 groups, as was the median number of injections. Previous observational studies have reported no significant benefit for switching from ranibizumab to aflibercept and for those maintained on ranibizumab alone.[26,27]

Loss to follow-up may introduce bias because eyes that discontinue treatment may do so because of a poor outcome. Real-world studies on the treatment outcomes of VEGF

inhibitors have reported dropout rates of approximately 23% to 24% at 1 year, 35% to 36% at 2 years, and 53% at 5 years.[7,8,11,15,28] The noncompletion rate at 3 years in the present study was similar for both the ranibizumab- and the aflibercept-treated eyes ($P = 0.21$). Noncompleters in each of the groups did not differ in mean baseline VA or mean change in VA from baseline at the time they dropped out, and the median numbers of injections that they received and visits they experienced were similar. Reasons for discontinuation, which were recorded in 144 eyes, were unlikely to be related to poor outcomes in most cases (61%), such as transfer to another physician and death. The reasons that probably would be related to poor outcomes, such as further treatment considered to be futile, were distributed equally between the 2 treatment groups.

The activity of the CNV lesion is an important parameter in assessing response to VEGF inhibitor treatments. A previous study reported no difference in the proportion of CNV inactivation between ranibizumab and aflibercept at 12 months.[15] We found that the proportion of visits at which the CNV lesion was graded as active was similar in both the treatment groups over 3 years in the present study. Noncompleters in the aflibercept group experienced more visits graded with an active CNV lesion than those in the ranibizumab group, but the mean VA at the time of dropout was similar between the 2 groups.

A limitation of our study is that treatment decisions in routine clinical practice, in contrast to clinical trials, are made without adjudication from a reading center or guidance by study protocols. Selection of cases and treatment regimen may differ among physicians. The reasons for the choice of a particular VEGF inhibitor for each eye and treatment switch cannot be deduced from our data. Nevertheless, we compared the 2 VEGF inhibitors as they are actually being used in routine clinical practice.

To conclude, we found that treatment outcomes of nAMD in routine clinical practice with either ranibizumab or aflibercept were similar at 3 years in terms of visual outcomes, treatment frequency, and visits. More eyes receiving ranibizumab switched to aflibercept than vice versa. Eyes that did not complete 3 years of treatment in both the groups were similar. These data suggest that ranibizumab and aflibercept achieve similar visual outcomes for nAMD in routine clinical practice with the same mean number of injections over a 3-year period. Other issues, such as cost, convenience, and availability, may be more useful to guide a patient's and physician's choice of drug, rather than the relative efficacy of the currently available drugs.

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Footnotes and Financial Disclosures

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Abbreviations and Acronyms:
CI = confidence interval; **CNV** = choroidal neovascularization; **FRB!** = Fight Retinal Blindness!; **nAMD** = neovascular age-related macular degeneration; **Q1** = first quartile; **Q3** = third quartile; **SD** = standard deviation; **VA** = visual acuity; **VEGF** = vascular endothelial growth factor.

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