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Twelve-Month Outcomes of Ranibizumab vs. Aflibercept for Neovascular Age-Related Macular Degeneration: Data from an Observational Study

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Purpose: To directly compare visual acuity (VA) outcomes with ranibizumab vs. aflibercept for eyes with neovascular age-related macular degeneration (nAMD) treated in routine clinical practice.

Design: Database observational study.

Participants: Treatment-naïve eyes with nAMD tracked by the Fight Retinal Blindness outcome registry that commenced anti−vascular endothelial growth factor therapy with ranibizumab or aflibercept between December 1, 2013, and January 31, 2015. Eyes were matched at baseline for VA, age, and choroidal neovascular membrane (CNV) size.

Methods: Locally weighted scatterplot smoothing curves were used to display VA results. Eyes that switched or discontinued treatment were included with their last observation carried forward.

Main Outcome Measures: Change in mean VA (number of letters read on a logarithm of the minimum angle of resolution chart); number of injections and visits; proportion of eyes with inactive CNV over 12 months.

Results: We identified 394 eyes (197 treated with ranibizumab and 197 with aflibercept) from 372 patients who received treatment from 34 practitioners. Baseline parameters were well matched. The mean (standard deviation [SD]) VA of ranibizumab-treated eyes increased from 58.6 (20.3) letters at baseline to 62.3 (23.9) (+3.7 [95% confidence interval {CI} 1.4−6.1]) letters ($P = 0.001$), compared with 58.9 (19.2) letters at baseline to 63.1 (21.5) (+4.26 [95% CI 2.0−6.5]) letters ($P < 0.001$) for eyes receiving aflibercept. The difference in change in crude VA of 0.6 letters between the 2 groups was not statistically significant ($P = 0.76$), nor was the difference in adjusted mean VA of the 2 groups ($P = 0.26$). In completers, the mean (SD) numbers of injections (8.1 [2.1] vs. 8.0 [2.3]; $P = 0.27$) and visits (9.6 [3.0] vs. 9.5 [3.1]; $P = 0.15$) did not differ between the 2 groups. The adjusted proportion of eyes in which the CNV lesion was graded as inactive during the study was similar between the eyes receiving ranibizumab and aflibercept (74% vs. 77%, respectively; $P = 0.63$).

Conclusions: Visual acuity outcomes at 12 months did not differ between ranibizumab and aflibercept used for nAMD in this large observational study, nor was a difference in treatment frequency found. *Ophthalmology 2016;■:1−9 © 2016 by the American Academy of Ophthalmology*

Current anti−vascular endothelial growth factor (VEGF) therapies delivered via intravitreal injections include ranibizumab and aflibercept, as well as off-label bevacizumab. International guidelines recommend these anti-VEGF agents as first-line therapy for treating neovascular age-related macular degeneration (nAMD).[1,2]

Randomized controlled trials (RCTs) with ranibizumab initially investigated visual acuity (VA) outcomes with monthly injections.[3−5] Subsequent studies demonstrated that similar outcomes could be achieved when ranibizumab was given as needed, or pro re nata (PRN).[5,6] A treat-and-extend (T&E) regimen of ranibizumab may provide better outcomes than PRN, with the potential to reduce the health care resource burden by reducing the number of clinic visits.[7] Overall, however, variable regimens used in community practice may produce divergent outcomes[8−17] that may be inferior to those of the strict monthly-visit regimens of clinical trials.[3−5]

Aflibercept was approved by the U.S Food and Drug Administration in November 2011.[18] Twelve-month visual outcomes with an injection every 2 months after 3 initial monthly injections of aflibercept were reported to be non-inferior compared with monthly 0.5 mg ranibizumab.[19] After an additional year under a variable dosing regimen, both drugs were equally effective in maintaining VA (loss of <15 letters from baseline).[20]

Aflibercept has been widely studied as an option for eyes with nAMD showing an insufficient response to ranibizumab.[21−27] Data regarding the binding affinity of ranibizumab and aflibercept to VEGF have yielded

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conflicting results in in vitro studies.[28–31] The duration of the therapeutic effect in the eye has not yet been evaluated in routine clinical practice. No randomized trials have compared aflibercept with ranibizumab for nAMD, apart from the pivotal phase III RCT of aflibercept.[19,20]

The aim of this study was to directly compare VA outcomes and frequency of injections of ranibizumab vs. aflibercept in treatment-naïve eyes with nAMD using observational data from a large registry of real-world treatment outcomes.

Methods

Design and Setting

This was an observational study of treatment-naïve eyes that had received intravitreal therapy for nAMD in routine clinical practice and had been tracked in the Fight Retinal Blindness (FRB) database.[32] Briefly, the FRB system collects data from each clinical visit, including the number of letters read on a logarithm of the minimum angle of resolution (logMAR) VA chart (best uncorrected, corrected, or pinhole); activity of the choroidal neovascular membrane (CNV), for which a definition is given on the data entry screen; treatment given, if any; and ocular adverse events.[32] At baseline only, lesion size and type and whether the eye had received prior treatment were recorded. Treatment decisions, including choice of drug, and visit schedules were determined by the treating physician in consultation with the patient, which reflects real-world practice. Institutional ethics approval was obtained from the Human Research Ethics Committees of the University of Sydney, the Royal Victorian Eye and Ear Hospital, the Royal Australian and New Zealand College of Ophthalmologists, and the University Hospital, Zurich. Ethics committees in Australia and New Zealand approved the use of "opt-out" patient consent. The research described adhered to the tenets of the Declaration of Helsinki. Data were collected from contributing practitioners located in Australia, New Zealand, and Switzerland. Practitioners using the FRB database were contacted to self-report their treatment approaches. The treatment regimens available for selection were monthly, PRN, and T&E.

Study Population and Groups

The study population consisted of treatment-naïve eyes starting monotherapy with either aflibercept or ranibizumab for nAMD from December 1, 2013, to January 31, 2015. Eyes with fewer than 3 injections within the first 12 months were excluded from analysis. To make groups comparable at baseline, a matching process including age, baseline VA, and lesion size was used. A caliper of 0.25 standard deviation (SD) was applied.[33]

Eyes (patients) were analyzed by treatment group by the drug given at the first injection. Completers were defined as eyes having received either only ranibizumab or only aflibercept treatment and completing 12 months of follow-up. Switchers were defined as eyes having $\geq$2 injections of the other treatment drug before completing 12 months of follow-up. Noncompleters were defined as eyes not completing 12 months of follow-up as of May 5, 2016, when the analysis was conducted, thus allowing at least 3 months for a follow-up visit to occur after the end of the 12-month observation period. As an example, an eye entering the study on January 31, 2015, with no visit from January 31, 2016, to May 5, 2016, was considered to be a noncompleter.

For completers, VA at 12 months was taken as the most recent VA reading within 12 months. When analyzing "all eyes," including completers, switchers, and noncompleters, the last-observation-carried-forward (LOCF) method was used for switchers and noncompleters.[34]

Study Measurements

Patient age (years) and sex, VA in logMAR letters, and lesion size (micrometers) and type were recorded at the time of the first injection by fundus fluorescein angiography. All treatments were recorded, along with VA, CNV lesion activity, and ocular adverse events at each visit. As previously described,[35] lesion activity status was graded by the treating physician based on funduscopy, optical coherence tomography, or fluorescein angiography, alone or in combination, at each visit. All ophthalmologists participating in this study agreed with the following statement: "Lesions were graded as active if there were features such as subretinal or intraretinal fluid or new hemorrhage that suggested that the CNV lesion was active."

Study Outcomes

The primary study outcome was change in mean VA of each group over 12 months after initiating treatment. Secondary outcomes were the mean number of injections given over 12 months, number of visits, proportion of eyes in which the CNV lesion was graded as inactive at some point in the study, number of eyes switching therapy, and noncompletion rates.

We also assessed the number of patients that would be required for an RCT to demonstrate a significant difference between the groups using the outcomes of this study, assuming a risk of error of 5% and power of 80%.

Statistical Analysis

Descriptive data are described as mean (SD), median (interquartile range [IQR]) or number (percentage). Student *t* test, chi-square, McNemar, and Fisher tests were used as appropriate to compare baseline characteristics between ranibizumab and aflibercept. Locally weighted scatterplot smoothing (Loess) curves were used to analyze VA throughout the follow-up.[14]

VA outcome between treatments at 12 months were assessed by mixed-effects regression models with the initial injection type as the main predictor variable. Adjusted means were used to assess the change in VA from baseline to 1 year considering adjustments for age, baseline VA, lesion size and type (fixed effects), and practice (random effect). This modeling strategy acknowledges the natural clustering by practice within the data. The numbers of injections and visits were compared by a Poisson regression model adjusted for age, baseline VA, lesion size and type, and practice, with log days of follow-up included as an offset variable. A logistic regression model adjusted for age, baseline VA, and lesion size and type was used to compare the overall proportion of CNV inactivation, switches, and noncompleters at 12 months between drugs. Cox proportional hazards regression analysis adjusted for age, baseline VA, and lesion size and type was used to compare the median time to noncompletion (discontinuation) and switching. Kaplan-Meier curve analysis was used to display the corresponding results. A post hoc sample size calculation was performed to estimate the number of patients that would be required to detect the observed difference between drugs.[36] All analyses were calculated using R with the lme4 package for mixed-effects regression analysis and the survival package for Kaplan-Meier analyses.[37]