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Real-World Vision in Age-Related Macular Degeneration Patients Treated with Single Anti–VEGF Drug Type for 1 Year in the IRIS Registry

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Purpose: The purpose of this study is to compare real-world visual acuity (VA) in patients with neovascular age-related macular degeneration (nAMD) treated with a single anti–vascular endothelial growth factor (VEGF) drug monotherapy for 1 year from the American Academy of Ophthalmology (AAO) Intelligent Research in Sight (IRIS) Registry.

Design: Retrospective, nonrandomized, comparative study.

Participants: IRIS Registry patients with nAMD who received bevacizumab, ranibizumab, or aflibercept only for 1 year between 2013–2016.

Methods: Participants were divided into 3 groups based on monotherapy type. Multivariate analysis of covariance models (ANCOVA) was constructed in a stepwise fashion.

Main Outcome Measures: The logarithm of the minimum angle of resolution (logMAR) VA at 1 year and mean change in logMAR VA between baseline and 1 year were compared between drug types.

Results: Of 13 859 patients, 6723 received bevacizumab, 2749 received ranibizumab, and 4387 received aflibercept only for 1 year. A total of 84 828 injections were performed. The mean number of injections (standard deviation) at 1 year was higher in the ranibizumab (6.4 [±2.4]) and aflibercept groups (6.2 [±2.4]) compared to bevacizumab group (5.9 [±2.4]; $P < 0.0001$). In the age-adjusted model, both ranibizumab and aflibercept achieved better logMAR VA at 1 year compared with bevacizumab (0.50 [±0.49], 0.49 [±0.44], 0.55 [±0.57]; $P < 0.0001$). However, this difference was not significant after multivariate adjustment (age, baseline VA, diabetes, posterior vitreous detachment, number of injections, race, insurance). There was no statistical difference in the age-adjusted or multivariate-adjusted mean logMAR VA change (standard deviation) at 1 year among treatment groups (−0.048 [0.44] bevacizumab, −0.053 [0.46] ranibizumab, −0.040 [0.39] aflibercept; $P = 0.46$). A higher percentage of patients achieved a ≥3-line VA improvement at 1 year in the bevacizumab group (22.7%) compared with ranibizumab (20.1%; $P = 0.0093$) and aflibercept (17.8%; $P < 0.0001$). However, after multivariate adjustment, aflibercept exhibited a greater log odds of a ≥3-line VA loss compared with bevacizumab only (1.25 log odds ratio; $P < 0.0016$).

Conclusions: This study suggests that all 3 drugs improve VA similarly over 1 year of monotherapy. *Ophthalmology 2017;■:1–7 © 2017 by the American Academy of Ophthalmology*

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Age-related macular degeneration (AMD) is the leading cause of irreversible blindness in those aged >65 years, with an estimated prevalence of up to 8% in the United States.[1,2] Neovascular AMD (nAMD) leads to rapid vision loss via bleeding, exudation, and fibrotic scarring.[3] Over the last several years, 3 intravitreal anti–vascular endothelial growth factor (VEGF) agents have revolutionized the treatment of nAMD, including off-label bevacizumab, ranibizumab (Food and Drug Administration approval in 2007), and aflibercept (Food and Drug Administration approval in 2011). However, the socioeconomic and treatment burden is growing, with estimated average annual Medicare expenditures per patient of up to $34 800 in the pre-aflibercept era.[4,5]

Numerous early landmark clinical trials have compared the visual outcomes of these anti-VEGF agents in nAMD, including ANCHOR (Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in AMD),[6] MARINA (Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD),[7] PIER (Phase IIIb, multicenter, randomized, double-masked, sham injection–controlled study of the efficacy and safety of ranibizumab in subjects with subfoveal CNV with or without classic CNV secondary to AMD),[8] PRONTO (Prospective OCT Study With Lucentis for Neovascular AMD),[9] VIEW 1 and 2 (VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet

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AMD),[10] and Comparison of AMD Treatments Trial (CATT; Comparison of Age-related Macular Degeneration Treatment Trials).[11,12] Subsequent real-world clinical studies have evaluated the clinical impact of these drugs separately when translated into routine clinical practice.[13,14] However, little is known about the clinical impact of all 3 drugs when compared head-to-head on a large, national epidemiologic scale. Arguably, vision is one of the most important factors that aids in patient counseling and drug choice.

The purpose of this study was to compare real-world visual acuity (VA) in patients with nAMD treated with a single anti-VEGF drug (bevacizumab only, ranibizumab only, or aflibercept only) for 1 year without switching in a cohort of the American Academy of Ophthalmology (AAO) Intelligent Research in Sight (IRIS) Registry.

Methods

Study Sample

This was a nonrandomized, retrospective, comparative review of patients with nAMD who received a single anti-VEGF drug (1.25 mg bevacizumab, 0.5 mg ranibizumab, or 2 mg aflibercept) for 1 year between January 1, 2013, and September 30, 2016. Individuals were part of the AAO IRIS Registry, the first US-based national comprehensive eye disease database. The IRIS Registry's electronic health record (EHR) base consisted of approximately 1790 ophthalmologist-based practices with 7791 participating physicians as of September 30, 2016. The study sample was constructed on the basis of International Classification of Diseases 9th and 10th Revision diagnostic codes from the IRIS Registry cohort. Aggregated data from the IRIS Registry are de-identified and do not require patient-level consent. Therefore, institutional review board approval was not required.

Inclusion criteria included all patients with a new or established diagnosis of nAMD who received at least 3 consecutive injections during a 1-year study period between January 1, 2013, and September 30, 2016. One eye per patient was included to avoid the potential for systemic drug crossover between eyes in a single patient.[15] Exclusion criteria were (1) a prior intravitreal anti-VEGF or corticosteroid injection in the study eye within 1 year of the study period; (2) any intravitreal injection in the contralateral eye during the study period; (3) any drug switch during the study period; (4) missing baseline or 1-year VA; or (5) a history of ocular disease in the study eye (rhegmatogenous retinal detachment, central or branch artery or vein occlusion, idiopathic choroidal neovascular membrane, unspecified retinal neovascularization, ocular histoplasmosis, intermediate or posterior uveitis, retinal vasculitis, pathologic myopia, or central serous chorioretinopathy). Patients with a history of a vitrectomy, photodynamic therapy, or focal laser photocoagulation in the study eye before or during the study period were also excluded. A total of 13 859 patients were ultimately included.

Real-World Visual Acuity

Real-world VA was defined as best-corrected VA (BCVA) reported at baseline, after the second and third intravitreal injections, at 6 months, and at 1 year. The BCVA was converted to logarithm of the minimum angle of resolution (logMAR) VA units for analysis. A 3-line vision gain or loss was defined as a 0.3 logMAR VA unit change from baseline. A BCVA vision gain or loss variable from baseline to 12 months was then constructed and defined as the following: *Vision gain* was a ≥0.3 logMAR VA unit improvement, *same or no change* was less than a 0.3 logMAR VA unit change, and *vision loss* was a ≥0.3 logMAR VA unit worsening.

Covariates

Baseline demographics were obtained, including age, gender, race, and insurance type. Insurance type was defined as Medicaid or Medicare, private insurance only, both private and Medicare/Medicaid, other insurance, or no insurance. Systemic comorbidities included a history of hypertension or diabetes mellitus. Concurrent ocular comorbidities in the study eye diagnosed at the time of or present within 1 year of the first injection were also collected, including lens status, posterior vitreous detachment, primary open-angle glaucoma, epiretinal membrane, macular hole, vitreomacular traction, and amblyopia. Mean number of injections by drug type were also obtained at 6 and 12 months. Treatment protocol (treat and extend or treat and pro re nata) and OCT characteristics were not assessed because of the lack of availability in most of the EHRs.

The *primary outcome* was the mean real-world VA at 1 year between drug groups as defined in logMAR units. *Secondary outcomes* included a mean difference in BCVA from baseline to 1 year by drug type and a VA gain or loss of at least 3 lines from baseline to month 12, by drug type. The mean cumulative number of injections at 12 months was also secondarily compared between drug groups.

Statistical Analysis

Baseline demographics and ocular and systemic comorbidities were compared between each drug type. Analyses of variance for continuous variables and chi-square tests for categoric variables were used to assess significance.

Age-Adjusted and Multivariate Model

An age-adjusted logistic regression model between baseline characteristics and mean logMAR VA at 1 year or mean logMAR VA difference between baseline and 1 year was first determined to assess for potential confounders. Variables related to both drug type and mean logMAR VA at 1 year or mean logMAR VA difference from a univariate logistic regression ($P < 0.10$) were chosen as a priori confounders. Next, a stepwise multivariate analysis of covariance model was constructed from the strongest to weakest odds ratios. P for interaction ($P < 0.10$) among confounders was also analyzed. Demographics and baseline characteristics that were statistically different by drug type *only* were then added to the model to assess for additional potential confounding (gender, hypertension, macular hole, vitreomacular traction, laterality). Given no change in the final outcome, these were removed in the ultimate multivariate analysis to create the most parsimonious model (Tables S1 and S2, available at www.aaojournal.org). Secondary analyses were similarly conducted for vision gain or loss of at least 3 lines and cumulative mean injections between drug groups using multinomial logistic regression models. Model assumptions were met. All data were analyzed using STATA software version 13.1 (StataCorp LP, College Station, TX) and SAS version 9.4 (SAS Institute Inc., Cary, NC).

Results

Participant Characteristics

A total of 204 749 patients were identified who underwent at least 3 intravitreal injections during the study period. Of those, 94 881 exhibited nAMD at the time of the first injection. Further