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Long-Term Outcomes in Eyes Receiving Fixed-Interval Dosing of Anti–Vascular Endothelial Growth Factor Agents for Wet Age-Related Macular Degeneration

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Purpose: To report on long-term visual outcomes in patients receiving continuous fixed-interval dosing of anti–vascular endothelial growth factor (VEGF) treatment in neovascular age-related macular degeneration (AMD).

Design: Single-practice retrospective chart review.

Participants: One hundred nine eyes with exudative AMD receiving continuous fixed-interval dosing (every 4–8 weeks) of anti-VEGF therapy (ranibizumab, bevacizumab, or aflibercept) for at least 5 years. Eyes were excluded if they averaged fewer than 6.5 injections per year.

Methods: Snellen visual acuity was recorded at baseline and all subsequent injections. Changes from baseline were calculated at yearly intervals.

Main Outcome Measures: The primary outcome measure was mean change in letter score at 5, 6, and 7 years; secondary outcomes included the percentage of patients with 20/40 vision or better at 7 years and the mean change in letter score at each yearly time point based on baseline visual grouping (20/40 or better, 20/50–20/100, 20/200 or worse).

Results: Forty-four, 75, and 109 patients with 7, 6, and 5 years, respectively, of continuous treatment were identified. Mean change in letter score at year 5 was +14.0 letters ($P = 3.9 \times 10^{-9}$), +12.2 letters at 6 years ($P = 1.5 \times 10^{-7}$), and +12.1 letters at 7 years ($P = 3.8 \times 10^{-5}$). Driving vision (20/40 or better) was achieved in 43.2% of treated eyes. Subanalysis revealed that the greatest visual gains at 5 and 7 years were seen in those patients with baseline visual acuity worse than 20/200 (+24.5 and +25.5 letters), followed by those with 20/50 to 20/100 vision (+6.7 and +6.9 letters), and finally those with 20/20 to 20/40 (+3.7 and +3.4 letters). Patients received an average of 10.5 injections per year.

Conclusions: Continuous fixed-interval dosing of anti-VEGF therapy in patients with exudative AMD results in favorable long-term preservation out to 7 years, with vision stabilizing or improving in 93.2% of eyes. Additionally, 43.2% of patients maintained driving vision in the treatment eye at 7 years compared with 10.1% at baseline. Our data suggest better outcomes with continuous therapy over published results with sporadic, as-needed therapy. *Ophthalmology 2015;■:1–6 © 2015 by the American Academy of Ophthalmology.*

Visual acuity outcomes in patients with exudative age-related macular degeneration (AMD) have been improved greatly by the advent of vascular endothelial growth factor (VEGF) inhibitors. By targeting a key factor in choroidal neovascular membrane proliferation and vascular permeability, further vascular maturation, proliferation, and leakage can be inhibited. However, treatment does not eliminate the underlying pathobiological features. After therapeutic levels of these drugs are depleted, patients remain at risk for recurrent activation of the previous vascular complexes, formation of new lesions, leakage, hemorrhage, and development of disciform scarring. This phenomenon highlights the chronic, persistent nature of this disease.[1]

Both the Anti-VEGF Antibody Fragment Ranibizumab for the Treatment of Predominantly Classic Choroidal Neovascularization in AMD (ANCHOR) and the Minimally Classic/Occult Trial of Anti-VEGF Antibody Fragment Ranibizumab in the Treatment of Neovascular AMD (MARINA) trials were pivotal studies demonstrating superior visual acuity results with monthly ranibizumab injections compared with photodynamic therapy and observation, respectively.[2–4] With the subsequent Food and Drug Administration approval of ranibizumab (Lucentis; Genentech, Inc, San Francisco, CA) in June 2006, widespread clinical use has resulted in markedly improved patient outcomes. Even before approval of ranibizumab, the benefits of off-label use of bevacizumab also were being reported in a few small case series. Phase 3 trials with the VEGF-trap fusion protein aflibercept (Eylea; Regeneron, Tarrytown, NY) also have resulted in excellent visual acuity results.[5]

Multiple randomized, controlled clinical trials have been conducted looking at the efficacy of as-needed (pro re nata

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[PRN]) and quarterly treatment regimens. With a few exceptions, these studies have shown less effective results compared with monthly therapy over 1 to 2 years.[6–11] One of the earliest exceptions was the phase 1/2 trial, Prospective OCT Study With Lucentis for Neovascular AMD (PrONTO Study) which treated 40 patients over 2 years with PRN dosing using vision, clinical, and optical coherence tomography parameters as guidelines for re-treatment.[12] Although the study contained no monthly treated control arm, these results approached those of ANCHOR and MARINA with nearly half the number of injections. In 2012, the 2-year data from the Comparison of Age-Related Macular Degeneration Treatments Trials were released demonstrating inferior visual gains in the bevacizumab PRN arm using PrONTO retreatment parameters when compared with the cohort receiving monthly ranibizumab.[13] The results of these PRN regimen strategies have prompted many treating specialists to switch to a method of treatment with interval extension, or treat and extend, after stability is noted. Although no large multicenter trial has investigated this method of treatment, it is touted as offering comparable visual outcomes with decreased treatment burden and additional cost savings.[14,15]

One argument for less frequent dosing stems from animal model and clinical studies suggesting progression of geographic atrophy (GA) in response to sustained exposure to anti-VEGF agents. Inhibition of retinal pigment epithelium (RPE)-derived VEGF-A and other isoforms may blunt neuroprotective and trophic effects on choriocapillaris and cone photoreceptors, thereby leading to tissue loss.[16,17] Some have suggested that the suppression of these factors may be the underlying cause of progressive RPE and choriocapillaris atrophy seen in various case series and reports. Although progressive atrophy has been reported with monthly, PRN, treat-and-extend dosing regimens, it is not well understood whether this is a direct effect of anti-VEGF suppression or merely the natural progression of the disease over the long term.[18–20]

Given that most trials are limited to observations over 1 to 2 years, little is known about the long-term effects of chronic anti-VEGF therapy 5 years and beyond. Furthermore, no studies have evaluated patients receiving continuous fixed-interval dosing over this period. The Open-Label, Multicenter Extension Study to Evaluate the Safety and Tolerability of Ranibizumab in Subjects With Choroidal Neovascularization (CNV) Secondary to Age-Related Macular Degeneration (AMD) or Macular Edema Secondary to Retinal Vein Occlusion (RVO) Who Have Completed a Genentech-Sponsored Ranibizumab Study, or HORIZON trial has reported 5-year data on patients initially receiving monthly treatment in the ANCHOR and MARINA studies who subsequently were crossed over to PRN treatment at the end of 2 years.[10] A small subset of the HORIZON cohort exited the study at year 4 of treatment and were followed out to 7.3 years by Rofagha et al.[21] After exit from HORIZON, these patients were treated at the discretion of their provider. These eyes were likely undertreated, receiving an average of only 1.9 injections per year on exiting HORIZON and losing an additional 10.3 letters. The aim of this study was to present the visual outcomes in eyes receiving significantly long-term, fixed-interval dosing with VEGF inhibitors.

Methods

Study Design

After approval by the Western Institutional Review Board, a retrospective review of patients in our practice with 5 or more years of continuous, fixed-interval injections every 4 to 8 weeks was performed. The practice's billing system was queried to identify patients who had undergone intravitreal injection between January 1, 2007, and January 1, 2014, with a concomitant diagnosis of exudative macular degeneration. Individual charts then were reviewed and included if they demonstrated a consecutive treatment span of more than 5 years. Snellen vision and date from initial injection and each subsequent visit were recorded, and injection intervals were calculated. Snellen visions were converted to logarithm of the minimum angle of resolution values and letter values in a standard fashion for statistical analysis. Patient eyes were excluded if they averaged fewer than 6.5 injections per year. Additionally, whether the patient had received other treatment, including laser, photodynamic therapy, or previous intravitreal injections, before committing to a fixed interval course of treatment also was recorded.

Study Objectives

The primary outcome of the study was the mean change in vision from baseline for all eyes at years 5, 6, and 7. Secondary outcome measures included the percentage of patients at 7 years with good vision (20/40 or better) and mean change of vision from baseline in eyes that initiated treatment with good vision (20/40 or better), impaired vision (20/50−20/100), and blindness (20/200 or worse).

Statistical Analysis

Data were collected from patient charts and the de-identified data were entered into a spreadsheet. Excel statistical calculators (Microsoft, Redmond, WA) were used to conduct paired 2-tail Student t tests to identify differences in visual changes between each yearly time point. Subanalyses exploring visual outcome differences between eyes receiving and not receiving previous treatment used a Mann−Whitney U test to compare visions between the 2 nonparametric samples.

Results

Eight hundred seventy-eight patients were identified from our practice as receiving intravitreal injections for wet AMD between 2007 and 2014. After reviewing charts, we identified 109 eyes in 89 patients who had received continuous, fixed-interval dosing every 4 to 8 weeks for at least 5 years. Among these, 75 and 44 had at least 6 and 7 years of treatment, respectively. Two additional patients had more than 5 years of treatment, but were excluded because of more prolonged treatment intervals (10−12 weeks). The remaining 787 patients had fewer than 5 years of treatment, with 183 (20.8%) actively receiving fixed-interval treatment every 4 to 8 weeks. The remaining excluded patients consisted of 199 (22.7%) who had left the practice or were lost to follow-up, 78 (8.9%) who were deceased, 213 (24.3%) who received treatment in our practice only seasonally, 53 (6%) who were discontinued by the treating physician because of endstage disease, and 61 (6.9%) whose treatment was stopped at the patient's request. Mean baseline visual acuity was approximately 20/125 with a median of 20/80 (mean and median baseline letter score, 45.6 and 54.9, respectively). Eleven (10.1%) of the 109 eyes had vision of 20/40 (good vision) or better at baseline, whereas 48.6% had visual acuity