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Long-Term Outcomes of Treatment of Neovascular Age-Related Macular Degeneration

Data from an Observational Study

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Purpose: To analyze the long-term outcomes of eyes with neovascular age-related macular degeneration (AMD) starting treatment with vascular endothelial growth factor (VEGF) inhibitors at least 5 years earlier.

Design: Database observational study.

Participants: Treatment-naïve eyes with neovascular AMD tracked by the Fight Retinal Blindness outcome registry that received at least 1 anti-VEGF injection.

Methods: Locally weighted scatterplot smoothing curves were used to display visual acuity (VA) results.

Main Outcome Measures: Change in mean VA and number of injections and visits from baseline up to 7 years after initiating treatment.

Results: The mean follow-up time of all 1212 identified eyes was 53.5 months, and 549 (45%) continued attending after 60 months. Mean VA improved from 55.1 to 61.4 letters after 6 months and remained above the mean presenting VA for approximately 6 years. After 7 years, mean VA was 2.6 letters lower than baseline for the 131 eyes still being followed; 40% had VA $\geq$70 (20/40) letters, and 18% had VA $\leq$35 letters (20/200). Of those with 20/40 VA before treatment, 40% had lost it after 7 years. Geographic atrophy affecting the fovea was thought to be the cause of a $\geq$10-letter loss after 6.5 years in 37% of a subset of such eyes that were retrospectively analyzed. A median of 6 injections and 9 visits were recorded over the first 12 months, and then 5 treatments and 7 to 9 visits per annum thereafter through 7 years. Treatment was discontinued for 663 eyes (53%) within the first 5 years. Despite initial gains in vision, the mean VA of these eyes had deteriorated to baseline or worse around the time treatment was discontinued. The rate of serious adverse events was low.

Conclusions: Good long-term outcomes of VEGF inhibition for neovascular AMD were found in this study. These results may be better than other reports because more injections were given to our patients, possibly associated with a greater incentive for the physician to treat. Further studies to determine how to maximize the proportion of eyes that retain the initial VA gains of anti-VEGF are warranted. *Ophthalmology 2015;■:1–9 © 2015 by the American Academy of Ophthalmology.*

*Supplemental material is available at www.aaojournal.org.

The treatment of neovascular age-related macular degeneration (AMD) with vascular endothelial growth factor (VEGF) inhibitors is generally regarded as a generational breakthrough in macular therapeutics. Unprecedented improvements of 1 to 2 lines of vision lasting up to 2 years have been reported by several pivotal phase III studies.[1–5]

Although short- to medium-term efficacy is undisputed, there are few data on long-term outcomes of VEGF inhibition for neovascular AMD, despite more than 7 years of access to approved anti-VEGF treatments in many countries. This is a serious gap in our knowledge because it seems that the majority of people require treatment indefinitely.[6] Because current trends in clinical practice to individualize treatment protocols, such as the pro re nata (PRN) and treat-and-extend protocols,[4,7] are resulting in fewer injections than was mandated in the pivotal studies, it is important to determine whether this approach is compromising long-term outcomes. On the other hand, the Comparison of Age-related Macular Degeneration Treatments Trials Research Group reported that more frequent treatment regimens that resulted in drier maculae increased the risk of new geographic atrophy, suggesting that long-term VEGF inhibition may lead to an increased risk of atrophic degeneration.[8] In the largest series with long-term outcomes, the

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SEVEN UP (Seven-year outcomes in ranibizumab-treated patients in ANCHOR, MARINA, and HORIZON trials) study found the mean visual acuity (VA) of a cohort of 65 eyes followed for over 7 years decreased to less than the baseline level 4 to 5 years after starting treatment and was 8.6 letters worse than baseline after 7 years.[9]

We describe in this article the outcomes of more than 1200 eyes that commenced treatment with VEGF inhibitors ≥5 years ago, including 131 eyes with 7 years' follow-up.

Methods

Design and Setting

This was an observational study of eyes that had commenced intravitreal therapy for neovascular AMD in routine clinical practice at least 5 years earlier and had been tracked in the Fight Retinal Blindness (FRB) database. Treatment decisions and visit schedules were determined by the treating physician in consultation with the patient. The details of the FRB database have been published.[10] In brief, 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 of uncorrected, corrected, or pinhole), activity of the choroidal neovascular membrane, treatment given, if any, ocular adverse events, and whether the eye had received prior treatment for neovascular AMD. 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. The project includes contributing practitioners located in Australia, New Zealand, and Switzerland.

Patient Selection and Variables

Patients included in the analysis were treatment naïve, never having received any form of treatment for neovascular AMD, and were treated with intravitreal therapy starting between January 2007 and January 2010, allowing at least 5 years of potential follow-up since starting treatment.

Outcomes

The main outcomes were the mean change in VA over time of the entire group, together with the frequency of injections and visits. Eyes were considered in 4 groups: all eligible eyes (N = 1212 of 1043 patients) and the overlapping subsets of eyes that were followed up for 3 (n = 868), 5 (n = 549), and 7 years (n = 131). Three-year outcomes were studied to compare with an observational study from the United Kingdom.[11] For each group of eyes, the mean baseline VA and mean final VA, as well as the proportions of eyes with VA of ≥70 letters (20/40) and ≤35 letters (20/200), were calculated at these same time points. The proportions of eyes avoiding moderate vision loss (<15 letters) and gaining >15 letters were also analyzed. The VA outcomes for eyes with very good initial vision (≥70 letters [20/40]) and eyes with poor initial vision (≤35 letters [20/200]) were compared with those of eyes with baseline VA between 36 and 69 letters. The VA trends for eyes that were lost to follow-up before 5 years also were analyzed. We also asked the major contributing physicians or centers to assess the cause of vision loss of ≥10 letters in eyes that received at least 6.5 years of treatment on the basis of spectral domain optical coherence tomography and the clinical notes.

Statistical Analysis

All analyses were performed using R, version 3.1.1.[12] Descriptive statistics included mean, standard deviation (SD), median, range, quartiles, and percentages where appropriate. Eyes were considered to have been observed from the first treatment visit to the most recent visit recorded. When subsets were taken for eyes followed up for at least 3, 5, or 7 years, the last observed VA was taken as the last observation within the time period: 3, 5, and 7 years. Locally weighted scatterplot smoothing (Loess)[13] curves were used to display VA results. Time ranges used to analyze follow-up periods were 0 to 6 months (0−180 days), 7 to 12 months (181−365 days), 13 to 24 months (366−730 days), 25 to 36 months (731−1095 days), 37 to 48 months (1096−1460 days), 49 to 60 months (1461−1825 days), and ≥60 months (≥1826 days). Intervals between injections and visits were grouped as ≤5 weeks (0−38 days), 6 to 7 weeks (39−52 days), 8 to 9 weeks (53−66 days), and ≥10 weeks (≥67 days). Some participating practitioners ran a 2-day service, assessing patients for treatment on 1 day and treating at a later time. To accommodate this, 2 visits within a 10-day period were considered a single visit. When relevant to the analyses, eyes were stratified by their baseline VA: ≥70 letters, 36 to 69 letters, and ≤35 letters.

Results

Anti-VEGF treatment for neovascular AMD was commenced in 1212 treatment-naïve eyes of 1043 patients whose details were entered in the FRB system between January 2007 and January 2010. These injections were given by 23 ophthalmologists from Australia, New Zealand, and Switzerland. Figure 1 shows the selection criteria and the number of eyes included in the final analysis. The study population had a mean age of 79.1 years at their first visit, with a mean baseline VA of 55.1 logMAR letters (Table 1). Given the time period of interest (2007−2010), most eyes were treated with only 1 type of anti-VEGF treatment: 648 (53.5%) with ranibizumab and 69 (5.7%) with bevacizumab. Of the 495 eyes that were treated with multiple agents, 74.8% of injections were with ranibizumab, 10.5% were with bevacizumab, and 14.7% were with aflibercept.

Outcomes of All Treatment-Naïve Eyes That Had Started Treatment ≥5 Years Earlier

A total of 1212 treatment-naïve eyes started treatment at least 5 years before the analysis, with varying duration of follow-up. They were followed for a mean of 53.5 months (SD, 26.1; median, 57.0; quartile 1, 34.0, quartile 3, 72.9 months). The mean baseline VA for these 1212 eyes was 55.1 letters (20/80+1) (SD, 18.8 letters), and the mean VA at the final observed follow-up visit was 55.7 letters (SD, 22.3 letters), representing an overall decline of 0.6 letters. Mean VA increased to a maximum of 61.4 letters, with a gain of 6.3 letters, 6 months after starting treatment. Analysis of VA outcomes over time revealed an apparent general improvement through 5 years followed by some loss of these gains by 7 years (Fig 2, Table 2).

Much of the apparent improvement of mean VA through 5 years compared with the baseline mean for the entire group was because the mean baseline VA improved for groups that continued to be followed longer (Table 2, Fig 2), indicating that eyes that persisted with the treatment for longer tended to have had better vision to begin with.