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Two-Year Outcomes of "Treat and Extend" Intravitreal Therapy for Neovascular Age-Related Macular Degeneration

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Purpose: To report 24-month outcomes of anti-vascular endothelial growth factor (VEGF) therapy for treatment-naïve eyes with neovascular age-related macular degeneration (nAMD) using a treat and extend treatment regimen in routine clinical practice.

Design: Database observational study.

Participants: We included treatment-naïve eyes receiving predominantly ranibizumab for nAMD in routine clinical practice treated using a treat and extend regimen that were tracked in the Fight Retinal Blindness observational registry.

Methods: A cohort of eyes treated by practitioners using exclusively a treat and extend regimen was extracted from the Fight Retinal Blindness observational registry.

Main Outcome Measures: Change in visual acuity (VA) over 2 years and number of injections and visits.

Results: Data from 1198 eyes from 1011 patients receiving anti-VEGF therapy using a treat and extend regimen for treatment-naïve nAMD between January 2007 and December 2012 and with 24-month follow-up were included in the analysis. Mean VA increased by +5.3 logarithm of the minimum angle of resolution letters from 56.5 letters (20/80+1) at initial visit to 61.8 (20/60+2) letters at 24 months. Mean VA gains improved and number of injections increased with successive years from +2.7 letters for eyes commencing in 2007 after a mean of 9.7 injections in 2 years, to +7.8 letters for eyes commencing in 2012 after a mean of 14.2 injections over 2 years. The proportion of eyes with VA >20/40 increased from 27% when starting treatment to 45% after 24 months; the proportion with vision of <20/200 remained unchanged (13% initial, 11% at 24 months). Of the included eyes, 90.5% avoided a vision loss of ≥15 letters. There was an overall mean of 13.0 injections over the 24 months, 7.5 injections in the first year and 5.5 in the second year, with a mean of 14.8 clinic visits.

Conclusions: These data indicate that eyes managed in routine clinical practice with a treat and extend regimen can achieve good visual outcomes while decreasing the burden of treatments and clinic visits. *Ophthalmology 2015;122:1212-1219 © 2015 by the American Academy of Ophthalmology.*

The management of neovascular age-related macular degeneration (nAMD) has been revolutionized by the introduction of anti-vascular endothelial growth factor (VEGF) agents, with pivotal clinical trials demonstrating efficacy in visual outcomes for ranibizumab[1,2] and aflibercept[3] using fixed treatment regimens. Variable treatment regimens subsequently evolved, based mainly on a judgment of the individual's disease activity, because patients and clinicians sought to decrease the burden and risks of fixed dose regimens. One common approach is pro re nata (PRN; as needed), in which therapy is withheld unless there are signs of activity of the choroidal neovascularization (CNV) lesion. The Comparison of Age-related macular degeneration Treatment Trials (CATT) and HARBOR randomized clinical trials[4–7] demonstrated that visual outcomes of management under a strict PRN treatment regimen could approach those of a fixed monthly treatment schedule with fewer injections, but monthly monitoring was still required. Treat and extend (T&E) is another treatment approach that aims to decrease the burden of both clinic visits and injection treatments, while similarly basing the management plan on assessment of disease activity. A T&E approach continues to treat irrespective of CNV activity, but gradually increases the intervals between treatments after the CNV has been stabilized to keep the lesion inactive with the fewest possible treatments. The T&E approach allows each individual to find a treatment frequency that controls their own CNV with little risk of leaving active CNV untreated for a prolonged period of time.

Although T&E seems to have become very common,[8] data on efficacy and outcomes are limited to small case series and 1 randomized clinical trial.[9–15] Here we report the 2-year real-world outcomes of a large cohort of patients with nAMD treated by practitioners throughout Australia and New Zealand who reported that they used a T&E treatment regimen.

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Methods

Study Design and Setting

This observational study included eyes treated with intravitreal therapies by practitioners who reported that they used a T&E protocol during the period studied. Although there was some individual variation in T&E protocols, the basic regimen involved initial treatment once every 4 weeks until signs of CNV activity had resolved, followed by extension of the treatment interval by 1 to 2 weeks as long as visual acuity (VA) was stable (within 5 letters of best VA achieved) and there were no clinical or ocular coherence tomography signs of CNV activity. Upon recurrence of CNV activity, the treatment interval was shortened.

We analyzed anonymized data from the Fight Retinal Blindness (FRB) registry, which were captured during routine clinical practice. All treatment decisions and visit schedules were entirely at the discretion of the treating physician and patient. Details of the FRB project data tracking system have been reported previously.[16] Briefly, at each visit, data was collected on VA letters read on a logarithm of the minimum angle of resolution (logMAR) chart (on which Early Treatment of Diabetic Retinopathy Study charts are based), activity of the CNV lesion as judged by the treating practitioner, whether the eye had received previous treatments for nAMD, type of treatment given, if any, and ocular adverse events. The best reading of uncorrected, corrected, or pinhole VA was used. Institutional ethics approval was obtained from the Human Research Ethics Committees of the Universities of Sydney, Melbourne, and Western Australia. Overarching ethical approval for the private centers was obtained from the Royal Australian and New Zealand College of Ophthalmologists' Human Research Ethics Committees. All ethics committees approved the use of "opt out" patient consent. The research described adhered to the tenets of the Declaration of Helsinki. This study included contributing practitioners located in Australia and New Zealand.

Participants and Variables

Practitioners using the FRB database were contacted to self-report their treatment approach(es) in each year from 2007 to 2013. Three treatment regimens were available for selection: monthly, PRN, and T&E, or a combination of these 3.

We included in the analysis all treatment-naïve eyes that started receiving intravitreal VEGF inhibitors from January 2007 to December 2012 (24 months before analysis) from practitioners at a time when they reported that they had been using a T&E protocol exclusively. Only eyes that had ≥24 months of follow-up were analyzed, but the baseline characteristics of these eyes were compared with those of participants who were lost to follow-up before 24 months.

Outcomes

Principal outcomes were the mean change in VA over time and the number and frequency of injections and visits. Mean 2-year change in VA was assessed from initial to last observed visit within the 24-month period. Other outcomes included the following: maximum gain in VA; the proportion of eyes maintained on treatment intervals of 4 weeks, 5 to 6 weeks, 7 to 8 weeks, and ≥9 weeks; the proportion of injections given to eyes with an inactive CNV grading; the proportion of eyes avoiding moderate (<15 letters) vision loss; the proportion of eyes with good vision (≥70 letters [20/40]) and eyes with poor vision (≤35 letters [20/200]); and ocular safety. To explore whether loss to follow-up had an effect on outcomes, we compared change in mean VA in the study cohort with that of eyes that had <24 months of follow-up but otherwise met study inclusion criteria.

Statistical Analysis

All analyses were performed using R, version 3.1.1.[17] Descriptive statistics included mean, standard deviation (SD), standard error of the mean, 95% CI, median, range, quartiles, and percentages where appropriate. An eye was considered to have 24-month follow-up if a visit was observed >730 days after the initial visit. The most recent VA reading preceding the 24-month time point was used as the VA at 24 months. Locally weighted scatterplot smoothing[18] (loess) curves were used when observations of VA were analyzed throughout the follow-up period. Time between visits was categorized into 5 groups: 4 weeks (10−34 days), 5 to 6 weeks (35−48 days), 7 to 8 weeks (49−62 days), 9 to 15 weeks (62−112 days), and ≥16 weeks (≥113 days). A small number of clinics participating in the FRB project run a 2-day service, with assessments and treatments on different days. To accommodate this, visits within a 10-day period were considered a single visit. Where relevant, eyes were stratified based on their initial VA: ≥70 letters, 36 to 69 letters, and ≤35 letters. We used analysis of variance and linear regression to compare means among years of treatment initiation. Eyes lost to follow-up were analyzed separately in the following periods: lost to follow-up within 0 to 3 months (0−90 days), 4 to 6 months (91−180 days), 7 to 12 months (181−365 days), and 13 to 24 months (366−730 days) after initial treatment. Comparisons between eyes exceeding 24 months of follow-up and eyes lost to follow-up before 24 months were made using Kolmogorov-Smirnov tests, *t* tests, and Pearson's chi square tests as appropriate.

A sensitivity analysis was performed for the primary outcome of change in VA over 24 months, which examined the effect of any correlation between eyes for the 187 patients with both eyes in the study by randomly removing 1 eye of each pair from the analysis.

Results

We included 1198 treatment-naïve eyes from 1011 patients with nAMD beginning intravitreal treatment between January 2007 and December 2012 and with 24 months of follow-up. Participants were treated by 19 ophthalmologists throughout Australia and New Zealand. Figure 1 shows the selection criteria and number of eyes included in the final analysis. The study population had a mean age of 79.4 years at their first visit with a mean initial VA of 56.5 logMAR letters (20/80+1). An additional 648 treatment-naive eyes received intravitreal treatment using a T&E protocol during the same time period but were excluded because they did not have data entered to 24 months.

Table 1 summarizes the baseline characteristics of the eyes observed. The mean initial VA of the 1198 eyes that completed the 24-month follow-up (56.5 letters) was significantly better than that of the eyes with <24 months of follow-up (48.4 [20/120+3]; *t* test; $P < 0.001$). Likewise, the proportion of eyes with an initial VA of ≥70 letters (≥20/40) was greater for eyes with >24 months of follow-up (27%) than for eyes lost to follow-up (17%; $P < 0.001$). Patients with <24 months of follow-up were a little older at initial visit (80.8 vs 79.4 years; $P = 0.01$). There was no difference between the lesion types for eyes with 24 months of follow-up and those with shorter follow-up ($P = 0.84$).

Three drugs were used: bevacizumab, ranibizumab, and aflibercept. Monotherapy with ranibizumab was received by 588 of the 1198 eyes (49%); 25 eyes (2%) received bevacizumab monotherapy, and no eyes received aflibercept monotherapy. A total of 585 eyes (49%) received a combination of ≥2 agents: of these injections, 9.2% were bevacizumab, 7.9% were aflibercept, and 82.9% were ranibizumab. Owing to the quality assurance features of the FRB web-based data entry system, data completeness was high for all variables (>99.5% VA, treatment given, adverse event