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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;■:1–8 © 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

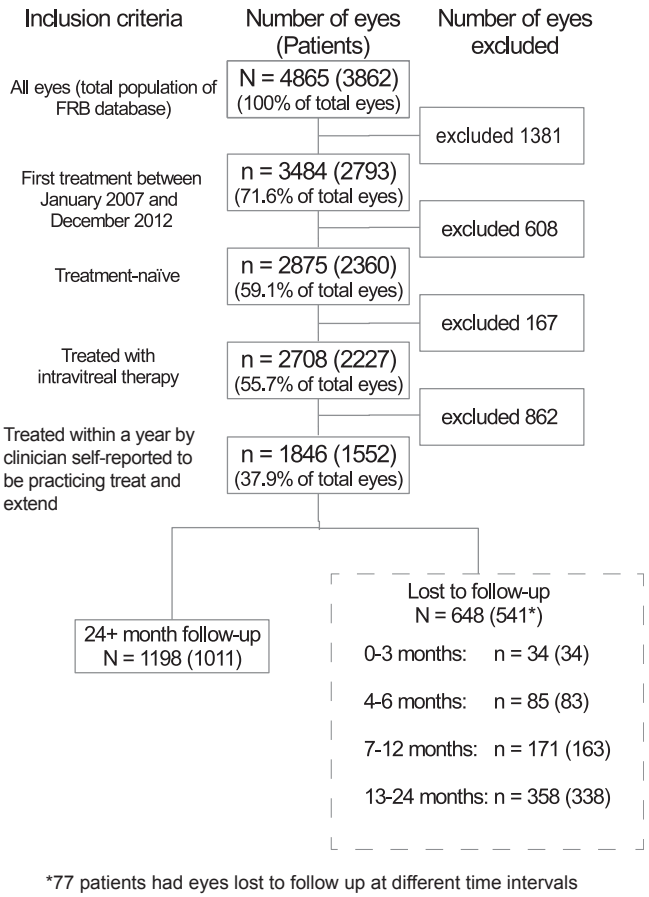

Figure 1. Diagram showing the number of eyes in the study and the inclusion criteria required for analysis.

and activity grading fields completed) with the exception of CNV lesion size (greatest linear dimension; 80% completed) and lesion type (88% completed).[19]

Change in VA in 24 Months

Mean initial VA increased from 56.5 (SD, 17.3) logMAR letters (20/80+2) at baseline to 61.8 (SD, 18.8; 20/60+2) after 24 months, a gain of +5.3 letters. A VA of ≥70 letters (≥20/40) was seen in 327 eyes (27.3%) at the initial visit and 533 eyes (44.5%) at 24 months. A VA of ≤35 letters (≤20/200) was seen in 158 eyes (13.2%) at initial visit and 130 eyes (10.9%) at 24 months. Moderate loss of vision (>15 letters) was avoided by 1084 eyes (90.5%). The mean VA peaked after around 6 months of treatment, with a mean VA of 63.0 (SD, 17.2) letters (20/60+3), a gain of 6.4 letters, and subsequently declined slowly (Fig 2).

For the 187 patients (18.5%) with both eyes in the analysis the intraclass correlation between paired eyes was 0.13. A sensitivity analysis was performed where 1 eye in each of these pairs was removed randomly. The mean initial VA for this reduced data set was 56.3 (SD, 17.1) logMAR letters increasing to 62.0 (SD, 17.5) letters.

Treatments and Visits

There was a mean of 7.5 (SD, 2.3) injections per eye in the first year, and 5.5 (SD, 2.9) in the second, giving a mean of 13.0 injections per eye over 24 months. The greatest proportion (11.7%) of eyes received 12 injections over the 2 years (Fig 3).

Table 1. Characteristics of Participants and Eyes Fulfilling the Inclusion Criteria Compared with the Group of Eyes Lost to Follow-up before 24 Months

Characteristics	24 Months Follow-up	<24 Months Follow-up	*P* value
No. of eyes	1198	648	
No. of patients	1011	595	
Left (%)	50.0	46.5	
Female (%)	61.3	61.7	
Mean baseline age, y (SD)	79.4 (8.1)	80.8 (7.7)	0.01*
Mean baseline VA, letters (range)	56.5 (2–90)	48.4 (0–90)	<0.001†
Baseline VA ≥ 70 letters (20/40 Snellen), %	27.3	17.1	<0.001‡
Year of baseline visit, n (%)			
2007	126 (10.5)	24 (3.7)	
2008	214 (17.9)	33 (5.1)	
2009	289 (24.1)	113 (17.4)	
2010	292 (24.4)	178 (27.5)	
2011	148 (12.4)	159 (24.5)	
2012	129 (10.8)	141 (21.8)	<0.001‡
Lesion type, n (%)			
Occult	600 (50.1)	320 (49.4)	
Minimally classic	218 (18.1)	116 (17.9)	
Predominantly classic	191 (15.9)	115 (17.7)	
Other	51 (4.3)	28 (4.3)	
Not recorded	138 (11.5)	69 (10.6)	0.84‡

*Kolmogorov–Smirnov test.
†*t* test.
‡Pearson's chi square test.

The mean number of visits was only slightly greater than the number of injections at 7.9 (SD, 2.3) in the first year and 6.7 (SD, 3.0) in the second year. The median time between visits was 4.2 weeks in the first 3 months increasing to 5.7 weeks in the second 3 months, 7.1 weeks in the second 6 months, and 8.0 weeks in the second year. In all the observed time periods, a treatment was administered in >83% of visits. For patients with both eyes included, 1 eye was treated and the other not in 7% of all visits. This accounts for 40% of the 17% of visits where no treatment was received.

Outcomes Over Time

Mean initial VA was similar for all years that treatment was commenced, but there was a significant improvement in mean change in VA with year of treatment initiation ($P < 0.001$, linear regression), as well as a significant increase in the mean number of injections with initial year of treatment ($P < 0.001$, analysis of variance; Table 2). There was a small correlation between the number of injections and the overall change in VA ($r = 0.1$). The proportion of clinicians self-reporting using an exclusively T&E regimen increased from 57% in 2007 (17 from 30 responders) to 79% in 2012 (30 from 38 responders).

Injection Frequency

The interval between treatments was classified as 4 weeks, 5 to 6 weeks, 7 to 8 weeks, 9 to 15 weeks, and ≥16 weeks. Most eyes were (72%) treated at 4-weekly intervals for the first 3 months. From 4 to 6 months, most eyes (59%) had extended to between 5 to 8 weeks. From 6 months on, around one-third of eyes (21%–29%) were

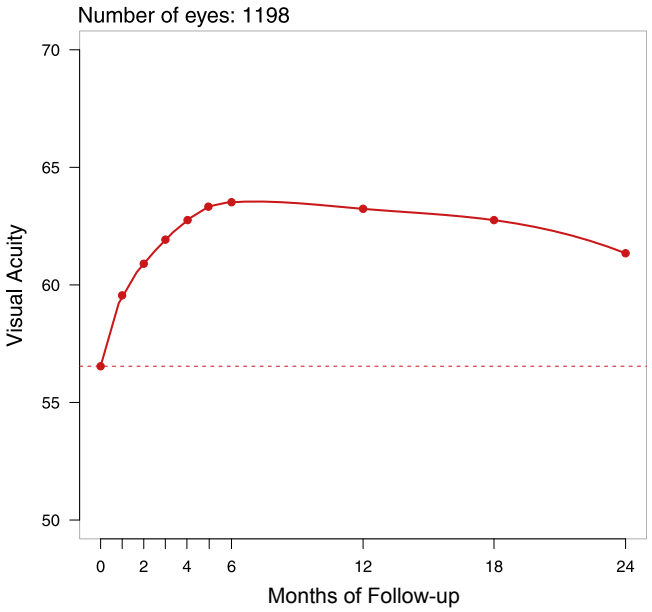

Figure 2. Loess curve showing the mean visual acuity change for Treat and Extend eyes with 24 months follow-up.

treated at intervals of 9 to 15 weeks. A small proportion of eyes (≤5%) were treated with an interval of ≥16 weeks (Table 3).

Over the observed 24 months, the proportion of visits with an inactive CNV reading increased from 4.5% to 61.3% (Fig 4). Consistent with a T&E regimen, the proportion of visits receiving injections when the disease was graded as inactive was 79.6%, not much less than 91.0% when it was graded as active. The large proportion of eyes that received treatment when they were graded as inactive is objective evidence of a T&E approach compared with a PRN approach. Also consistent with a T&E regimen is that the mean number of times the treatment interval per eye was reduced by 2 weeks (≥14 days) was 2.2 times (SD, 2.0; median, 2) over the 2-year period.

Safety

Ocular adverse events are summarized in Table 4. These events resulted from 15 554 injections and 19 451 visits. The rate of endophthalmitis (both infectious and noninfectious) was 1 per 7272 injections (0.013%).

Change in VA in Eyes Lost to Follow-Up

During the first 24 months from the initial injection, 648 eyes were lost to follow-up. Table 5 shows the mean initial and final VA as well as the change in VA by time period when eyes were lost to follow-up. The earlier the eyes were lost to follow-up, the lower their mean initial VA ($P < 0.001$, analysis of variance). Length of time of follow-up was not related to final change in VA ($P = 0.3$, regression analysis). The majority of eyes were lost after 1 year of follow-up and had a good VA gain of +4.5 letters.

Discussion

We report outcomes for the largest cohort of patients undergoing anti-VEGF therapy by a T&E regimen yet presented. We found that this regimen had good efficacy over 2 years in an unselected group of patients with nAMD managed in the community practice. Treatments were given at nearly 80% of visits at which lesions were graded as inactive, which together with an increasing time between injections as time progressed, was consistent with a T&E approach. There was a peak mean gain of VA of +6.4 letters after starting treatment, which gradually subsided to a gain of +5.1 letters at 24 months. The proportion of eyes with VA of ≥20/40 increased from 27% at baseline to 45% after 2 years of treatment. Two-year mean VA gains improved over time from 2007 to 2012, coinciding with an overall upward trend in the mean total number of

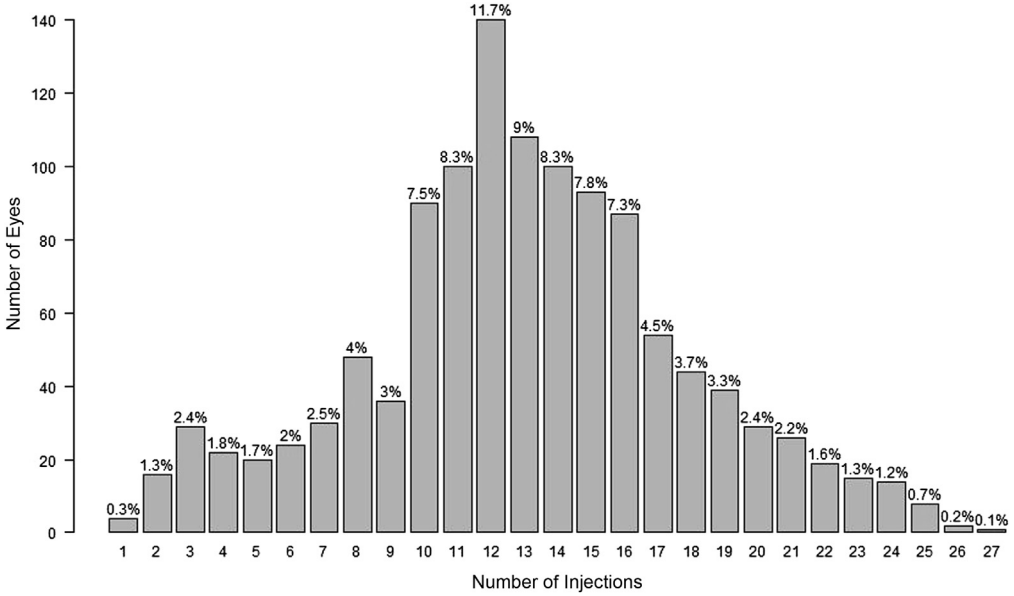

Figure 3. Distribution of total injections received by individual eyes in the first 24 months of intravitreal treatment.

Table 2. Change in Visual Acuity (VA) Over Time*

Initial Year	Mean Initial VA (SD)	Mean Change in VA from Initial Vision at 24 Months (SE)	Mean Total Number of Injections over 24 Months (SD)
2007	56.8 (17.2)	2.7 (0.5)	9.7 (4.5)
2008	55.8 (17.2)	3.8 (0.5)	11.9 (5.0)
2009	55.3 (16.8)	3.6 (0.5)	13.4 (5.0)
2010	56.7 (17.2)	5.3 (0.5)	14.0 (4.2)
2011	56.3 (19.6)	9.6 (0.5)	13.9 (4.9)
2012	60.3 (16.1)	7.8 (0.4)	14.2 (4.0)

SD = standard deviation; SE = standard error.
*55 letters = 20/80, 60 letters = 20/60.

injections per eye over 2 years. The rate of adverse events was acceptable and similar to previous reports.

Outcomes, particularly gains in VA, demonstrated in randomized clinical trials using anti-VEGF therapy for nAMD have not always translated into similar gains in unselected groups of people treated in the real-world setting during routine clinical practice. A UK study reported real-world outcomes using a central database for a large cohort of eyes treated with PRN ranibizumab, including 4990 eyes with 2 years of follow-up. In the UK study, mean VA had increased by 1 letter from 55 (20/80) to 56 after 2 years, whereas in this study there was a 5.3-letter increase from 56.5 to 61.8 (20/60+2) over the same period. Vision of ≥20/40 was achieved by 16% at baseline in the UK study increasing to 30% after 2 years compared with 27% increasing to 45% in this study. Moderate (15-letter) loss of vision was avoided by 84% in the UK study compared with 90% in this study. The UK researchers noted that capacity constraints preventing intended monthly review, combined with reduced treatment frequency, were likely to have contributed to this poorer visual outcome.[20]

The median number of treatments for eyes followed up for ≥3 years in the UK study was 5 in the first year and 4 in the second, and the median number of outpatient visits was 9.2 and 8.2, respectively. By contrast, in this study there was a mean of 7.5 injections per eye in the first year and 5.5 in the second, whereas the mean number of visits was only slightly greater at 7.9 in the first year and 6.7 in the second. Thus, the better VA results in the present study were achieved with more treatments and fewer visits than reported by the UK study, which stated that PRN treatment was "almost universal" in their population.

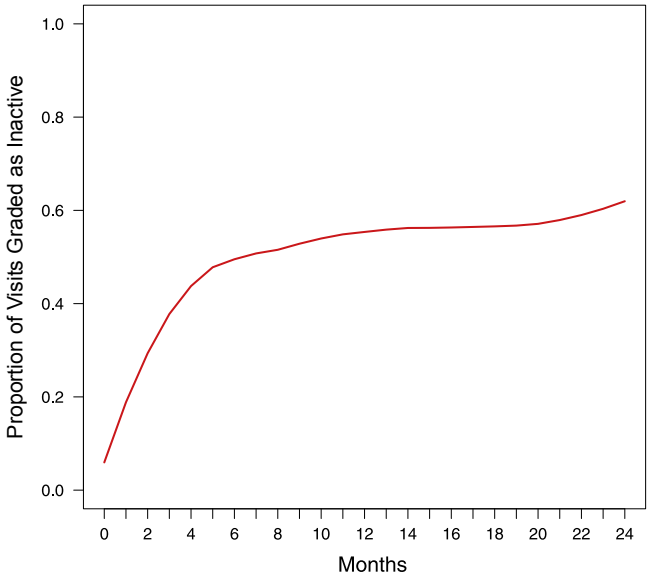

Figure 4. The proportion of visits with an inactive choroidal neovascular (CNV) grading, by time from treatment initiation.

Eyes were not treated at 100% of visits in this study, as might be expected in a strict T&E protocol. Some eyes may not have received strict T&E dosing; however, treatment was given at 80% of visits when the disease was graded as inactive and 91% when it was graded as active. A true PRN approach would give treatments at 0% of visits at which lesions were graded as inactive. Reasons for not treating an eye under a T&E protocol include visits at which a fellow eye was treated, visits for monitoring of adverse events or other ocular conditions, or visits when treatment was deferred owing to ocular or systemic comorbidities, patient preference, and other factors.

The strategy of T&E is to individualize the treatment intervals based on an ongoing assessment of the treatment response. Treatment is generally given monthly until the neovascular lesion is inactive; thereafter, injection treatments continue to be given at each subsequent clinic visit. The interval to the next review and injection visit varies and is determined by an assessment of lesion activity: the interval is increased if the lesion is inactive and decreased if the lesion is active. After several episodes of lesion reactivation after attempted extensions, the treatment interval necessary to control activity can often be determined for each individual eye. In this study, 19% of eyes were still requiring injections

Table 3. Percentage of Eyes Being Treated and Mean Treatment Interval

Treatment Period (mo)	Mean Treatment Interval (%)				
	4 Weeks	*5–6 Weeks*	*7–8 Weeks*	*9–15 Weeks*	*≥16*
0–3	72	25	3	1	0
4–6	27	41	18	14	0
7–12	20	29	22	25	4
13–24	19	26	20	29	5
Overall	29	29	18	21	3

Table 4. Adverse Events

Adverse Event	Total Frequency	%
Hemorrhage reducing BCVA by >15 letters	6	0.039
Infectious endophthalmitis	1	0.006
Noninfectious endophthalmitis	1	0.006
Intraocular surgery	23	0.148
Retinal detachment	4	0.026

BCVA = best-corrected visual acuity.

Table 5. Initial and Final Visual Acuity (VA) for Eyes Lost to Follow-up before 24 Months

Time Period Eye Was Lost to Follow-up (mo)	n	Mean Initial VA (SD)	Final VA	Change in VA (logMAR Letters)
0–3	34	40.6 (19.4)	40.3 (20.1)	−0.3
4–6	85	42.4 (24.8)	45.5 (26.8)	+3.1
7–12	171	48.1 (21.2)	50.0 (26.0)	+1.9
13–24	358	50.7 (18.9)	55.2 (21.0)	+4.5

logMAR = logarithm of the minimum angle of resolution.
40 letters = 20/160; 50 letters = 20/100.

every 4 weeks during the second year of treatment, whereas 34% were only requiring treatment ≥9 weeks apart, including 5% who received treatment ≥16 weeks apart. This concept that an individualized, eye-specific retreatment interval can be established is supported by studies measuring VEGF levels in the anterior chamber during anti-VEGF therapy. A patient-specific period of complete VEGF suppression was observed and this intraindividual suppression time was stable over multiple injection events within a period of ≤3 years.[21]

The increase in injection numbers in our cohort over time reflects a change in clinical practice, which may be owing to a hardening of retreatment criteria.[4–7,22] This practice is likely to be a factor in the higher gains in mean VA to +9.6 letters in eyes commencing treatment in the later years of patient enrollment. The increase in injection frequency might also be partly owing to practitioners replacing their time-domain with spectral-domain ocular coherence tomography machines, which would provide increased sensitivity to detect signs of CNV activity. The mean VA gain approaching 10 letters is similar to the registration in the ANCHOR, MARINA, and VIEW clinical trials, although the patients we studied had a wider range of inclusion criteria[1,2,23] and fewer injections.

The efficacy of PRN regimens incorporating strict ocular coherence tomography retreatment criteria has been addressed in randomized clinical trials. The CATT study compared ranibizumab and bevacizumab given monthly or PRN with monthly monitoring. Both groups achieved significant VA gains over a 2-year period, but these were marginally yet statistically significantly less in the PRN group.[4,5] The HARBOR study compared 0.5 and 2 mg of ranibizumab given monthly or PRN with monthly monitoring with the PRN groups having somewhat lower VA gains through 24 months, but these were considered to be neither clinically nor statistically significant. The mean number of injections over the first 24 months in the PRN treatment groups in these studies was 12.6 to 14.1 in the CATT study and 13.3 in the HARBOR study (ranibizumab 0.5 mg), which was similar to the 13.0 injections observed in our cohort. Although a PRN regimen requires monthly monitoring, the use of a T&E regimen allowed a reduction in the burden of clinic visits to a mean of 14.8 over the first 24 months in the present study.[6,7]

Some care should be taken when interpreting these results, particularly because 648 of the 1845 eyes (35%) that started treatment ≥2 years previously were lost to follow-up and not included in the main analysis. These eyes had worse VA at baseline than those eyes with 2-year data: mean baseline VA was 48.4 (20/100-2) versus 56.5 (20/80+2) letters, respectively, whereas the proportion with VA of ≥20/40 was 17% versus 27%. The proportions that did drop out were relatively greater in eyes starting treatment in the later years, suggesting perhaps that, with experience, practitioners learned in which eyes treatment was worth pursuing and in which eyes further treatment was futile based on the initial response. Although it is possible that patient discouragement may have contributed to loss to follow-up, a survey performed in a clinic participating in the FRB registry found that only 11% of patients declined further treatment.[24] The mean VA of the 119 of the 648 eyes (18%) that were lost to follow-up in the first 6 months did not improve dramatically, but the mean VA improvement of the eyes that dropped out in the second year of treatment, which was the majority (358/648 [55%]), was +4.5 letters, indicating that many of those who dropped out had VA gains similar to the group that continued for 2 years and was the subject of the main analysis.

There was a rapid increase in the percentage of injections performed on inactive eyes during between the first 0 to 3 months and then from 3 to 6 months. This increase implies that there was a rapid decrease in the number of active eyes throughout this follow-up period. Gillies et al[25] reported that the mean time until inactivation of CNV was 15 weeks (approximately 4 months).

Choice of anti-VEGF agent was influenced by physician preference, as well as local constraints in supply and funding of drugs. Because funded ranibizumab was available in Australia from 2006 but funded aflibercept only from December 2012, ranibizumab was the predominant drug used during the study period: during the 24-month follow-up period, 49% of eyes received ranibizumab monotherapy and another 49% received >1 anti-VEGF agent. No eligible eyes received aflibercept monotherapy for 2 years, so a comparison of outcomes between different anti-VEGF agents was not possible in this cohort.

This study confirms the utility of large-scale, prospective, pooled audit in demonstrating treatment outcomes in the community. Although the FRB database mandates that every field is filled in at each visit, the number of fields is kept to a minimum allowing complete data entry in real time in the context of a busy retinal practice. Unlike clinical trials, the patient group is unselected and subject to treatment constraints from patient comorbidities. Despite the vagaries of routine clinical practice, however, we have been able to demonstrate here that a T&E regimen can produce good results with fewer visits than other approaches.

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Abbreviations and Acronyms:
CNV = choroidal neovascularization; **FRB** = Fight Retinal Blindness; **logMAR** = logarithm of the minimum angle of resolution; **PRN** = pro re nata; **nAMD** = neovascular age-related macular degeneration; **SD** = standard deviation; **T&E** = treat and extend; **VA** = visual acuity; **VEGF** = vascular endothelial growth factor.

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