Neovascular age-related macular degeneration at treatment intervals of 14 weeks or greater

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ABSTRACT

Background: We assessed the proportion of eyes with neovascular age-related macular degeneration (nAMD) in routine clinical practice that reach ≥14 week treatment intervals and their outcomes.

Method: We analysed data from the Fight Retinal Blindness! (FRB!) Project database, a prospectively designed registry of “real-world” outcomes. Treatment-naive eyes starting vascular endothelial growth factor (VEGF) inhibitors for nAMD from 1st January 2006 were included. Eyes were defined to have reached the ≥14 week treatment interval if they received ≥2 consecutive injections at treatment intervals of ≥14 week but not exceeding 26 weeks. Outcomes were reported in a subgroup of eyes that had 12 months of follow-up from reaching this interval.

Results: Of the 3907 treatment-naive eyes that started treatment during the identified periods on a treat-and-extend regimen and received at least 8 injections over the first 2 years, 402 (10%) eyes received at least 2 consecutive injections at an interval of ≥14 week during their follow-up. Fifty-two percent of these eyes maintained vision to 12 months, however only 40% stayed at this interval and 25% of the lesions reactivated.

Conclusion: We found that only 10% of eyes with nAMD were extended beyond a 13-week injection interval and that over half had returned to a shorter interval by 12 months. Eyes that stayed at this extended treatment interval maintained stable vision. More data on the outcomes of eyes treated with intervals longer than 3 months are required to establish whether emerging VEGF inhibitors provide a more sustained effect than the currently available drugs.

Keywords: neovascular age-related macular degeneration, anti-vascular endothelial growth factor, treatment interval
1. INTRODUCTION

Improvement or stabilization of vision in nearly all eyes with neovascular age-related macular degeneration (nAMD) was first seen with 4 weekly intravitreal anti-vascular endothelial growth factor (VEGF) treatments (1) (2). This imposed a heavy burden on both patients and health systems in routine clinical practice, so alternative treatment protocols were developed. The PrONTO Study reported that a variable-dosing regimen guided by optical coherence tomography (OCT) gave comparable visual acuity outcomes, with fewer injections, to the phase III clinical trials (3) in contrast to quarterly treatments (4, 5). A treat-and-extend regimen was devised and has since became a well-accepted paradigm for treating nAMD. (6) (7, 8) Many practitioners cap treatment interval extensions at 12 weeks, first defined as the longest interval between injections by the LUCAS trial (9) and later incorporated into American Academy of Ophthalmology (AAO) Anti-VEGF treatment algorithm recommendations for retinal diseases (10) but there is little evidence that this is necessary in all eyes. A panel of UK retinal experts recently provided recommendations of implementing a treat-and-extend approach with aflibercept to a maximum interval of 16 weeks (11). This interval was chosen as Essex et al (2016) demonstrated that the risk of disease reactivation in treat-and-extend Anti-VEGF therapy for nAMD reached a maximum of 20.9% at an interval of 16 week in the clinical setting (8).

Extension of the interval between treatments beyond 12 weeks would reduce the treatment burden while maintaining vision in some patients, but there are only limited data on the outcomes of treating so infrequently. A previous analysis by FRB! of 2-year treat-and-extend regimes in clinical practice reported 24% of patients treated with aflibercept reach an interval of 12 or more weeks (12), but only 3% of eyes get beyond an injection interval of 15 weeks in a predominantly ranibizumab treatment setting (7). We assessed the outcomes of eyes whose treatment interval with bevacizumab, ranibizumab and aflibercept was extended to ≥14 weeks in routine clinical practice, despite this treatment interval representing a small minority.
2. METHODS

2.1 Study Design and Setting
Data were entered voluntarily by practitioners into the prospectively designed web-based Fight Retinal Blindness! (FRB!) registry of real-world outcomes.(13) The FRB! registry records outcomes of various retinal diseases including nAMD, diabetic macular edema, and retinal vein occlusion, and is compliant with the International Consortium for Healthcare Outcome Measurement’s (ICHOM) minimum standard set of treatment outcomes for macular degeneration.(14) This study included patients attending practices in Australia, New Zealand, and Switzerland. Ethics approval was obtained from the Royal Australian and New Zealand College of Ophthalmologists, the University of Sydney, and the Cantonal Ethics Committee Zurich, Switzerland.

2.2 Data Sources and Measurements
Data were collected from each clinical visit and included the number of letters read on a logarithm of the minimum angle of resolution (LogMAR) visual acuity (VA) chart (best of corrected, uncorrected or pinhole), treatment administered (if any), activity of the choroidal neovascular (CNV) lesion (inactive, active [any combination of intraretinal, subretinal, or haemorrhage excluding subretinal fluid only], or active [subretinal fluid only]), and ocular adverse events. Macular atrophy (MA) (15) (14) and subretinal fibrosis (SRFi) (16) were graded in visits entered after April 2016 as either subfoveal, extrafoveal, or not present. Treatment decisions including drug choice and extension of treatment intervals were based on the judgement of the treating clinician in consultation with the patient, reflecting routine clinical practice.

2.3 Study Population and Definitions
Treatment-naïve eyes starting anti-VEGF treatment for neovascular age-related degeneration receiving at least 8 injections over a 2-year period (to ensure patients were not significantly under-treated) were considered for this analysis. We also calculated the proportion of visits in which an injection was received for each year of treatment initiation and country and included only time periods during which the
median proportion of injection visits for that country was greater than 80%, which suggests a treat-and-extend regimen. (7) These periods were 2008 onwards for Australia, 2015 onwards for New Zealand, and 2014 onwards for Switzerland. Eyes were defined to have reached the ≥14 week treatment interval if they received at least 2 injections at treatment intervals ≥14 week but not exceeding 26 weeks. Furthermore, the extension prior to reaching the ≥14 week interval was required to be less than 4 weeks to ensure that the extension was intentional. Analysis of time to first instance of shortening the treatment interval below 14 weeks interval and transition between treatment interval groups over time was analysed using all eyes that reached the ≥14 week treatment interval. Visual outcomes after reaching the ≥14 week treatment interval were reported in the subgroup of eyes that had at least 12 months of follow-up after reaching the interval. We also investigated outcomes by whether it took <3 years to reach the 14 weeks interval vs. ≥3 years. MA and SRFi were only reported for patients which these data were available, from 2016 onwards.

2.4 Outcome Measures
The primary outcome measure was the change in visual acuity (VA) from the time of first reaching the ≥14 week treatment interval to 12 months later. Secondary outcomes included the proportion of eyes that reached the ≥14 week treatment interval, the proportion of eyes that had their interval subsequently reduced, the proportion of eyes whose lesion was inactive upon reaching the ≥14 week interval and subsequently re-activated, the proportion of eyes with MA and SRFi and the transition between treatment intervals (<8 weeks, 8-13 weeks, 14-17 weeks, 18-26 weeks and >26 weeks) after reaching the ≥14 week interval. We also compared the differences in outcomes with eyes between those that reached the ≥14 week interval within 3 years of commencing treatment compared with those that took longer to reach the ≥14 week interval.

2.5 Statistical Analysis
Data were described using the mean, standard deviation (SD), median, 25th and 75th percentiles (Q1, Q3) and percentages as appropriate. Within-group change in
VA at 12 months after reaching the $\geq 14$ week treatment interval was analysed using the paired t-test. The proportion of eyes reaching, and subsequently leaving, the $\geq 14$ week treatment interval was reported using Kaplan-Meier survival curves. The proportion of eyes whose lesion re-activated after reaching the $\geq 14$ week interval was also analysed using Kaplan-Meier survival curves. The transition of eyes between treatment intervals over time was analysed using multi-state Markov models with an additional ‘absorbing state’ which includes formal discontinuation of follow-up as recorded by the treating physician (includes non-treatment related causes such as patient death) or if it had been at least 6 months since their last recorded visit. Cox-proportional hazards models were used to assess factors associated with reaching the $\geq 14$ week treatment interval and included age and VA at baseline, defined as the time of the first injection, angiographic lesion type, time until first grading of lesion inactivity and anti-VEGF agent used (the injection used at the first visit of the $\geq 14$ week interval with the last injection used if they did not reach the interval), with adjustments for nesting with practitioner and patient for bilateral cases (random-effects).

A p-value of 0.05 was considered statistically significant. Analyses were conducted in R version 4.0.0 using the survival package (V 3.1-12) for Kaplan-Meier analysis, the coxme package (V 2.2-16) for Cox-proportional hazards models, and the msm package (V 1.6.8) for multi-state Markov models. (17-20)

### 3. RESULTS

#### 3.1 Study Population

We identified 5830 treatment-naive eyes that started treatment during the identified periods of likely treat-and-extend in each country, of which 3907 received at least 8 injections over the first 2 years. Of these, 402 (10%) eyes received at least 2 consecutive injections at an interval of $\geq 14$ week at any time during their follow-up. These eyes had received a median (Q1, Q3) of 14 (9, 20) injections over a median of 856 (541.5, 1315.8) days before reaching the $\geq 14$ week treatment interval and were then followed for a median of 518 (240.25, 1097.5) days. Baseline demographic and clinical characteristics of these eyes are summarised in Table 1.
Table 1: Characteristics of all eyes that reached the ≥14 week treatment interval and eyes that had an additional 12 months of follow-up afterwards, at baseline and upon reaching the ≥14 week interval.

<table>
<thead>
<tr>
<th></th>
<th>All ≥14 week eyes</th>
<th>12-month completers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eyes</td>
<td>402</td>
<td>270</td>
</tr>
<tr>
<td>Patients</td>
<td>382</td>
<td>260</td>
</tr>
<tr>
<td>Gender, % female</td>
<td>69.6%</td>
<td>70%</td>
</tr>
<tr>
<td>Age at baseline, mean (SD)</td>
<td>80.3 (8)</td>
<td>79.9 (7.5)</td>
</tr>
<tr>
<td>VA at baseline, mean (SD)</td>
<td>60.3 (17.1)</td>
<td>60.4 (16.8)</td>
</tr>
<tr>
<td>VA at reaching interval, mean (SD)</td>
<td>64.7 (19.3)</td>
<td>66.4 (17.9)</td>
</tr>
<tr>
<td>VA change from baseline, mean (95% CI)</td>
<td>4.5 (2.8, 6.1)</td>
<td>5.9 (4, 7.9)</td>
</tr>
<tr>
<td>VA ≤35 letters, baseline % / interval %</td>
<td>9% / 10%</td>
<td>9.6% / 7.4%</td>
</tr>
<tr>
<td>VA ≥70 letters, baseline % / interval %</td>
<td>35.3% / 54%</td>
<td>35.6% / 57.4%</td>
</tr>
<tr>
<td>Macular atrophy, baseline % / interval %</td>
<td>28.9% / 53.5%</td>
<td>32.8% / 51.7%</td>
</tr>
<tr>
<td>Subretinal fibrosis, baseline % / interval %</td>
<td>14% / 21.1%</td>
<td>15.5% / 20.7%</td>
</tr>
<tr>
<td>Activity Status Interval, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active</td>
<td>60 (14.9%)</td>
<td>38 (14.1%)</td>
</tr>
<tr>
<td>Inactive</td>
<td>311 (77.4%)</td>
<td>206 (76.3%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>31 (7.7%)</td>
<td>26 (9.6%)</td>
</tr>
<tr>
<td>Time until interval, median days (Q1, Q3)</td>
<td>856 (541.5, 1315.8)</td>
<td>889 (525, 1334)</td>
</tr>
<tr>
<td>Injections until interval, median (Q1, Q3)</td>
<td>14 (9, 20)</td>
<td>14 (9, 21)</td>
</tr>
</tbody>
</table>

Data available for 114 and 58 eyes for all ≥14 week eyes and 12-month completers, respectively.

3.2 Visual Outcomes
Of the 402 eyes that were extended to a treatment interval of ≥14 weeks 270 eyes completed at least 12 months follow up (67%). Visual acuity of these eyes had improved from a mean (SD) of 60.4 (16.8) letters at baseline to 66.4 (17.9) letters upon reaching the ≥14 week treatment interval and then dropped to 63.2 (20.3) letters by 12 months, a reduction in VA from the time of entering the ≥14 week treatment interval (-3.2 [95% CI: -4.4, -2.0] letters; P < 0.001). Half (52%) had a VA change between -4 and 4 letters, while 18% lost 5-9 letters, 17% lost ≥10
letters, 10% gained 5-9 letters, and 3% gained ≥10 letters of vision 12 months after reaching the ≥14 week interval. Visual outcomes at all time points for eyes that took <3 years to reach the ≥14 week treatment interval were quite similar to those that took ≥3 years (Table 2).

**Table 2: Overall outcomes of eyes 12 months after reaching the ≥14 week treatment interval, and partitioned by whether it took <3 years or ≥3 years to reach the ≥14 week treatment interval.**

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>&lt;3 Years</th>
<th>≥3 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eyes</td>
<td>270</td>
<td>114</td>
<td>156</td>
</tr>
<tr>
<td>VA at baseline, mean (SD)</td>
<td>60.4 (16.8)</td>
<td>60.9 (18.8)</td>
<td>60 (15.3)</td>
</tr>
<tr>
<td>VA at interval, mean (SD)</td>
<td>66.4 (17.9)</td>
<td>66.2 (20.1)</td>
<td>66.5 (16.2)</td>
</tr>
<tr>
<td>VA 12 months after interval, mean (SD)</td>
<td>63.2 (20.3)</td>
<td>63.7 (22)</td>
<td>62.8 (19)</td>
</tr>
<tr>
<td>VA change from interval, mean (95% CI)</td>
<td>-3.2 (-4.4, -2.5 (-4.1, -3.7 (-5.4, -1.9)</td>
<td>1.9</td>
<td></td>
</tr>
<tr>
<td>Loss ≥10 letters, n (%)</td>
<td>44 (16.3%)</td>
<td>19 (16.7%)</td>
<td>25 (16%)</td>
</tr>
<tr>
<td>Loss 5-9 letters, n (%)</td>
<td>52 (19.3%)</td>
<td>22 (19.3%)</td>
<td>30 (19.2%)</td>
</tr>
<tr>
<td>-4 to 4 letter change, n (%)</td>
<td>139 (51.5%)</td>
<td>60 (52.6%)</td>
<td>79 (50.6%)</td>
</tr>
<tr>
<td>Gain 5-9 letters, n (%)</td>
<td>26 (9.6%)</td>
<td>8 (7%)</td>
<td>18 (11.5%)</td>
</tr>
<tr>
<td>Gain ≥10 letters, n (%)</td>
<td>9 (3.3%)</td>
<td>5 (4.4%)</td>
<td>4 (2.6%)</td>
</tr>
<tr>
<td>Macular atrophy, interval % / final %</td>
<td>53.8% / 54.4%</td>
<td>42.9% / 49.2%</td>
<td>59.6% / 57.1%</td>
</tr>
<tr>
<td>Subretinal fibrosis, interval % / final %</td>
<td>28% / 29.4%</td>
<td>22.4% / 23%</td>
<td>32.8%</td>
</tr>
<tr>
<td>Injections, median (Q1, Q3)</td>
<td>4 (4, 5)</td>
<td>4 (4, 5)</td>
<td>4 (4, 5)</td>
</tr>
<tr>
<td>Time until inactivity, median days (Q1, Q3)</td>
<td>74 (35, 174)</td>
<td>63 (28, 142)</td>
<td>90 (56, 217)</td>
</tr>
<tr>
<td>Remained at ≥14 week interval, % (95% CI)</td>
<td>46.8% (40.9, 52.1)</td>
<td>48.3% (38.9, 56.2)</td>
<td>45.7 (37.8, 52.5)</td>
</tr>
<tr>
<td>Reactivation rate, % (95% CI)</td>
<td>24.7 (19.0, 30.0)</td>
<td>26.0% (16.8, 34.1)</td>
<td>23.7% (16.4, 30.4)</td>
</tr>
</tbody>
</table>

* Data available for 143, 49 and 94 eyes for the overall, <3 years, and ≥3 Years groups, respectively

b Estimate from Kaplan-Meier survival analysis

c Only eyes that were inactive at the ≥14 week interval for this analysis (206/270 eyes)

3.3 Proportion of Eyes Reaching and Leaving the ≥14 Week Interval
Kaplan-Meier survival curves of the percentage of eyes reaching and leaving the ≥14 week treatment interval are shown in Figure 1 (A, B and C). The estimated percentage (95% CI) of eyes reaching the ≥14 week treatment interval was 5.1% (4.4, 5.9) and 9.1% (8.0, 10.2) after 2 and 3 years of treatment, respectively. Almost half (47% [95% CI: 41, 52]) of the 402 eyes that reached the ≥14 week treatment interval were estimated to have their interval shortened to less than 14 weeks at least once during the year after reaching the ≥14 week treatment interval. The percentage of eyes reaching a treatment interval of ≥14 week was independent of which anti-VEGF they received (bevacizumab, ranibizumab or aflibercept) (Figure 1B).

3.4 Lesion Activity
Approximately three quarters of eyes (77.4%) were inactive when they were extended to ≥14 weeks. Of these eyes, almost a quarter (24.7% [95% CI: 19.0, 30.0]) had their lesion re-activate within the first 12 months (Figure 1D). The percentage of eyes on each Anti-VEGF agent upon reaching the ≥14 week interval was similar for all inactive eyes (81% [21/26] bevacizumab, 76% [120/157] aflibercept, and 78% [170/219] ranibizumab).

Figure 1: Kaplan-Meier survival curve showing A) the overall percentage of eyes reaching the ≥14 week treatment interval over time, B) the percentage of eyes reaching the ≥14 week interval by drug type (only data from 2013 onwards), C) the percentage of eyes that subsequently had their interval reduced below 14 weeks at least once, and D) the percentage of eyes whose lesion re-activated after reaching the ≥14 week interval. The number of eyes remaining at risk each year is shown at the top. The 95% confidence interval for plots A, C and D is shaded grey. BEV = bevacizumab; AFL = aflibercept; RAN = ranibizumab.
3.5 Transition Between Intervals Over Time

We studied the treatment intervals of the 270 eyes that completed 12 months of follow-up after they had been first extended to ≥14 weeks (Figure 2). The proportion of eyes on 14-17 week treatment intervals dropped to 40%, while the proportion on 18-26 week intervals remained relatively stable at 6.4% after 1 year. The proportion of eyes that dropped to <8 week and 8-13 week intervals increased through 6 months, whereupon it remained fairly stable through to 12 months (8% of eyes treated at <8 week and 21% at 8-13 week intervals at 12 months). Less than 1% were ever on an interval >26 weeks at any time.
**Figure 2:** Observed proportion of eyes within each treatment interval group after reaching the ≥14 week interval, as estimated from multi-state Markov models. n: number of eyes in each treatment interval.

### 3.6 Macular Atrophy and Subretinal Fibrosis

Macular atrophy and SRFi data have been recorded in the FRB! database since 2016, these were available for 114/402 (28%) of eyes that reached ≥14 week treatment interval from their baseline visit. The proportion of these 114 eyes with MA and SRFi increased from 30% and 15% respectively at baseline to 53% and 22% at the time of reaching the ≥14 week treatment interval. The proportion of eyes with MA and
SRFi remained stable after 12 months in the subgroup of 143 eyes that were followed for an additional 12 months after reaching the ≥14 week treatment interval (Table 2).

4. DISCUSSION

Ten percent of the 3907 eyes from the FRB! nAMD database reached a treatment interval of ≥14 weeks after a mean of 2.3 years and 14 injections. With contemporary treat-and-extend AAO guidelines that cap interval extension at 12 weeks, this is not a true representation of eyes that could be extended to an interval of ≥14 weeks, rather it indicates the outcomes of those that were. Half of these eyes were not maintained at this interval for the subsequent 12 months and only 7% of eyes that reached an interval of ≥14 weeks were extended further to treatment intervals beyond 18 weeks. Kaplan-Meier survival analysis estimated that 9.1% of eyes would reach the ≥14 week treatment interval after 3 years of treatment under the current circumstances in which not all practitioners may attempt to extend treatment intervals beyond 3 monthly. No difference between anti-VEGF treatment drug was found in the proportion of eyes that reached a treatment interval of ≥14 week. These findings suggest that only a few eyes can safely be treated with the currently available VEGF inhibitors at injection intervals ≥14 weeks.

The eyes that did reach a treatment interval of ≥14 week gained 6.0 letters after an average of 2.3 years of treatment, this was similar whether it took less than 3 years or more than 3 years to reach the interval. A meta-analysis of real-world outcomes of intravitreal ranibizumab for nAMD found similar improvements in vision for 5,358 eyes across all treat-and-extend treatment intervals (+8.8 at 1 year; +6.7 at 2 years; +5.4 letters at ≥3 years of treatment) (21). Prior FRB! analyses of 2-year outcomes of treat-and-extend have also reported similar outcomes (+5.3 letters for ranibizumab and +6 letters for aflibercept). (7) (12) The comparable gain in VA of eyes that eventually reached a treatment interval of ≥14 weeks suggests that these eyes at time of extension to this interval did not have poorer visual prognosis. Vision typically declines gradually during the maintenance phase of nAMD treatment, losing less than 1 letter per year on average (8). On average, the small proportion of
the eyes that had their treatment interval extend beyond ≥14 week for at least 12 months had stable vision (-3.2 letters). Only a third of the eyes at this extended interval lost ≥5 letters, presumably some of them due to lesion re-activation, as a quarter of the lesions did.

We determined the proportion of eyes with SRFi and MA to assess whether the eyes that were extended ≥14 weeks had a poorer anatomical prognosis at treatment initiation with data that were available from 2016. The proportion of eyes with fibrosis when they first started treatment that reached the ≥14 week interval was 14% and reached 22% after 2.3 years of treatment, similar to a previous analysis of the FRB! database that included all injection intervals where the prevalence of SRFi at was 14% at treatment initiation and estimated at 26% 24 months post treatment (16). In contrast to SRFi, more eyes that were extended to ≥14 weeks intervals had MA when they started treatment than in previous clinical trial and observational cohorts. Thirty percent of eyes that were extended to ≥14week interval at some point had MA when they started treatment, increasing to 53% by the time they reached the ≥14weeks interval; in contrast, RIVAL, CATT and FRB! had only 6%, 7% and 10% respectively of eyes with MA when treatment started which increased to 35%, 21% and 20% by 2 years. (22) (23) (15). Eyes in this extended treatment interval were at least 3 times more likely to have MA when they started treatment, which is strongly associated with subsequent loss of vision (24). Perhaps some eyes were treated less frequently because the practitioner felt that too many treatments might exacerbate the atrophy, as suggested by the CATT study (23). Perhaps some eyes with MA were simply treated less frequently because they had poor vision, however the relatively good mean VA when eyes reached the ≥14week interval suggests this was not common. Whether eyes with MA simply require fewer injections to control the coexistent neovascularization warrants further investigation.

We acknowledge several limitations of this study, many of which are inherent to observational studies. We have no direct knowledge of the way clinicians reached management decisions, why some patients are extended beyond the 12-week interval and whether some clinicians believe it is not safe to do so. The grading of lesion activity, MA and SRFi was done by the practitioner, who was usually a retinal specialist, without reference to a central reading centre. We assumed that clinicians
made management decisions based on a treat-and-extend paradigm, however our data demonstrated interval extension in eyes with active lesions. This highlights the difficulties of real-life practice with other factors such as financial and time burdens influencing clinical practice. The FRB! database has been recording SRFi and MA since 2016, so only 114/402 (28%) eyes in the present analysis had these data at the baseline visit and were subsequently included in the sub-analysis. We believe that this number can give an indication of the characteristics of eyes treated at the extended interval, however more data are required to confirm these findings.

To conclude, we found that only 10% of eyes treated with VEGF inhibitors for nAMD reached an injection interval of ≥14 week at some point in their treatment journey. At least half of these returned to a shorter interval within 12 months however, those that remained at the extended interval for 12 months, maintained vision. It appears only a small proportion of eyes with nAMD are treated at intervals of 14 weeks or more using the currently available VEGF inhibitors in the current clinical setting. Phase III clinical trials are currently investigating newer VEGF inhibitors at intervals greater than 14 weeks including faricimab and brolucizumab (25) (26) (27). More trial and clinical data on the outcomes of eyes at treatment intervals beyond 12 weeks is required for both the current and the emerging VEGF inhibitors to help ease the nAMD treatment burden.
REFERENCES


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