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

Data from an Observational Study

Mark C. Gillies, MBBS, PhD, Anna Campain, PhD, Daniel Barthelmes, MD, PhD, Judy M. Simpson, PhD, CStat, Jennifer J. Arnold, MB, BS (Hons), Robyn H. Guymer, MBBS, PhD, Ian L. McAllister, MB, BS, Rohan W. Essex, MB, BS, Nigel Morlet, MB, BS, Alex P. Hunyor, MB, BS, on behalf of the Fight Retinal Blindness Study Group*

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 ≥70 (20/40) letters, and 18% had VA ≤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 ≥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.

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. 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.

Because current trends in clinical practice to individualize treatment protocols, such as the pro re nata (PRN) and treat-and-extend protocols, 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. In the largest series with long-term outcomes, the
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, New Zealand, and Switzerland approved the use of the FRB system for the research purposes described. 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.
In total, 131 eyes continued follow-up for 7 years. The mean final VA among patients followed for 7 years was 58.4 letters, which was 2.6 letters lower than their mean baseline VA, but 3.3 letters better than the mean baseline VA for all patients in the study sample. Although the proportion of eyes with baseline vision of \( \geq 70 \) letters (20/40) remained constant over time at approximately 30% to 35%, the baseline proportion of the group measured at each time point with 20/40 vision increased progressively from 23% at baseline for the whole group to 32% of the group followed for 7 years. Likewise, although the proportion that had VA of \( \leq 35 \) letters (20/200) stayed the same through 7 years, the baseline proportion of eyes with <20/200 vision decreased with the duration of follow-up. Approximately 28% of eyes had lost 15 letters by 7 years, but there were still 16% that had gained 15 letters at 7 years. Of the 42 eyes (32%) that had baseline VA \( \geq 20/40 \), 25 (60%) retained this level of vision after 7 years.

Outcomes of Eyes Followed for 5 Years Stratified by Baseline Visual Acuity

To study the relationship of baseline VA with VA gain, we looked at the outcomes after stratifying by baseline VA. The 549 eyes with data for at least 5 years were stratified into 3 groups relating to baseline VA: (a) “good baseline vision,” \( \geq 70 \) letters (20/40) (166 eyes); (b) “intermediate baseline vision,” between 36 (20/200) and 69 letters (333 eyes); and (c) “poor baseline vision,” \( \leq 35 \) letters (50 eyes). The mean VA of eyes with good baseline vision was initially 75.2 (SD, 4.7). It remained stable for 3 years but had decreased by 4.5 letters by 5 years (Fig 3). The mean values for the first and final VA of eyes with intermediate baseline VA was similar to that of the entire cohort (Fig 3), increasing from 56.6 (SD, 8.7) initially to 58.6 (SD, 19.3) at 5 years, an increase of 2 letters. Eyes with poor baseline vision had a mean initial VA of 22.6 letters (20/400), which had increased by 12.6 letters (20/200) at 5 years; all of this improvement occurred in the first year of treatment.

Causes of Loss of Vision in Eyes That Received Long-Term Treatment

Loss of \( \geq 10 \) letters occurred in 42 of 131 (32%) of the eyes that continued treatment for \( \geq 6.5 \) years. Optical coherence tomography images were examined from 4 of the largest contributing practitioners or centers, representing 81% of the total number of eyes that were treated for this long. Table 3 shows the causes of loss of VA in these eyes. Geographic atrophy at the center of the fovea was the most common cause but accounted for only 37% of the total. Subretinal fibrosis, at least 2 cases of which were caused by large submacular hemorrhages, occurred in 31%. Unoperated cataract was the cause in 6%.

Outcomes of Eyes That Did Not Complete 5 Years Follow-up

A total of 663 eyes from 631 patients were lost to follow-up before 5 years. Follow-up intervals include eyes that ceased treatment between 0 and 6 months (\( n = 48 \), not plotted), 7 and 12 months (\( n = 50 \)), 13 and 24 months (\( n = 100 \)), 25 and 36 months (\( n = 144 \)), 37 and 48 months (\( n = 172 \)), 49 and 60 months (\( n = 149 \)), and \( \geq 60 \) months of follow-up (\( n = 549 \)). The duration of time eyes continued to receive treatments seemed to be related to their response to treatment (Fig 4). The mean VA for all groups increased initially but decreased markedly to the level of baseline VA around the time the treatment was discontinued in each group.

Injections and Visits

Over the first year, the median number of injections administered was 6 per eye (mean, 6.1; SD, 2.9), with the largest group (47%) receiving injections every 4 to 5 weeks. The median (and mean) number of injections in the second to fifth years were 5 (4.9; SD,
3.1), 5 (4.9; SD, 3.5), 6 (5.4; SD, 3.3), and 5 (4.9; SD, 3.3), respectively. The number of injections in the sixth and seventh years remained similar at 5.5 (5.1; SD, 3.5) and 5 (4.7; SD, 3.4), respectively. After the first year of treatment, the proportion of eyes receiving treatments at 4 to 5 weeks, 6 to 7 weeks, 8 to 9 weeks, and ≥10 weeks were approximately equal and remained similar through the seventh year (not shown).

The median number of visits was 9 in the first year (mean, 8.7; SD, 3.3). This declined after the first year to a median of 7 for the second and third years. The median number of visits (and mean) for the fourth to seventh years was 8 (7.9; SD, 3.7), 7 (7.4; SD, 3.6), 9 (8.3; SD, 3.5), and 8 (7.8; SD, 3.3), respectively.

Adverse Events

A small list of significant adverse events was tracked by the FRB system. The frequency of these events was observed for all 1212 eyes over the 7 years of the study, involving a total of 24 547 injections (Table 4). The rate of endophthalmitis (both infectious and noninfectious) was 13 per 24 547 injections (0.05%).

Table 2. Summary of Visual Acuity for all 1212 Eyes at Baseline and the Subsets of Eyes Followed for 3, 5, and 7 Years

<table>
<thead>
<tr>
<th></th>
<th>All Eyes (n = 1212)</th>
<th>3 Yrs (n = 868)</th>
<th>5 Yrs (n = 549)</th>
<th>7 Yrs (n = 131)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean baseline VA (SD)</td>
<td>55.1 (18.8)</td>
<td>58.2 (17.1)</td>
<td>60.1 (16.7)</td>
<td>61.0 (15.0)</td>
</tr>
<tr>
<td>Final VA letters (SD)</td>
<td>—</td>
<td>60.4 (21.0)</td>
<td>59.4 (20.4)</td>
<td>58.3 (21.7)</td>
</tr>
<tr>
<td>Change in VA</td>
<td>—</td>
<td>2.2</td>
<td>0.7</td>
<td>—2.7</td>
</tr>
<tr>
<td>Change in VA at 6 months</td>
<td>6.3</td>
<td>5.9</td>
<td>5.3</td>
<td>5.5</td>
</tr>
<tr>
<td>VA ≥70 letters (baseline/final)</td>
<td>23%/32%</td>
<td>27%/37%</td>
<td>30%/43%</td>
<td>32%/40%</td>
</tr>
<tr>
<td>VA ≤35 letters (baseline/final)</td>
<td>17%/21%</td>
<td>12%/18%</td>
<td>9%/12%</td>
<td>7%/18%</td>
</tr>
</tbody>
</table>

Discussion

This study represents the largest series of long-term outcomes of patients receiving VEGF inhibitors for neovascular AMD to date. We found somewhat better VA outcomes than previous reports of longer-term outcomes. The mean VA of the 549 eyes (45%) that persisted with treatment for ≥5 years remained above the baseline level for 5 years and had only decreased 2.6 letters below the baseline level of the limited subset of 131 eyes (11%) that were followed for 7 years. Somewhat more injections were given in our study compared with other reports of outcomes using variable protocols,9,11 with a median of 6 injections given in the first year, decreasing to 5 thereafter through 7 years. The eyes that received treatment for the longest period tended to have better baseline VA. Adverse events were infrequent and consistent with previous reports.

Analysis of data from observational studies must take into account participants who discontinue treatment for...
whatever reason. Less than 10% of eyes in this study dropped out in the first 2 years, increasing to 46% from the third to the fifth years after commencing treatment. The mean VA of eyes that were lost to follow-up tended to have decreased below the mean baseline level at the time that treatment was stopped, indicating that one of the reasons for discontinuing may have been perceived lack of efficacy by the patient, the practitioner, or both. However, an analysis of reasons for discontinuing treatment from one of the larger centers contributing to the FRB audit found that the practitioner believing that “further treatment was futile” was cited in only approximately 20% of patients who stopped treatment.14 Other reasons included the practitioner believing that further treatment was unnecessary (~10%), the patients declining further treatment (~20%) for reasons including discomfort and difficulty attending, referral to another practice (~20%), more severe intercurrent illness (10%), and death (10%).

Visual acuity data from observational studies such as this can be reported in many ways. From the perspective of a patient starting treatment, the analysis of the entire cohort’s outcome may be the most informative. Of all 1212 eyes studied, mean VA was essentially unchanged after a mean follow-up of 53.5 months. This is generally reassuring because the natural history of neovascular AMD is progressive visual loss, with untreated controls in the Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD study losing approximately 3 lines of vision over 2 years. Another outcome measure is the VA of the highly selected subset of patients who, in the present study, continued being followed for 7 years. We found that 40% of eyes had VA ≥20/40 after 7 years, up from 32% at baseline. It is important to compare the outcomes with the baseline values of only this subset rather than the entire group because we found that the mean initial pretreatment VA was better in those who were treated longer. Eyes with better baseline VA tend to have better longer-term outcomes,15 so patients are more likely to persist with treatment.

Presenting VA may vary from one service to the next, so a more detailed examination that stratified the presenting acuity, as in this study, may allow easier and more valid comparison between studies. Eyes with worse VA to begin with have higher initial gains, but eyes with better VA maintain better levels of vision despite much lower net gain in mean VA. When we stratified outcomes by baseline VA, we found these expected ceiling and floor effects: Eyes with the poorest initial VA cannot get much worse, and eyes starting with the best VA cannot get any better. Figure 3 shows the relationship between change in VA and baseline VA was not simply a manifestation of regression to the mean;16 although eyes with initial VA ≤35 letters improved toward the mean over the first 12 months, eyes starting with VA ≥70 letters do not change, on average, for the first 3 years.

These long-term results of VEGF inhibition for neovascular AMD are notably better than in other reports. In the SEVEN UP study (65 eyes followed for a mean of 7.3 years), after 7 years, 23% of eyes achieved a VA of ≥20/40 and 37% of eyes had VA of ≤20/200. By contrast, the present study reports 40% of 131 eyes achieved VA ≥20/40, and only 18% ended with VA ≤20/200. There was an overall mean decline of 8.6 letters in the SEVEN UP study compared with a mean loss of 2.6 letters in the present study after 7 years.

Table 3. Causes of Loss of ≥10 Letters after 6.5 Years Compared with Baseline from the 4 Largest Contributors to the Database

<table>
<thead>
<tr>
<th>Cause of Loss of Vision</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Geographic atrophy</td>
<td>13 (37)</td>
</tr>
<tr>
<td>Subretinal fibrosis</td>
<td>11 (31)</td>
</tr>
<tr>
<td>Structural damage (loss of ellipsoid)</td>
<td>4 (11)</td>
</tr>
<tr>
<td>Infectious endophthalmitis</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Unoperated cataract</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Active lesion</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Retinal pigment epithelial rip</td>
<td>1 (3)</td>
</tr>
</tbody>
</table>
Figure 4. Loess regression curves showing change in visual acuity (VA) over time for eyes that began treatment at least 5 years before analysis but were lost to follow-up before 5 years, grouped by follow-up time: 50 eyes (49 patients) lost between 6 and 12 months (A), 100 eyes (99 patients) lost between 12 and 24 months (B), 144 eyes (134 patients) lost between 25 and 36 months (C), 172 eyes (160 patients) lost between 37 and 48 months (D), 149 eyes (141 patients) lost between 49 and 60 months (E), and 549 eyes (473 patients) continued treatment beyond 60 months (F). The shaded region indicates area of progressive decrease in the number of eyes, resulting in increased volatility of Loess predictions.
One major difference between the SEVEN UP study and the present one was dosing. The SEVEN UP study’s participants received a mean of 6.8 anti-VEGF injections during the mean 3.4-year interval between exit from the Open-Label Extension Trial of Ranibizumab for Choroidal Neovascularization Secondary to Age-Related Macular Degeneration (HORIZON) extension study and the end of the study (i.e., ~2 per year). A subgroup of patients from the SEVEN UP study who received ≥11 anti-VEGF injections in the 3.4 years after leaving HORIZON had a significantly better mean gain in letter score. Participants in the present study received a mean of approximately 5 injections per year from the second year onward, at least twice as many as the participants in HORIZON.

Subretinal fibrosis (31%) and structural damage (11%) affecting the ellipsoid region were together as common as geographic atrophy (37%) in eyes that lost ≥10 letters after 6.5 or more years of treatment. By contrast, the SEVEN UP study reported that 90% of eyes that had received 7 years of treatment had atrophy involving the foveal center. The risk of atrophy affecting the central lesion that we report is certainly an underestimate because it is likely that many patients who developed central macular atrophy before 6.5 years of treatment would have discontinued treatment, particularly because there are no clear guidelines for treatment in this situation. Nevertheless, the SEVEN UP study report that 90% of their patients had atrophy of the center of the fovea seems inconsistent with the fact that 25% of their patients had VA ≥6/12.

An observational study from the United Kingdom reported mean VA had decreased 2 letters after 3 years of treatment. The mean change from 58 letters at baseline was +3 letters at the peak gain time point, +2 letters at 52 weeks, +1 letters at week 104, and 0 letters at week 120. By contrast, in the present study, eyes that continued for 5 years had a mean VA of 60 letters at baseline and still the same VA 5 years after starting treatment, after which the mean VA began to gradually slip below the baseline level (~6 years) (Fig 2). The peak gain in mean VA of this group was 5.3 letters achieved 6 months after starting treatment. In the UK study, vision of ≥20/40 was achieved by 16% at baseline, increasing to 29% after 3 years. In the present study, the proportion of the entire group with vision at 20/40 at baseline was 23%, increasing to 37% after 3 years, although the proportion of the group of eyes that was followed for 3 years with vision of 20/40 at baseline was also greater at 27% than that of the entire population.

In the UK study, the median number of injections per year was lower and the number of visits was higher than in the present study. The median number of treatments for eyes followed up for at least 3 years in the UK study was 5, 4, and 4 in the first, second, and third years of follow-up, respectively, compared with 6, 5, and 5, respectively, in the present study. The median number of outpatient visits in the UK study was 9, 8, and 8, respectively, compared with 9, 7, and 7, respectively, in the present study. More treatments with fewer visits, as is the case in the present study compared with the UK study, are consistent with a treat-and-extend approach, which is more predominant in Australia, whereas the reverse is more consistent with a PRN regimen, which is said to be “almost universal” in the United Kingdom.

There are several potential reasons why our results may have been better than in the SEVEN UP and the UK studies. Although it is possible that a treat-and-extend approach, such as seems to have been favored by the investigators in this study, is superior to a PRN approach that was used by the UK study, we believe it is more likely due to the increased number of injections given in the present study compared with the other 2. The other possibility is the level of vision when patients entered the study. As we showed in the current study, patients with better vision tend to have lower gains but better final outcomes. Although mean VA at baseline was the same for the UK study and the present study (55 letters), the proportion with ≥20/40 was just 16% in the UK study compared with 23% in the present study.

One group is treated outside clinical trial protocols, differences in the health care systems of the respective countries in which studies have been conducted may explain at least some of the differences in injection frequency and numbers. In environments where there is no incentive, or a disincentive, to perform more frequent injections, this may be reflected in a lower number of treatments. The majority (83%) of treatments in this study were performed in Australia. In comparison with the UK National Health Service (which provides the majority of treatments in the United Kingdom), in Australia the majority of treatments are provided in private practice on a fee-for-service basis. Therefore, ophthalmologists in Australia may have a greater financial incentive to perform more injections, whereas ophthalmologists in the United Kingdom are relatively disincentivized. Reimbursement for the intravitreal injection procedure itself is significantly greater in Australia and Switzerland than in the United States.

We do not know the actual cause of visual loss in eyes on long-term treatment with VEGF inhibitors from the FRB data collected, but the SEVEN UP study found a strong correlation with atrophic AMD. It is possible that the eyes in the SEVEN UP study were more predisposed to develop atrophy as a result of the monthly ranibizumab dosing they received for 2 years during the Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in AMD and Minimally Classic/OcclusiveTrial

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>No.</th>
<th>Risk Rate per Injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemorrhage reducing BCVA by &gt;15 letters</td>
<td>28</td>
<td>0.11%</td>
</tr>
<tr>
<td>Infectious endophthalmitis</td>
<td>10</td>
<td>0.04%</td>
</tr>
<tr>
<td>Noninfectious endophthalmitis</td>
<td>3</td>
<td>0.01%</td>
</tr>
<tr>
<td>Intraocular surgery</td>
<td>82</td>
<td>0.33%</td>
</tr>
<tr>
<td>Retinal detachment</td>
<td>5</td>
<td>0.02%</td>
</tr>
<tr>
<td>RPE tear</td>
<td>9</td>
<td>0.04%</td>
</tr>
</tbody>
</table>

BCVA = best-corrected visual acuity; RPE = retinal pigment epithelium.
of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD studies.17

We performed the primary analyses to provide information on the likely long-term outcome of an eye commencing treatment for neovascular AMD. Thus, we applied no restrictions apart from an eye that was treatment-naïve that had at least 1 intravitreal injection ≥5 years before the analysis. We included all eyes in the primary analysis, including patients who discontinued treatment at any point. We also adjusted for the mean baseline VA of the group at each point studied, which tended to increase the longer eyes were tracked in the system (Fig 2). By including all eyes in the analyses, we were able to observe long-term trends and changes in vision for eyes that were lost to follow-up and eyes that continued with treatment (Fig 4). There seemed to be a propensity for patients to stop treatment when the initial improvement in VA was lost (Fig 4A–E). Long-term trends (Fig 4F) can be used to give expected vision outcomes for eyes undergoing neovascular AMD treatment.

Study Limitations and Strengths

This study has several weaknesses and strengths that should be acknowledged. In contrast to a phase III study, treatment decisions were made by clinicians in routine practice without reference to reading center adjudications and study protocols. Thus, the study has lower internal validity than in a phase III clinical trial, but it is still meaningful because this is how these clinically important decisions are actually being made in the real world. The measurement of logMAR VA, the main outcome, is reasonably objective. Also, case selection and treatment regimens in observational studies may be very different than in clinical trials and among different ophthalmologists. However, data on long-term outcomes of VEGF inhibition for neovascular AMD are urgently required because the few studies that are currently available suggest that they may be poor.

This and other studies emphasize the importance of phase IV studies in establishing the real value of VEGF inhibitors for our patients with neovascular AMD. Care must be taken when analyzing data from these studies. Eyes with worse VA to begin with have higher initial gains, but eyes with better VA end up with better vision despite much lower net gain in mean VA. Also, results from long-term observational studies may be affected by external factors, for example, patient aging. We have shown that patients with a longer follow-up period tend to have better starting visual function. Even by taking this into account, the results of this study are better than have been previously reported. The main difference seems to be that participants in this study had more injections than in previous studies. Although the outcomes we describe are reasonably good, 40% of eyes that had VA ≥20/40 when starting treatment had decreased below this level after 7 years. Further research is warranted to determine whether more eyes with good presenting VA can be induced to retain it. References

Footnotes and Financial Disclosures

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1 The Save Sight Institute, Sydney Medical School, The University of Sydney, Sydney, New South Wales, Australia.
2 Department of Ophthalmology, University Hospital Zurich, University of Zurich, Zurich, Switzerland.
3 School of Public Health, University of Sydney, Sydney, New South Wales, Australia.
4 Marsden Eye Specialists, Parramatta, New South Wales, Australia.
5 Centre for Eye Research Australia, University of Melbourne, Royal Victorian Eye and Ear Hospital, Victoria, Australia.
6 Lions Eye Institute, Centre for Ophthalmology and Vision Science, University of Western Australia, Perth, Australia.
7 Academic Unit of Ophthalmology, Australian National University, Acton, ACT, Australia.
8 University of Western Australia Department of Population Health, Perth, Australia.
9 Retina Associates, Chatswood, New South Wales, Australia.

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Author Contributions:
Research design: Gillies, Barthelmes, Simpson, Arnold, Guymer, McAllister, Essex, Morlet, Hunyor
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Abbreviations and Acronyms:
AMD = age-related macular degeneration; FRB = Fight Retinal Blindness; logMAR = logarithm of the minimum angle of resolution; PRN = pro re nata; SD = standard deviation; VA = visual acuity; VEGF = vascular endothelial growth factor.

Correspondence:
Daniel Barthelmes, MD, PhD, Department of Ophthalmology, University Hospital Zurich, Frauenklinikstrasse 24 8091 Zurich, Switzerland. E-mail: daniel.barthelmes@usz.ch.