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Outcomes of Suspending VEGF Inhibitors for Neovascular Age-Related Macular Degeneration When Lesions Have Been Inactive for 3 Months

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Purpose: Currently, little evidence supports the safety of suspending vascular endothelial growth factor (VEGF) inhibitors for neovascular age-related macular degeneration (nAMD). We assessed the outcomes of eyes in which this seems to have been attempted.

Design: Observational study from a prospectively designed database.

Participants: Eyes enrolled in the Fight Retinal Blindness! registry of nAMD treatment outcomes were considered to have suspended treatment if they had a 3-month or longer documented period of inactivity of the choroidal neovascular lesion with no further treatments unless the lesion re-activated.

Methods: Time and proportion to re-activation of the lesion were analyzed using Kaplan-Meier survival curves. Visual outcomes after treatment suspension were assessed with paired *t* tests.

Main Outcome Measures: The proportion of eyes resuming treatment because of lesion re-activation, change in visual acuity (VA) at time of re-activation, and recovery of vision 12 months later.

Results: We identified 434 eyes in which treatment was suspended and that were tracked for at least 12 months thereafter. The estimated percentage of eyes re-activating in the first year after treatment suspension was 41%, increasing to 79% by the fifth year. The median time to re-activation was 504 days. The 275 eyes whose lesion was observed to re-activate lost a mean of 4.2 letters (95% confidence interval [CI], −5.6 to −2.8 letters; $P < 0.001$) from the last injection to the time of re-activation; 206 eyes resumed treatment for at least 12 months after re-activation and recovered a mean of +1.2 letters (95% CI, −0.4 to 2.7 letters; $P = 0.133$), resulting in a net loss of 3.3 letters (95% CI, 2.3–5.1 letters; $P < 0.001$) compared with VA at treatment suspension. Lower VA at the time of suspension and longer duration of treatment were associated with reduced risk of re-activation. Median time to re-activation was substantially greater when eyes had been treated for at least 3 years.

Conclusions: Fewer than half of the eyes in which treatment was suspended re-activated in the first year, but most re-activated by the fifth year. Caution should be exercised to avoid suspending treatment prematurely. Further research is warranted to identify the eyes in which treatment may be suspended safely. *Ophthalmology Retina 2019;3:623-628 © 2019 by the American Academy of Ophthalmology*

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Variable treatment regimens, including pro re nata and treat and extend (T&E), have evolved for treatment of neovascular age-related macular degeneration (nAMD) with vascular endothelial growth factor (VEGF) inhibitors to reduce the ongoing burden of treatment for patients without compromising outcomes.[1,2] For patients receiving a T&E regimen, generally the re-treatment intervals will be extended if the choroidal neovascularization (CNV) lesion is inactive. No strict guidelines exist for how far treatments may be extended, although it has been reported that intervals exceeding 3 months are associated with a substantial increase in the risk of lesion re-activation.[3]

The treat-extend-stop variant of the T&E protocol suspends treatment for nAMD, possibly indefinitely, when the treatment interval reaches 12 weeks and the lesion remains inactive for 3 consecutive visits.[4] One report of the consequences of suspending treatment in eyes in which the CNV lesion is inactive for at least 3 months indicates a 91% rate of recurrent lesion activity over a mean follow-up of 18 months and warns against discontinuing treatment in eyes that seem to have been treated successfully.[5] Thus, it may be that treatment is required indefinitely to prevent recurrent lesion activity and vision loss, despite concerns regarding the prolonged use of anti-VEGF,

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particularly the risk of geographic atrophy developing.[6] We tested these findings among a larger cohort for whom treatment for nAMD had been suspended after at least 3 months of lesion inactivity and to whom no further treatments were administered unless the lesion re-activated.

Methods

Study Design

This observational study used data from a prospectively designed database.

Setting

Eligible patients were identified from the Fight Retinal Blindness! database, the details of which have been published elsewhere,[7] which tracks real-world outcomes for patients with nAMD and complies with the International Consortium for Healthcare Outcome Measurement's minimum standard set of treatment outcomes for macular degeneration.[8] Ethics approval was obtained from the human research ethics committees of the Royal Victorian Eye and Ear Hospital, the Royal Australian and New Zealand College of Ophthalmologists, the University of Sydney, and the Cantonal Ethics Committee, Zurich, Switzerland. The use of opt-out patient consent was approved by the ethics committees in Australia and New Zealand. Patient data were anonymized before provision to researchers for this analysis. This study conformed to the tenets of the Declaration of Helsinki. Patients and practices from Australia, New Zealand, and Switzerland were included in the analysis.

Data Sources and Measurements

Data were collected at each clinical visit, including the number of letters read on a logarithm of the minimum angle of resolution visual acuity (VA) chart (best of uncorrected, corrected, or pinhole), treatment given, CNV lesion activity (an active grading indicated the presence of intraretinal or subretinal fluid attributable to leak from the CNV lesion or fresh hemorrhage and was based on funduscopy, OCT, fluorescein angiography, or a combination thereof), and ocular adverse events. At the baseline visit only, previous treatments received, angiographic lesion subtype (occult [type 1], predominantly and minimally classic [type 2], or other [type 3 neovascularization, polypoidal choroidal vascularization]), as determined by the practitioner based on retinal angiography and lesion size (greatest linear dimension) were recorded. Because this was a real-world study, treatment decisions (e.g., drug choice and treatment regimen) were at the discretion of the practitioner in consultation with the patient.

Participants

Eyes with nAMD tracked by the Fight Retinal Blindness! registry commencing anti-VEGF therapy from January 1, 2006, regardless of prior treatments, were considered for this analysis. An eye was considered to have suspended treatment if the patient first had received a minimum of 5 injections to allow a reasonable time for extension of treatment intervals, followed by a 3-month or more period of documented lesion inactivity with no further treatments administered, unless the lesion re-activated. Eyes also were required to have at least 12 months of follow-up after treatment suspension. The start of treatment suspension was defined as the visit of the last injection. Eyes that explicitly were discontinued from treatment by a physician with the explanation that "further treatment [is] futile" or that did not resume treatment despite re-activation of the lesion (presumed discontinuation of treatment) were excluded from the analysis. One eye was selected at random from patients with both eyes being treated.

Outcome Measures

Primary outcomes were (1) proportion of eyes with lesion re-activation after suspension of treatment and in which anti-VEGF treatment was resumed, (2) VA change from the last injection at the time of re-activation, and (3) subsequent change in vision 12 months after resuming treatment. Secondary outcomes included the effect of age and VA at the time of treatment suspension and lesion type on risk of re-activation, VA change from baseline to time of last injection, and time and total injections received until treatment suspension.

Statistical Analysis

Descriptive data were summarized using the mean, standard deviation (SD), median, interquartile range (IQR), and percentages where appropriate. The proportion and time to re-activation of the lesion were analyzed using Kaplan-Meier survival analysis. Nested Cox proportional hazard models were used to test the effects of prior treatment, age and VA at the time of treatment suspension, lesion type, and number of years receiving treatment before suspension with a nesting variable for patients within practices. Paired *t* tests were used to assess the change in vision at the following time points: (1) start of suspension from baseline, (2) time of lesion re-activation from start of suspension, and (3) 12 months after resuming treatment. All analyses were conducted in R software version 3.4.4[9] (R Foundation for Statistical Computing, Vienna, Austria) using the survival package (version 2.42-4; Therneau TM) for Kaplan-Meier analysis[10] and the coxme package[11] (version 2.2-10; Therneau TM) for nested Cox proportional hazards models.

Results

Study Population

We identified 470 eyes in which treatment had been suspended for 3 months or more with no further treatments for at least 12 months unless the lesion re-activated. We randomly excluded 36 eyes from patients with 2 ineligible eyes. Nineteen patients had been included in a previous single-center analysis investigating long-term treatment suspension.[5] Of the 434 eligible eyes, 275 eyes re-activated and resumed treatment; 206 of these eyes underwent an additional 12 months of follow-up after resuming treatment.

Eyes received a median of 10 injections (IQR, 7−14 injections) after a median of 687 days (IQR, 443−967 days) before treatment was suspended. The median treatment interval at the time of treatment suspension was 77 days (IQR, 49−98 days); approximately 40% of patients were treated at an interval of 12 weeks or more before suspension. The median follow-up after treatment suspension was 1000 days (IQR, 617−1562 days); 287 eyes had 2 years of follow-up, 186 eyes had 3 years of follow-up, 126 eyes had 4 years of follow-up, and 74 eyes had 5 years of follow-up. During the treatment suspension, eyes were being monitored approximately every 2 months (median interval, 64 days [IQR, 43−108 days] between visits). Demographic characteristics of these patients are summarized in Table 1.

Table 1. Demographic Characteristics of the Study Population

Characteristic	Data
No. of patients	434
Female gender, no. (%)	283 (65.2)
Baseline age (yrs), mean (SD)	78.2 (8.2)
Baseline VA (letters), mean (SD)	56.3 (17.9)
≥70, no. (%)	114 (26.3)
≤35, no. (%)	54 (12.4)
Baseline lesion size (μm), median (IQR)	2350 (1500–3300)
Angiographic lesion type (%)	
1	52.8
2	22.7
Other	11.5
Not recorded	8.5

IQR = interquartile range; SD = standard deviation; VA = visual acuity.

Time and Proportion of Lesion Re-activation

Kaplan-Meier survival curves of time and proportion of lesion re-activation are presented in Figure 1. The estimated percentage of eyes whose lesions re-activated in the first year of treatment suspension was 41% (95% confidence interval [CI], 37%–46%); by the fifth year, the estimated percentage of re-activation was 79% (95% CI, 72%–84%). The median time to re-activation was 504 days (95% CI, 399–608 days; Fig 1A).

Visual acuity at time of treatment suspension and number of years receiving treatment before suspension were associated significantly with re-activation risk. Eyes with intermediate (VA, 36–69 letters) or good (VA, ≥70 letters) vision (hazard ratio [HR], 1.9 [95% CI, 1.2–2.9]; $P = 0.006$) were twice as likely to show re-activation and resume treatment than eyes with poor vision (≤35 letters; HR, 2.1 [95% CI, 1.3–3.2]; $P = 0.013$; Fig 1B). The HR of re-activation for each year receiving treatment before suspension was 0.87 (95% CI, 0.78–0.97; $P = 0.015$). The median time until re-activation estimated from the survival curve was 298 days for eyes in which treatment was suspended within the first year of treatment, increasing to 480 days for eyes in which treatment was suspended 2 to 3 years after initiating treatment, 995 days for eyes in which treatment was suspended 3 to 4 years after initiating treatment, and 1010 days for eyes in which treatment was suspended after more than 4 years of treatment (Fig 1C).

Visual Outcomes

The mean change in VA from baseline to the time of treatment suspension was +3.9 letters (95% CI, 2.2–5.6 letters; $P < 0.001$). The mean VA at treatment suspension was 60.3 letters (SD, 21.1 letters); 200 of 434 eyes (46%) showed VA of 70 letters or more (Snellen equivalent, 20/40), and 66 of 434 eyes (21%) showed of VA 35 letters or fewer (Snellen equivalent, 20/200). The mean VA 12 months after suspension was 57.6 letters (SD, 23.4 letters), giving a mean change of −2.6 letters (95% CI, −3.6 to −1.6 letters; $P < 0.001$) from the last injection. For eyes whose lesion did not re-activate (n = 159; median follow-up, 708 days), the mean change in VA 12 months after suspension was −3.2 letters (95% CI, −5.0 to −1.3 letters; $P = 0.001$) and the mean change in VA from the last injection to their last recorded visit was −5.7 letters (95% CI, −8.0 to −3.4 letters; $P < 0.001$).

Eyes in which the lesion re-activated (n = 275) lost a mean of 4.2 letters (95% CI, −5.6 to −2.8 letters; $P < 0.001$) from the last injection to the time of re-activation; of the eyes in which re-activation occurred, 138 of 275 showed VA of 70 letters or more at treatment suspension, but 38 of 138 eyes (28%) showed a VA of fewer than 70 letters when the lesion re-activated.

Two hundred six of 275 eyes (75%) resumed treatment for at least 12 months after re-activation of the lesion, receiving a median of 6 injections (IQR, 3–8 injections). These eyes went on to recover a mean of +1.2 letters (95% CI, −0.4 to 2.7 letters; $P = 0.133$) 12 months after resuming treatment; approximately half of the eyes that no longer showed VA of 70 letters or more at re-activation and resumed treatment for at least 12 months regained VA of 70 letters or more (15/28 eyes [54%]). The 206 eyes that resumed treatment for at least 12 months showed a net VA loss of 3.3 letters (95% CI, 2.3–5.1 letters; $P < 0.001$) from the time of treatment suspension to 12 months after resuming treatment after re-activation.

Discussion

Many risks are associated with prolonged use of anti-VEGF injections to treat nAMD, most notably infectious endophthalmitis and the potential risk of geographic atrophy, which may cause severe permanent loss of vision, although a direct cause-and-effect relationship of the latter has been difficult to establish.[6,12,13] We explored the outcomes of suspending anti-VEGF treatment in a cohort of eyes whose lesion had been inactive for at least 3 months and no further treatments had been administered unless the lesion had re-activated. Loss of vision was observed 12 months after treatment suspension. We found 41% of eyes showed re-activation within the first year of treatment suspension, increasing to 79% at 5 years. Vision gains achieved before suspension were lost after re-activation of the CNV lesion and were recovered only partly after resuming treatment for 12 months. Thus, it is important when deciding to suspend treatment to ensure that the risk of re-activation of the lesion is low, because patients may lose vision gained from anti-VEGF therapy, even if treatment is resumed. Eyes with lower visual acuity at the time of suspension and more years receiving treatment before suspending treatment were found to have a significantly lower risk of re-activation.

Reports of outcomes of discontinuing VEGF inhibitors for nAMD have found variable results. A single-center study by Adrean et al[14] that investigated outcomes of the treat-extend-stop regimen reported a 30% recurrence of CNV after treatment suspension (mean follow-up, 14 months) with good recovery of vision after treatment was resumed. A recent report of the treat-extend-stop regimen from the same center found much better long-term visual outcomes (mean gain, 8.7 letters over an average 8-year follow-up period) than clinical trials and other real-world studies, suggesting that the population they studied is achieving better outcomes than the general population, possibly for geographic, racial, or socioeconomic reasons.[4,6,12,15,16] A retrospective analysis investigating outcomes of treatment suspension in a cohort of eyes that had received 3 consecutive injections at 16-week intervals also found promising results, with only a 13% recurrence rate

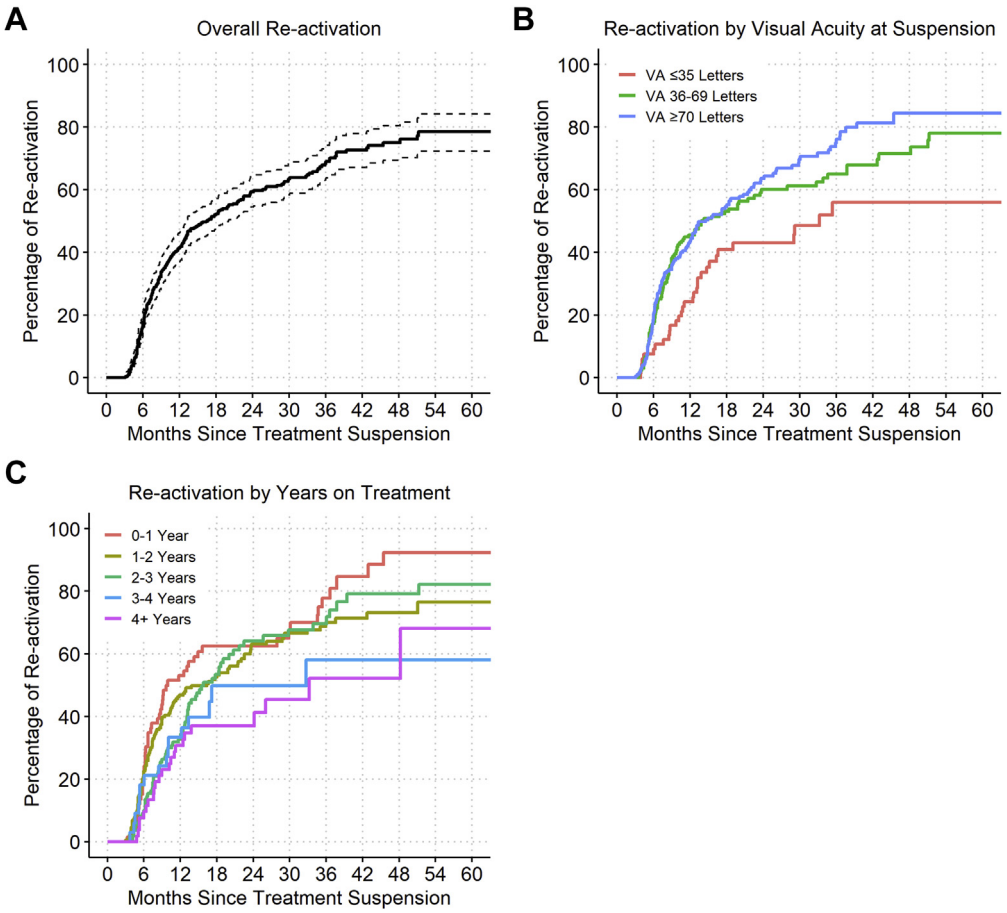

Figure 1. Graphs showing time to re-activation of lesion activity for (**A**) the overall cohort (with 95% confidence intervals [dashed lines]), (**B**) visual acuity at suspension, and (**C**) number of years of treatment before suspension. VA = visual acuity.

after a relatively short mean follow-up of 37 weeks.[17] A previous single-center report by Vaze et al[5] investigated suspension in eyes whose CNV lesion was inactive for at least 3 months and found a 91% rate of recurrent lesion activity over a mean follow-up of 18 months. However, the study population included only eyes being treated for nAMD from 2006 through 2009, during which anti-VEGF treatments were still relatively new and real-world outcomes were quite poor. A subgroup analysis of the VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration clinical trials reported that vision loss could not be recovered despite re-treatment of lesion recurrences following an as-needed regimen.[18] The Lucentis Compared to Avastin clinical trial reported irreversible loss of vision in some eyes following a T&E regimen when intervals were extended to 12 weeks even without treatment suspension,[19] suggesting that extended periods without treatment could put some patients at risk.

Unlike previous studies, we had no direct control over the treatment protocols used by individual practitioners, and although most practitioners enrolled in Fight Retinal Blindness! likely use some variation of T&E,[2] the decision regarding whether to suspend treatment and under what conditions varies substantially across practitioners. The treat-extend-stop protocol used by Adrean et al,[4,14] by contrast, outlines a clear requirement that patients are to be treated at 12-week intervals for 3 consecutive visits before treatment can be suspended. Similarly, a previous investigation into defining a so-called exit strategy for patients undergoing a T&E regimen suspended treatment only if patients had received 3 consecutive injections at 16 weeks apart.[17] Our patients were treated for a median of 2 years and received a median of 10 injections; thus, it is likely that treatment for the patients in this analysis was suspended earlier than for those in previous studies. We found that a longer duration of treatment before suspension was associated with a lower risk of re-activation, suggesting that premature treatment suspension might have led to poorer outcomes compared with previous studies. Time to re-activation was much greater for eyes that had been treated for at least 3 years than eyes treated for fewer than 3 years: a median of approximately 3 years before re-activating versus approximately 1 year, respectively. A decrease in vision of 3.2 letters 12 months after suspension was observed in eyes whose lesions did not re-activate, which also may be a consequence of premature suspension. Assessment of lesion activity was at the discretion of the treating physicians, who may not be perfect

graders.[20] Thus, it is also possible that active lesions were undetected on OCT, resulting in delayed treatment or a failure to resume treatment in some patients.

There are several other limitations in the present analysis we wish to acknowledge. Regular monitoring of patients after treatment suspension was another variable that is likely to have varied across practitioners and is an important consideration when stopping treatment. Our selection criteria presumed that a consistently dry lesion indicated good outcomes, although it is possible that some of our patients had suspended treatment because of poor outcomes such as development of atrophy. We excluded patients whose treatment explicitly was discontinued by the physician because of treatment futility; however, this information might not always have been recorded. Regardless, the incentives for preventing loss of vision in eyes with intermediate or good vision arguably are much greater because more would be at risk if treatment were suspended. Patients who were lost to follow-up also may have influenced our results, although the impact is not clear and the rationale for drop-out may differ from other studies because patients had achieved reasonably good outcomes before treatment suspension. Finally, without a matched control group, it was not possible to determine whether the loss of vision observed in our cohort would have occurred naturally even with continued treatment. We note that a minor recovery occurred in eyes in which treatment resumed after lesion reactivation, so it is possible that vision would have been maintained had treatment not been suspended.

To conclude, some patients with nAMD may be able suspend treatment for some period, particularly if vision is poor and they have been treated for at least 3 years with VEGF inhibitors, but caution should be exercised to avoid suspending treatment prematurely. Vision gained during the course of therapy potentially could be lost if eyes show reactivation and may not be regained even if treatment is resumed, so it is important that treatment be suspended only in eyes with a low risk of recurrence. Although there may be a subset of the population whose treatment can be suspended safely under carefully controlled conditions, further research is warranted to establish who they are and when it is safe to do so, because most eyes eventually do show reactivation.

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Footnotes and Financial Disclosures

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No animal subjects were included in this study.

Author Contributions:

Conception and design: Nguyen

Analysis and interpretation: Nguyen, Vaze

Data collection: Fraser-Bell, Arnold, Essex, Barthelmes, Gillies

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Abbreviations and Acronyms:
CI = confidence interval; **CNV** = choroidal neovascularization; **IQR** = interquartile range; **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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