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Treatment Patterns and Visual Outcomes during the Maintenance Phase of Treat-and-Extend Therapy for Age-Related Macular Degeneration

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Purpose: To present the treatment patterns, disease activity, and visual outcomes of eyes in the maintenance phase of a treat-and-extend regimen for neovascular age-related macular degeneration (nAMD). To compare the maintenance phase behavior of eyes with a shorter induction phase (≤3 injections) with those requiring a longer induction phase (>3 injections).

Design: Database observational study.

Participants: Eyes with nAMD receiving anti-vascular endothelial growth factor (VEGF) treatment using a treat-and-extend protocol. Persistently active eyes were excluded, as were eyes with <12 months follow-up during the maintenance phase.

Methods: Clinical information from a large prospective international voluntary registry of nAMD was analyzed. The maintenance phase was defined as starting at the first clinician-reported grading of lesion inactivity.

Main Outcome Measures: For analyses by eye: treatment interval at first reactivation; time to first reactivation; and visual acuity change during the study period. For analyses by visit: choroidal neovascular membrane activity graded by the treating physician; time since previous injection; and visual acuity loss since previous injection (>0 letters and ≥15 letters).

Results: The mean change in visual acuity during the maintenance phase was +1.0 letters at 12 months −0.6 letters at 24 months and −1.5 at 36 months. Median treatment interval increased from 35 days at study entry to 63 days at 12 months and was 60 days at 36 months. 38.5% of eyes remained inactive at all observed visits during the maintenance phase (minimum 1 year follow-up, mean 945 days). The most common treatment interval at first reactivation was 8 weeks. Treatment intervals beyond 12 weeks seemed to be associated with increased risk of disease reactivation, with risk of reactivation reaching 37.4% at treatment intervals of ≥20 weeks. Eyes with a longer induction phase had worse visual outcomes in the maintenance phase, and earlier and more-frequent disease reactivation, although they received injections less frequently.

Conclusions: The detailed behavior of eyes in the maintenance phase of treat-and-extend management for nAMD is presented. Visual acuity was well maintained during the study period. The most common interval at which reactivation first occurred was 8 weeks. Longer duration of induction phase was associated with worse visual acuity outcomes and earlier disease reactivation, perhaps because of undertreatment. *Ophthalmology 2016;■:1–8 © 2016 by the American Academy of Ophthalmology.*

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The treat-and-extend approaches to the management of neovascular age-related macular degeneration (nAMD) have become increasingly common, used by greater than 66% of retinal specialists in the United States in 2015.[1] Treat-and-extend protocols for intravitreal therapy allow individualized review and treatment intervals based on observed lesion behavior, thus reducing the number of injections in less-active eyes while still allowing more-active eyes to receive more-frequent injections. Provided visual outcomes are maintained, it is desirable to reduce both the number of visits patients are required to attend and the number of injections they receive. Additionally, there are concerns that there is an increase in lesion-associated atrophy in eyes receiving monthly treatment when compared with those treated less frequently.[2,3]

We have previously presented 2-year outcomes of treat-and-extend therapy for nAMD in a large registry-based cohort. There was sustained improvement in mean visual acuity to 24 months (+5.3 letters) with a mean of 13.0 injections.[4] We have also recently reported an analysis of the

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induction phase of treatment for nAMD, which we defined as the period until the first clinician-reported inactivation of the neovascular lesion.[5] In this study, 61.1% of eyes were reported as inactive after ≤3 injections, although those rendered inactive with fewer injections actually received injections more frequently than the slower responders during the induction phase.

In this article, we describe in more detail the treatment patterns and clinical outcomes during the maintenance phase of treat-and-extend management of nAMD, which we define as the period after the first clinician-reported grading of inactivity. We also set out to explore whether the number of injections required to render the lesion inactive during the induction phase (≤3 or >3) was predictive of subsequent lesion behavior. This study cohort overlaps with the previously published treat-and-extend cohort, but it is substantially larger because of broader inclusion criteria (treatment commencement date and duration of follow-up).

Methods

Study Design and Setting

We analyzed anonymized longitudinal data obtained from a large international voluntary registry of nAMD (the Fight Retinal Blindness [FRB] registry). Data were captured during routine clinical practice, and all treatment decisions, visit schedules, and grading of lesion activity were at the discretion of the treating physician. Institutional ethics approval was obtained from the Human Research Ethics Committees of the Universities of Sydney, Melbourne, and Western Australia. Overarching ethics approval for the private centers was obtained from the Human Research Ethics Committee of the Royal Australian and New Zealand College of Ophthalmologists. The research described adhered to the tenets of the Declaration of Helsinki. This study included contributing practices located in Australia.

Details of the FRB project data tracking system have been reported previously.[6] At each visit, the clinician must determine the activity of the choroidal neovascularization (CNV) as *active*, *inactive*, or *unsure*. This grading is performed by the treating clinician based on fundoscopy, optical coherence tomography, and (less frequently) fluorescein angiography. All clinicians contributing to this study agreed with the following statement: "Lesions were graded as active if there were features such as sub- or intra-retinal fluid, or new haemorrhage, that suggested that the CNV lesion was active."[7] If the grading of CNV activity was missing (7.1% of all visits), the value was imputed using the last observation carried forward.

Participants and Variables

Practitioners using the FRB database were contacted to self-report their treatment approach(es) from 2006 to 2014. The treatment regimens available for selection were monthly, pro re nata (PRN), treat and extend, or a combination of these. All eyes being treated with intravitreal VEGF inhibitors by practitioners who reported to have been exclusively using a treat-and-extend protocol were eligible for inclusion. We did not offer a strict definition of treat and extend to our users. Although there is no single definition, most treat-and-extend protocols share the following features:

- Monthly treatment (during the induction phase) until the lesion is inactive
- Increase in treatment interval only when disease is inactive
- Reduction in treatment interval if disease is active

Most protocols (e.g., that of Berg et al[8]) also allow eyes to settle on a fixed treatment interval eventually rather than on repeated cycles of extension to failure.

We focused exclusively on the period beginning when the lesion was first graded *inactive*. Eyes that were persistently active were not included in the analysis. Eyes were also required to have at least 12 months of follow-up from first grading of inactivity to allow sufficient time to observe the effect of extending the treatment intervals. There was no upper limit to the duration of follow-up included in the analysis. Time was calculated in the study from the first grading of inactivity (rather than from presentation or first injection).

At each visit, the time from previous injection (treatment interval), lesion activity, and visual acuity were recorded. Treatment intervals were divided into the following groups: 4 weeks (10−34 days), 6 weeks (35−48 days), 8 weeks (49−69 days), 12 weeks (70−97 days), 16 weeks (98−125 days), and 20 weeks (126−365 days). Treatment intervals exceeding 365 days were not included in the analyses, as they were likely associated with confounding factors rather than a deliberate extension of the treatment interval. For each visit, the change in vision from previous visit was calculated and was classified as a loss of >0 letters or ≥15 letters if visual acuity decreased from the previous visit.

The treatment interval at which each eye was first observed to develop recurrent CNV activity was determined (referred to as the *treatment interval at first reactivation*), and grouped as 4, 6, 8, 12, 16, or 20 weeks, as described for treatment intervals. Additionally, for each eye, the number of injections required to render the lesion inactive during the induction phase of treatment (prior to study entry) was known. Eyes were grouped as *short induction phase* if they were graded as inactive after ≤3 injections and *longer induction phase* if it took >3 injections to render them inactive.

Outcomes

The outcomes for each eye are as follows: treatment interval at first reactivation, time to first reactivation, visual acuity change during the study period, and number of injections received.

The outcomes for each visit are as follows: CNV activity, time since previous injection, and visual acuity loss since previous injection (>0 letters or ≥15 letters).

Statistical Analyses

All analyses were performed using R, version 3.2.2.[9] Descriptive statistics included the mean, standard deviation, and percentages where appropriate.

Generalized linear mixed-effects models were fitted to the data to estimate the risk of loss of vision and first reactivation of CNV activity for each treatment interval, adjusted for age and index visual acuity. Eye and practice were included as random effects to account for repeated visits by eye and natural clustering by practice within the data. Adjusted risks were estimated by computing the average marginal probabilities from the mixed-effects models. Treatment interval was analyzed as a categorical variable. Change in visual acuity from the previous visit was compared between treatment-interval groups and tested for significant deviations from 0 using t tests with a Bonferroni correction for multiple comparisons.

Time to first reactivation was estimated using Kaplan−Meier survival analysis. For this analysis, eyes that reactivated were classified based on the treatment interval at which reactivation occurred.