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Early and Late Retinal Pigment Epithelium Tears after Anti–Vascular Endothelial Growth Factor Therapy for Neovascular Age-Related Macular Degeneration

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Purpose: To investigate when retinal pigment epithelium (RPE) tears occur and their associated treatment patterns and long-term visual outcomes in patients with neovascular age-related macular degeneration (nAMD) during anti–vascular endothelial growth factor (VEGF) treatment.

Design: Case-control analysis from a prospectively designed observational database.

Participants: Treatment-naïve eyes enrolled in the Fight Retina Blindness! observational study that commenced anti-VEGF treatment for nAMD between January 2006 and January 2017 were identified. Cases were defined as eyes in which an RPE tear developed during treatment. Three control eyes per case were matched for age, baseline visual acuity (VA), lesion size, treatment duration before tearing, and duration of follow-up.

Methods: Cases were classified as having early or late tears using a segmented regression model. Baseline characteristics were compared between the 2 groups. Comparisons of VA and injections received between tear eyes and control eyes were performed at baseline, before and immediately after the tear, and then 12 and 24 months later. Visual acuity also was compared among different visits within each group.

Main Outcome Measures: Visual acuity, time to tear, and injections received.

Results: Fifty-five cases and 165 matched control eyes were included. The segmented regression estimated a breakpoint for the time to tear at 182 days. We therefore defined eyes as having early tears if they tore before the breakpoint (38/55 eyes [69%]), and as late tears if they tore afterward (17/55 eyes [31%]). Baseline VA was significantly lower in early compared with late tears (53.6 vs. 63.4 letters; $P = 0.009$). Visual acuity had improved in early tears before the tear (+5.6 letters from baseline; $P = 0.01$), decreased immediately after the tear (−8.3 letters; $P = 0.002$), then recovered with no difference compared with control eyes 12 and 24 months later ($P > 0.05$ for both). Late tear eyes had significantly lower VA than control eyes before tearing (55.5 vs. 66.9 letters; $P < 0.001$). Visual acuity did not decrease significantly after the tear, but continued to decline compared with control eyes at all end points. Both early and late tear eyes received more injections than control eyes after tearing.

Conclusions: Retinal pigment epithelium tears act differently depending on when they occur. Long-term visual outcomes in eyes affected by RPE tearing may be related more to the patient's response to therapy than to the tear itself. *Ophthalmology 2017;■:1–8 © 2017 by the American Academy of Ophthalmology*

Tears of the retinal pigment epithelium (RPE) are a well-known complication of neovascular age-related macular degeneration (nAMD), particularly in eyes with RPE detachments (pigment epithelial detachment [PED]).[1] Anti–vascular endothelial growth factor (VEGF) treatment has radically improved the prognosis of nAMD;[2,3] however, it does not seem to prevent RPE tears.[4] On the contrary, it seems to increase the risk of early tearing, possibly by shrinking the neovascular complex, thereby stretching the RPE to the breaking point.[5] Consistent with this hypothesis, a post hoc analysis of phase III studies reported that more eyes receiving anti-VEGF sustain a tear within the first 3 months of treatment than untreated eyes, although the overall number of RPE tears did not differ between treated and untreated eyes over a span of 2 years.[4]

Despite the increasing prevalence of nAMD worldwide,[6] there are only limited data on the relationship of tears with anti-VEGF therapy and their long-term visual outcomes. Several studies have reported that eyes that continued to receive anti-VEGF injections after tearing obtained better visual outcomes than those that discontinued the treatment after the tear, suggesting that the treatment may still be beneficial despite the complication.[4,7,8] However, long-term outcomes are less encouraging, with more than half of the tear-affected eyes reported to have become legally blind 12 months later, even with persistent treatment.[9] The aim of the present study was to investigate the timing of RPE tear occurrence, the treatment patterns before and after the tear, and the long-term visual outcomes in patients with nAMD who sustain an RPE tear during

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anti-VEGF treatment using data from a large registry of real-world treatment outcomes.

Methods

This study followed the STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) checklist items for reporting observational study data.

Design and Setting

Data were obtained from the Fight Retinal Blindness! (FRB) database, which tracks real-world outcomes of treatments for nAMD during routine clinical practice prospectively and complies with the International Consortium for Health Outcomes Measurement's macular degeneration standard set.[10,11] In brief, the FRB project has designed an efficient Web-based data collection tool specifically to track the outcomes of treatment of macular disease in routine clinical practice. The system records a number of baseline features of the patients, such as lesion size and the choroidal neovascularization (CNV) type, and tracks parameters such as the number of treatments, the type of anti-VEGF injected, and best-corrected visual acuity (VA) variations over time. Details of the FRB database have been described previously.[10] To satisfy the audit component of practitioners' annual registration with the Australian Medical Board, which participation in the audit fulfills, they confirm that they have entered data into the registry for at least 85% of patients beginning treatment for nAMD.

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 and New Zealand approved the use of opt-out patient consent. The research described adhered to the tenets of the Declaration of Helsinki. This study included patients and practices from Australia, New Zealand, and Switzerland.

Data Sources and Measurements

The FRB system collects data from each clinical visit, including the number of letters read on a logarithm of the minimum angle of resolution VA chart (best of uncorrected, corrected, or pinhole); treatment given, if any; and ocular adverse events, including RPE tears.[10] At baseline only, overall lesion size (including PED, if present) and type and prior treatment were recorded. Treatment decisions, including choice of drug and visit schedules, were entirely at the discretion of the practitioner in consultation with the patient, thereby reflecting real-world practice.

The VA immediately after the tear was defined as the VA measured at the visit when the tear was recorded, whereas the VA before the tear was defined as the VA recorded in the visit immediately before the tear. Although overall lesion size is recorded in the FRB database, neither the PED height nor largest diameter is recorded. However, these measurements are known to be correlated directly with the risk of an RPE tear developing.[12,13] We asked the practitioners who were treating the patients to provide these measurements at baseline by reviewing the OCT and fundus fluorescein angiography studies. We also asked practitioners to provide data about the RPE tears' greatest linear diameter in the vector direction and the degree of foveal involvement when the tear was first observed. This allowed us to grade RPE tears according to the classification recently proposed by Sarraf et al.[14] Briefly, grade 1 tears were defined as smaller than 200 μm, grade 2 tears were between 200 μm and 1 disc diameter, grade 3 tears were more than 1 disc diameter, and grade 4 tears were defined as grade 3 tears that involved the center of the fovea.

Participants

This study considered treatment-naïve eyes commencing treatment with anti-VEGF for nAMD between January 1, 2006, and January 5, 2017. Cases were defined as eyes that were recorded as having an RPE tear that developed during treatment. These eyes were divided into early and late tear categories based on a segmented regression analysis of time to tear, as described below in "Statistical Analyses." Analyses of outcomes 12 (and 24) months after tear required eyes to have completed 12 (or 24) months of follow-up after the RPE tear.

A matched control cohort consisting of 3 control eyes per case was identified from the FRB database to compare visual outcomes over time. Control eyes were matched on the following characteristics: baseline VA, baseline age, baseline lesion size, and treatment duration before tear. Control eyes also were required to have had at least as much follow-up as their respective cases.

Outcomes

The primary outcome was the change in VA immediately after and then 12 and 24 months after the tear. Secondary outcomes included the time until tear, the number of injections, the treatment interval before and then at 12 and 24 months after the tear, and a comparison of baseline characteristics between early and late tear eyes. The prevalence of different tear grades also was compared between the 2 groups.

Statistical Analyses

Descriptive statistics for continuous variables included the mean, standard deviation (SD), median, and quartiles (first quartile [Q1] and third quartile [Q3]) where appropriate. Categorical variables were summarized as percentages. Time and number of injections until RPE tear were assessed using Kaplan-Meier survival curves. Eyes were classified as having early or late tears using the breakpoint estimated by segmented regression via maximum likelihood. Early tears were defined as eyes that sustained tears before (and including) the breakpoint, whereas late tears were defined as those eyes that tore after the breakpoint. Comparison of baseline characteristics between eyes with early and late tears were conducted using the Student *t* test, the Wilcoxon rank-sum test, and the Fisher exact test where appropriate. Within-group change in VA was analyzed using paired *t* tests. Comparisons of VA and injections received between tear eyes and their matched control eyes were performed using mixed-effects and Poisson regression models with an identifier variable to indicate clustering in matched patients as a random effect. Poisson regression models also included log days' follow-up as an offset variable. All statistical analyses were conducted using R software version 3.3.2 (R Project - The R Foundation for Statistical Computing, Vienna, Austria) with the segmented package (version 0.5-1.4) for segmented regression, the survival package (version 2.40-1) for Kaplan-Meier survival analysis, and the lme4 (version 1.1-12) package for mixed-effects regression analysis.[15–17]

Results

This study included 55 eyes from 52 patients who experienced an RPE tear during anti-VEGF treatment for nAMD. Six of 13 doctors (46%) responded to the request for additional measurements of the PED at baseline as well as the size of the RPE tears. These doctors