AMERICAN ACADEMY OF OPHTHALMOLOGY®

Outcomes in Neovascular Age-Related Macular Degeneration when Neovascular Lesion Activity Is Uncertain: Observational Study

Eugene A. Lowry, MD,[1,2] *Vuong Nguyen, PhD,*[1] *Vincent Daien, MD, PhD,*[1,3,4] *Daniel Barthelmes, MD, PhD,*[1,5] *Mark C. Gillies, MB, BS, PhD, FRANZCO*[1]

Purpose: To determine the characteristics and outcomes of eyes with neovascular age-related macular degeneration (nAMD) in which choroidal neovascular (CNV) lesion activity was graded as uncertain.

Design: Prospective, database, observational study.

Participants: Treatment-naïve patients with nAMD tracked by the Fight Retinal Blindness! (FRB!) registry initiating treatment between January 1, 2008, and January 1, 2014, with 2 years of follow up.

Methods: Lesion activity was determined by the clinical judgment of the providing physician on the basis of clinical examination with ancillary testing. Eye-based analysis investigated clinical characteristics and outcomes by proportion of visits with uncertain CNV lesion activity. Encounter-based analysis investigated CNV lesion grading over time with corresponding treatment and follow up.

Main Outcome Measures: Change in mean visual acuity (number of letters read on a logarithm of the minimum angle of resolution chart) at 2 years. Secondary outcomes included the number of visits and injections.

Results: We identified 1631 eyes of 1419 patients with 27 974 visits to 46 retinal specialists. The CNV lesion activity was uncertain at 4601 encounters (16.4%) and experienced by the majority of eyes (52%) and providers (72%). Uncertainty of CNV lesion activity did not significantly decline with increasing number of visits in individual patients ($P = 0.97$) but did decline from 32% in 2010 to 4% in 2015 ($P < 0.001$). Eyes having no visits with uncertain CNV lesion grading gained more letters (mean, 7.0) than eyes with moderate or high levels of uncertainty (mean, 3.98 and 3.37; $P = 0.03$ and 0.02, respectively). The mean probability of receiving an injection was higher in visits with active (0.89) compared with inactive (0.68, $P < 0.001$) and uncertain (0.69, $P < 0.001$) CNV lesion activity. Subsequent follow-up length was also decreased in visits with active (mean ± standard deviation [SD], −0.9±39 days) compared with inactive and uncertain CNV lesion activity (mean ± SD, 1.9±39 days, $P < 0.001$, and 2.4±39 days, $P < 0.001$, respectively).

Conclusions: Rates of uncertainty regarding CNV lesion activity were high, and eyes with higher rates of uncertain CNV activity had worse outcomes. Further studies are warranted to establish whether eyes should be treated more aggressively when the activity status of the CNV lesion is uncertain. *Ophthalmology Retina 2017;■:1–8* © *2017 by the American Academy of Ophthalmology*

Supplemental material available at www.ophthalmologyretina.org.

Anti–vascular endothelial growth factor (VEGF) agents have transformed the treatment of neovascular age-related macular degeneration (nAMD), resulting in substantial gains in visual acuity (VA) in both randomized clinical trials and observational studies.[1–5] Initial clinical trials of anti-VEGF agents showed the best results with monthly or every second month injections.[1–3] Given the burden of such frequent injections, both pro re nata and treat-and-extend dosing schedules have emerged as alternatives with potentially good results.[6,7]

Under both a treat-and-extend and a pro re nata protocol, clinicians judge disease activity to determine follow-up interval or whether to give intravitreal injections, respectively. Typical features of disease activity include reduced VA, retinal hemorrhage, subretinal or intraretinal fluid on spectral domain OCT, and leakage on fluorescein angiography.[8–11] Although clinical studies generally define activity as the presence or worsening of any of these abnormalities, the final assessment of these factors is determined by the treating clinician.[6,12,13] In fact, this qualitative clinical assessment may lead to more frequent treatment and better visual outcomes than a cutoff based purely on the best-corrected VA or central foveal thickness.[10,14]

Although typical features of choroidal neovascularization (CNV) lesion activity are well established, the final determination is not always straightforward and clinicians may

https://doi.org/10.1016/j.oret.2017.10.002
ISSN 2468-6530/17

be uncertain of CNV lesion activity. Treatment decisions and clinical outcomes in the setting of uncertainty remain unclear. In this study, we assessed outcomes among eyes with nAMD having varying proportions of visits at which CNV activity was graded as uncertain; we further describe the frequency and timing of uncertainty of CNV lesion activity and subsequent changes in the follow-up interval.

Methods

This article followed the STrengthening the Reporting of OBservational studies in Epidemiology checklist items for reporting observational study data.[15]

Study Design and Setting

This was an observational study of treatment-naïve eyes initiating intravitreal anti-VEGF therapy for nAMD. The data were collected prospectively in the Fight Retinal Blindness! (FRB!) database, which has been described in detail by Gillies et al.[16] Briefly, the FRB! database collected information from multiple ophthalmologists in Australia, New Zealand, and Switzerland. Participating clinicians are recruited at professional conferences and local and international congresses. They may be in private, academic, or group practices and agree to voluntarily contribute data for at least 80% of their patients with neovascular macular degeneration to reduce the risk of reporting bias as part of the participation protocol. Information was entered prospectively at each visit for patients with nAMD, including demographics, prior treatments, VA defined by number of letters able to be read on a logarithm of minimal angle of resolution VA chart (best of uncorrected, corrected, or pinhole), treatments, and adverse events. Clinicians were also requested to assess CNV lesion activity to the best of their clinical judgment, and although prospective standardized criteria were not explicitly defined, lesions were considered active if there was intraretinal or subretinal fluid due to leak from active CNV or fresh hemorrhage. This was based on clinical examination and OCT at the discretion of the investigator. Imaging results from ancillary testing were not uploaded to the FRB! database. Physicians were able to enter a grading of active, inactive, or uncertain for CNV lesion activity during the study period. Treatment decisions were made as clinically indicated in the judgment of providing physicians in consultation with their patients. Data collection for the FRB! database received institutional ethics approval from the Human Research Ethics Committees of the University of Sydney, the Royal Victorian Eye and Ear Hospital, and the Royal Australian and New Zealand College of Ophthalmologists. Data were de-identified before provision to researchers for this analysis. The research adhered to the tenets of the Declaration of Helsinki.

Participants and Variables

The study population included treatment-naïve eyes that commenced treatment between January 1, 2008, and January 1, 2014, with 2 years of follow up and practitioner grading of CNV lesion status at the majority of visits. The 2-year follow-up visit for outcomes analysis was defined as the visit closest to without exceeding 730 days and had to be at least 650 days after initiating treatment. Patients were excluded if their initial CNV activity status or lesion subtype was not assessed, if CNV activity was not assessed at least 50% of follow-up visits, if they had previous treatment for macular degeneration, or they did not meet follow-up criteria listed. After October 28, 2015, "uncertain" was no longer collected as a CNV variable because of challenges in contemporaneous analyses of these data regarding timing of CNV inactivation with uncertain CNV grading,[17] so no encounters beyond this end point were analyzed.

Eyes were stratified into cohorts on the basis of the proportion of visits with uncertain CNV lesion grading. Eyes with no uncertain visits were defined as a cohort, and those with any visits with uncertain CNV were divided into 3 equal-sized cohorts based on the proportion of visits with uncertainty out of total visits in which CNV status was evaluated. These 3 cohorts were then defined as low, medium, and high rates of uncertainty. Baseline demographics and clinical assessments were compared among groups. Number of injections, visits, and change in VA were recorded across follow up.

Encounters were divided into an induction phase and maintenance phase. The induction phase was defined as the period until first grading of inactive CNV activity, at which point patients were defined to be in maintenance phase as previously described.[18] The rates of uncertain encounters were determined for both sequential visits within each patient (e.g., first visit, second visit) and calendar year (2008−2015). Changes in follow-up interval after a visit were determined by subtracting the days to the subsequent follow-up visit from the days to the prior visit. Change in follow up was analyzed as a continuous variable.

Outcomes

Outcomes by eye included change in VA, number of visits, and number of injections all measured at the 2-year follow-up visit. Outcomes by encounter included the proportion of uncertain visits by visit number and year, and subsequent follow-up interval in days.

Statistical Analysis

For eye-based analyses, baseline features were compared among groups with varying proportions of visits with uncertain CNV activity using Pearson chi-square tests for categoric variables and Kruskal−Wallis tests for continuous variables. Two-year VA outcomes were analyzed with mixed-effects linear regression modeling with CNV certainty, baseline VA, total visits, total injections and type of CNV lesion as fixed effects and patient, practitioner, and year treatment started as random effects. Poisson regression was used for analysis of total injections and total number of visits, adjusting for baseline VA, type of CNV lesion, patient, practitioner, and year of treatment with an offset to standardize for total follow-up length. A second similar Poisson regression was performed on number of injections but with offset for number of visits to determine whether there was a significant difference in injection rates.

For encounter-based analysis, differences in proportion of uncertain visits were determined over visit number and calendar year using binomial regression modeling with baseline vision and visit number or calendar year as fixed effects, whereas eye, patient, and practitioner were modeled as random effects. Change in follow-up interval in days was analyzed with linear mixed-modeling controlling for baseline vision, eye, patient, and practitioner. Both an eye-based and encounter-based analysis were necessary given there were multiple encounters per eye, and several outcome variables (i.e., 2-year VA) had a single measure per eye, whereas others (i.e., change in follow-up length) had a unique measure for every encounter.

Pairwise comparisons were undertaken for each result that was significant in group-wide comparisons at a P value ≤ 0.05. These comparisons were performed with the same statistical method as group-wide analysis, but with all pairwise P values adjusted for the