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Recurrence Rate of Choroidal Neovascularization in Neovascular Age-Related Macular Degeneration Managed with a Treat–Extend–Stop Protocol

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Purpose: To examine visual outcomes and recurrence rates in patients with choroidal neovascularization (CNV) resulting from neovascular age-related macular degeneration (nAMD) with successful cessation of therapy using a treat–extend–stop (TES) protocol.

Design: Cohort study.

Participants: Three hundred eighty-five eyes of 321 patients with nAMD identified in clinical practice and treated with a TES protocol between 2008 and 2016.

Methods: Retrospective review of patients initially managed with 3 anti–vascular endothelial growth factor (VEGF) injections at 4-week intervals; treatment was extended if the macula remained "dry" based on spectral-domain OCT, using a TES protocol. Treatment was stopped if warranted and was reinitiated if there was a new or recurrent CNV.

Main Outcome Measures: Percentage of eyes meeting criteria for treatment cessation and percentage experiencing recurrence after treatment cessation, average time to recurrence, and visual function at each of these time points, including recovery of vision after reinstitution of therapy.

Results: A total of 37.3% of eyes met criteria for treatment cessation, with an average follow-up of 27 months. Overall recurrence rate was 29.4% at a mean time interval of 14 months for patients who stopped anti-VEGF therapy. In those patients whose CNV recurred, 54.8% recurred in the first year and 26.2% recurred in the second year after treatment was stopped. Average initial vision was 20/70 and improved to 20/50 ($P < 0.001$) after patients met criteria for cessation of therapy. A mean loss of vision occurred with recurrence (20/60; $P < 0.003$). However, once therapy was reinitiated, visual acuity recovered to the level at TES completion and wasn't statistically different than at final treatment (20/50; $P < 0.34$). Overall, 54.8% of eyes that demonstrated a recurrence of CNV had final vision of 20/40 or better compared with 45% of patients at the time of recurrence and 60% before recurrence.

Conclusions: After completing the TES protocol, 29.4% of patients showed recurrence of CNV. Patients who lost vision with recurrence recovered to the level of vision at treatment cessation with reinstitution of therapy. Patients managed with a TES protocol may stop therapy successfully and maintain improved vision even if the CNV recurs. *Ophthalmology Retina 2017;■:1–6 © 2017 by the American Academy of Ophthalmology*

Age-related macular degeneration (AMD) is a major cause of vision loss in the elderly population. In patients with AMD, the rate of conversion from degenerative to neovascular AMD (nAMD) ranges from 10% to 15%.[1] More than 200 000 new cases of nAMD are diagnosed each year in North America.[2]

First-line therapies for the management of nAMD are anti–vascular endothelial growth factor (VEGF) agents. There are 3 main treatment strategies to control and improve the disease process. The first strategy is fixed dosing at a predetermined interval, which is the mainstay of randomized clinical trials.[3–6] Another treatment strategy is pro re nata (PRN), or dosing as needed with recurrence of disease, and usually is preceded by a loading dose of 3 injections. The third strategy is treat and extend (TREX). Patients are treated until the macula is dry, then the interval between treatments is extended. If the patients show increased fluid or decreased vision, the interval is reduced.[7] This is the main treatment strategy used by retina specialists in the United States.[8]

The purpose of this study was to examine the rate of recurrence of choroidal neovascularization (CNV) in patients with nAMD managed with a TREX protocol. As soon as these patients reached a point of stability, therapy was not performed and then patients were monitored carefully; this treatment approach may be described as a treat–extend–stop (TES) protocol. The study also examined the number of injections required to reach stability in the TES protocol, the interval at which the recurrence of the CNV occurred, and the visual acuity (VA) outcomes using this approach.

http://dx.doi.org/10.1016/j.oret.2017.07.009
ISSN 2468-6530/17

Methods

The study was approved by a local institutional review board and followed the tenets of the Declaration of Helsinki. The clinical database of a retina-only practice was searched for patients with a diagnosis of nAMD who had received intravitreal anti-VEGF injections. Records of patients with nAMD who were examined in the clinic between January 2008 and January 2016 were included in the analysis. Participants were excluded from the study if they had less than 1 year of follow-up or if they received fewer than 7 anti-VEGF injections. A total of 385 eyes of 321 patients were identified who met the inclusion and exclusion criteria. The data then were examined to determine the rate of recurrence of the CNV after cessation of anti-VEGF therapy.

The patients in the study underwent comprehensive ophthalmic examination, spectral-domain (SD) OCT, and fluorescein angiography at initial presentation. Anti-VEGF agents, including bevacizumab (Avastin; Genentech, Inc, South San Francisco, CA), aflibercept (Eylea; Genentech, Inc), and ranibizumab (Lucentis; Roche Pharmaceuticals), were selected as therapeutic options for treating the CNV. Patients initially were managed with anti-VEGF injections every 4 to 5 weeks, for a minimum of 3 injections, until a dry macula was observed, as determined by SD OCT. During therapy, at any time point in the TES protocol, if patients failed to respond (no decrease in fluid or increase in VA) or if treatment response was inadequate (increasing fluid, decreasing vision, or both related to the CNV process) as determined by vision and SD OCT findings, the anti-VEGF agent was changed. As soon as the macula was determined to be fluid free, visit intervals were extended on a careful TES protocol. Treatment intervals were extended successively by 1 to 2 weeks if the macula remained dry. If there was increasing fluid on the SD OCT, then the interval between treatments was reduced by at least 2 weeks. The TES protocol was continued until patients were extended to a 12-week interval. Patients then received 2 injections, each 12 weeks apart. Anti-VEGF treatments were stopped if the macula was dry at the third 12-week visit. After treatments were stopped, the patients were followed-up 4 weeks later to monitor carefully for any signs of recurrence. They were evaluated again in a stepwise fashion, increasing by 2-week intervals until the follow-up time was extended to 12 weeks. Patients were followed up subsequently at 3-month intervals.

At each visit, patients were monitored by SD OCT and VA was assessed using the Snellen chart. Fluorescein angiography was performed at initial presentation, at the end of the TES series, and at other time points at the discretion of the investigator. Patients were instructed to return to the clinic sooner than scheduled if they noted any visual changes or an increase in metamorphopsia. If at any point there was a recurrence or new CNV, then treatment was reinitiated immediately. The presence of a recurrence or new CNV was determined by clinical examination and was corroborated with OCT findings.

Study data were analyzed using the Student t test. A P value less than 0.05 was considered statistically significant.

Results

Three hundred eighty-five eyes in 321 patients identified in clinical practice met inclusion criteria for the study cohort; 37.3% of eyes (143 eyes of 120 patients) met criteria for cessation of therapy. After completion of the TES protocol, patients were followed up for an average of 14 months (range, 9–42 months). The average number of anti-VEGF injections required to complete the TREX protocol was 22 (range, 7–48 injections).

Recurrence of CNV after cessation of therapy was assessed. Of the eyes for which therapy was stopped, 29.4% (42 eyes of 36 patients) showed recurrence of the CNV and required further anti-VEGF therapy. The average period from completion of the TES protocol to recurrence of CNV was 14 months (range, 4–42 months). The interval until recurrence then was examined. Specifically, 23.8% of eyes (10/42 eyes) recurred at 4 to 6 months, 31.0% of eyes (13/42 eyes) recurred at 7 to 12 months, 19% of eyes (8/42 eyes) recurred at 13 to 18 months, 7.1% of eyes (3/42 eyes) recurred at 19 to 24 months, and 19% of eyes (8 eyes) recurred at more than 2 years after cessation of anti-VEGF therapy. Overall, 54.8% of this population demonstrated a CNV recurrence in the first year and 26.2% demonstrated a recurrence in their second year after anti-VEGF therapy was stopped (Fig 1).

Mean VA before treatment and at study entry was 20/70 (range, 20/25–counting fingers [CF]). The mean VA after completion of the TES protocol and before therapy cessation improved to 20/50 (range, 20/20–CF; $P < 0.001$), an average increase of 2 lines of vision or approximately 10 letters of vision.

Vision before recurrence was compared with vision after CNV recurred. The mean VA before recurrence was 20/50 (range, 20/20–CF) and decreased significantly to 20/60 (range, 20/20–CF; $P < 0.003$) after recurrence (Fig 2). Notably, 54.8% of eyes (23/42 eyes) demonstrated recurrence without a loss of vision, whereas 31.0% of eyes (13/42 eyes) lost only 1 to 2 lines of vision and 14.3% of eyes (6/42 eyes) lost more than 3 lines of vision. Interestingly, among the 6 patients who lost more than 3 lines of vision, 2 patients lost more than 6 lines of vision. One patient who lost more than 6 lines of vision had been lost to follow-up for 2 years and returned with a large CNV recurrence. However, 33% of those eyes (2/6) demonstrated vision either returning to baseline or notably improving. Nonetheless, overall visual function after cessation of therapy, even considering episodes of recurrence, was comparable with the VA at final treatment in the TES protocol, and no statistically significant loss of vision was detected (average, 20/50; $P < 0.34$).

At presentation, 29% of eyes (12/42 eyes) had 20/40 vision or better. At completion of the TES protocol, 60% of eyes (25/42

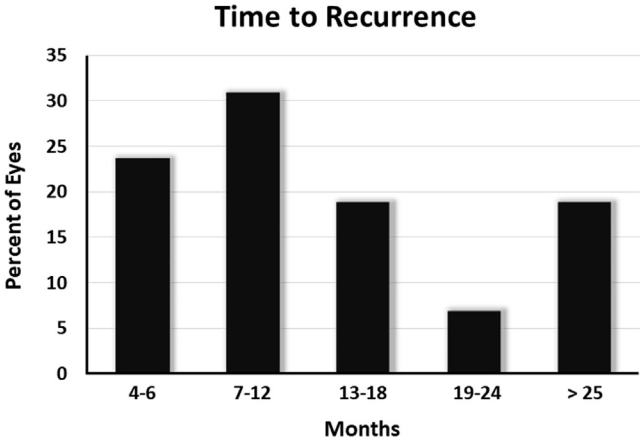

Figure 1. Bar graph showing time to choroidal neovascularization recurrence after cessation of therapy: 23.8% of eyes (10/42 eyes) recurred at 4 to 6 months, 31.0% of eyes (13/42 eyes) recurred at 7 to 12 months, 19.0% of eyes (8/42 eyes) recurred at 13 to 18 months, 7.1% of eyes (3/42 eyes) recurred at 19 to 24 months, and 19.0% of eyes recurred after 2 years.