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Recurrent Neovascular Age-Related Macular Degeneration after Discontinuation of Vascular Endothelial Growth Factor Inhibitors Managed in a Treat-and-Extend Regimen

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Purpose: To investigate the recurrence rate of active macular neovascularization in patients with neovascular age-related macular degeneration (nAMD) previously followed up in a treat-and-extend (TE) regimen in which treatment had been stopped because of disease stability.

Design: Prospective cohort study.

Participants: One hundred five patients with nAMD previously followed up in a TE regimen treated with aflibercept injections.

Methods: All patients with a dry macula on 3 consecutive visits 12 weeks apart were eligible to participate in the study. Patients were examined at baseline and then monitored for disease recurrence 4, 6, 8, 10, and 12 months after the last injection.

Main Outcome Measures: The proportion of patients with recurrent disease within 12 months after the last injection. Change in best-corrected visual acuity (BCVA) at the time of recurrence and after resumed therapy.

Results: Evidence of recurrent nAMD was seen in 54 of 102 patients (52.9%) after 12 months of follow-up. The mean time to recurrence after the last injection was 6.7 ± 2.2 months. The BCVA decreased from 71.7 ± 10.0 Early Treatment Diabetic Retinopathy Study (ETDRS) letters at baseline to 68.1 ± 11.1 ETDRS letters at the recurrence ($P = 0.12$). After treatment resumed, BCVA increased to 71.4 ± 10.0 ETDRS letters ($P =$ not significant compared with baseline). Patients with a pigment epithelial detachment (PED) at baseline showed a 74% (14/19) recurrence rate compared with 48% (40/83) in patients without a PED ($P < 0.05$). Only 22 of 54 patients (40.7%) with recurrent disease showed symptoms of visual loss or metamorphopsia.

Conclusions: Recurrent nAMD is common in previously stable patients for whom anti-VEGF injections have been suspended. It is difficult to predict which patients will experience a recurrence, and most of these patients do not show symptoms in the early stages of reactivation. Long-term follow-up is important, and early detection of recurrent disease can improve the chances for maintained visual function. *Ophthalmology Retina 2021;■ :1–6 © 2021 by the American Academy of Ophthalmology. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).*

Age-related macular degeneration is a leading cause of visual impairment and blindness among older individuals.[1] With the introduction of intravitreal anti–vascular endothelial growth factor (VEGF) injections, the visual outcome for this patient group has improved substantially.[2] During the last decade, the frequency of anti-VEGF injections has grown exponentially and today present a considerable economic burden and logistic challenge for the ophthalmologic community and health care services.[3,4] Therefore, the possibility of discontinuing therapy in patients who have shown disease stability over extended periods is of great interest.

The main treatment strategy in patients with neovascular age-related macular degeneration (nAMD) is the treat-and-extend (TE) algorithm.[5] Patients are treated at extended intervals as long as the macula is dry, and the interval is reduced with recurrent macular edema.[6] Previous retrospective studies showed variable anatomic stability after cessation of therapy with observation alone.[7,8] The purpose of this study was to investigate prospectively the recurrence rate of active macular neovascularization (MNV) and visual outcomes in patients with nAMD previously undergoing a TE regimen for whom treatment had been discontinued because of disease stability.

Methods

The study adhered to the tenets of the Declaration of Helsinki, and the regional ethical review board in Stockholm approved the

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protocol. The study is registered on www.clinicaltrials.gov (identifier, NCT04659512). All patients provided informed consent.

Study Population and Study Design

All study participants had nAMD and were treated at diagnosis with 3 monthly aflibercept injections and subsequently were followed up in a TE regimen with extensions by 2 weeks if no signs of disease activity were seen. Hemorrhage, intraretinal macular edema, or subretinal fluid seen on OCT were considered signs of disease activity. Patients reaching 12-week intervals without any evidence of disease activity on 3 consecutive visits, best-corrected visual acuity (BCVA) between 35 and 88 letters (Snellen equivalent, 20/200−20/20), and near vision of at least 24 points were eligible for study inclusion. At the baseline visit, angiographic subtype was determined according to the new consensus nomenclature for reporting nAMD (type 1 MNV, type 2 MNV, type 3 MNV, and polypoidal choroidal vasculopathy).[9] This was recorded based on previous retinal angiography (fluorescein and indocyanine green) or OCT angiography performed at the time of the first diagnosis. The distribution of lesion subtypes according to method of diagnosis is shown in Table 1. After the informed consent form was signed, eligible patients received another aflibercept injection and were followed up at 4 months and then bimonthly, with the last visit 12 months after the last injection. If signs of recurrent disease activity were found during the follow-up, the bimonthly follow-up was concluded, and intravitreal therapy was resumed. Between scheduled visits, patients were encouraged to monitor their vision at home using monocular visual assessments and were advised to return earlier than planned if symptoms of visual deterioration or metamorphopsia occurred. At baseline and at every follow-up visit, all patients underwent a full dilated ophthalmic examination. OCT images were obtained using the Zeiss Cirrus OCT instrument (Carl Zeiss Meditec, Inc., Dublin, CA). A pigment epithelial detachment (PED) was identified as an elevation of the retinal pigment epithelium band and included both serous and fibrovascular PED. OCT angiography was carried out using the AngioVue XR Avanti (Optovue, Freemont, CA) at baseline and at month 12 or at the time of disease recurrence. Patients who were extended consecutively to 12-week intervals without any episodes of recurrence were termed "rapid responders." These 56 patients received 8 anti-VEGF injections each before enrolling in the study. The BCVA was measured at a distance of 4 m (or at 1 m if needed) by ophthalmologic nurses using an Early Treatment Diabetic Retinopathy Study (ETDRS) chart. Near vision was tested at 40 cm with the addition of +3 diopters to the BCVA refraction. For near vision assessment, we used the LIX adult A chart (Ortho-KM, Lund, Sweden) graded in typographic points, the largest text being 24 points and the smallest being 4 points.

Outcome Measures

The primary outcome measure was the proportion of patients with recurrent disease within 12 months after the last injection. Secondary outcome measures included change in BCVA at the time of recurrence and after resumed therapy, effect of age, lesion type, anatomic parameters (PED, geographic atrophy [GA], and submacular fibrosis), previous episodes of recurrence, and total number of injections before suspension on risk of reactivation.

Statistical Analysis

For statistical analyses, the independent Student *t* test was used for continuous variables, and the Fisher exact test (to compare differences in distributions between the groups) was used for categorical data. For continuous variables, mean ± standard deviation was used, and counts with percentages were used for categorical variables. A *P* value of less than 0.05 was considered statistically significant.

Results

Study Population

Between October 1, 2017, and February 28, 2019, 105 patients with stable nAMD without signs of active disease were enrolled consecutively. Three patients died during the study. The remaining 102 patients completed the follow-up. Baseline characteristics are presented in Table 1.

Disease Recurrence

Evidence of recurrent nAMD was seen in 54 of 102 patients (52.9%) after 12 months of follow-up. The mean time to recurrence after the last injection was 6.7 ± 2.2 months (median, 6 months; range, 4−12 months; Fig 1). The bimonthly proportion of disease recurrence was 13%, 20%, 13%, 5%, and 3% at 4, 6, 8, 10, and 12 months, respectively. In 46 of 54 patients (85.2%), the recurrence took place during the first 8 months of follow-up. No significant age-dependent difference in risk for recurrence was found in the study cohort.

Table 1. Baseline Characteristics of the Study Population

Parameter	Study Group (n = 102)
Age (yrs)	79.8 ± 7.2
Gender (male:female)	29:73
Lesion type	
Type 1 MNV	
FA/ICGA	33 (35.3)
OCTA	3 (2.9)
Type 2 MNV	
FA/ICGA	22 (21.6)
OCTA	2 (2.0)
Type 3 MNV`	
FA/ICGA	33 (32.3)
OCTA	5 (4.9)
PCV	10 (9.8)
Undetermined	1 (1.0)
BCVA, all patients (ETDRS letters)	71.0 ± 10.2
Near vision points, all patients (median ± SD)	5 ± 4.5
Rapid responder*	56 (55)
Type 1 MNV	14 (39)†
Type 2 MNV	12 (54)†
Type 3 MNV	22 (67)†

BCVA = best-corrected visual acuity; ETDRS = Early Treatment Diabetic Retinopathy Study; FA = fluorescein angiography; ICGA = indocyanine green angiography; MNV = macular neovascularization; OCTA = OCT angiography; PCV = polypoidal choroidal vasculopathy; SD = standard deviation.
Data are presented as no. (%) or mean ± SD, unless otherwise indicated.
*Patients whose treatment were extended from 4-week intervals at the time of diagnosis to 12-week intervals without any episodes of recurrent active disease.
†Significantly more patients with a type 3 MNV were rapid responders compared with patients with a type 1 or 2 lesion: $P < 0.05$.

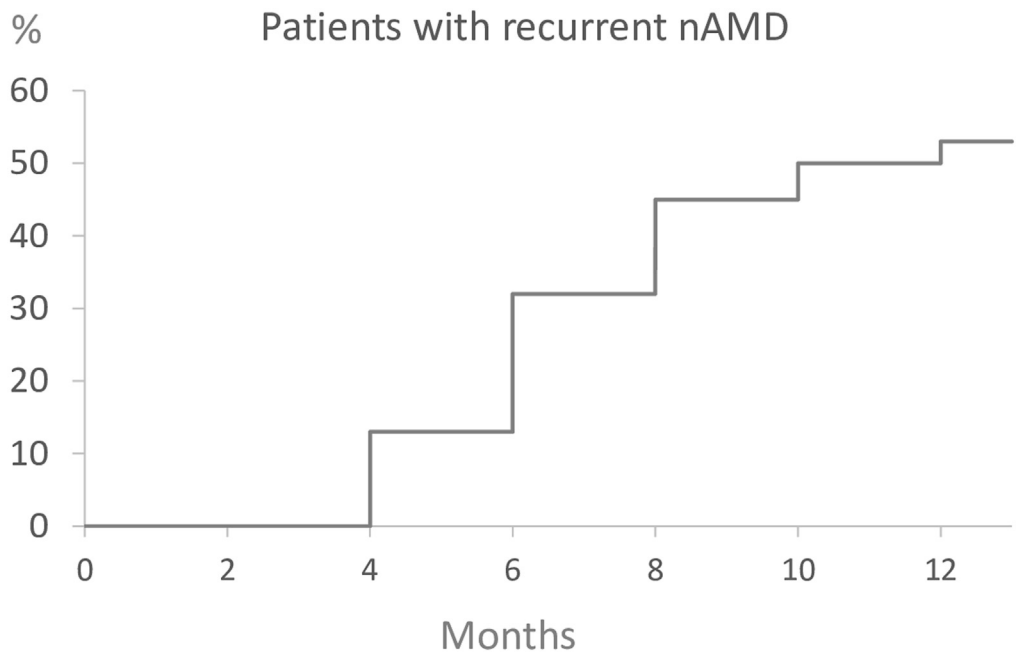

Figure 1. Kaplan-Meyer curve showing time to reactivation after treatment suspension. nAMD = neovascular age-related macular degeneration.

Visual Outcomes

Overall, in patients with recurrence, BCVA decreased from 71.7 ± 10.0 ETDRS letters (median, 72 letters; range, 43−90 letters) at baseline to 68.1 ± 11.1 ETDRS letters (median, 69 letters; range, 41−90 letters) at the time of relapse ($P = 0.12$). Of the patients with recurrent disease, 16.7% (9/54) and 5.6% (3/54) lost at least 2 and 3 ETDRS lines, respectively (median, −12 letters; range, −25 to −10 letters). After treatment was resumed, the BCVA increased to 71.4 ± 10.0 ETDRS letters (median, 74 letters; range, 44−95 letters; P = not significant [NS] compared with baseline) and only 11.1% (6/54) lost 2 ETDRS lines or more (median, −10 letters; range, −12 to −10 letters). No patients lost 3 ETDRS lines or more at the end of follow-up. Only 22 of 54 patients (40.7%) with recurrent disease showed symptoms of visual deterioration. These patients sustained a significant loss of BCVA from 73.0 ± 8.4 ETDRS letters at baseline to 65.9 ± 11.1 ETDRS letters at recurrence ($P = 0.02$). After resumed therapy, they regained BCVA to 72.4 ± 10.0 ETDRS letters (P = NS compared with baseline). The number of patients with a BCVA of 70 ETDRS letters or more (Snellen equivalent, 20/40) was 35 of 54 patients (64.8%) at baseline and 32 of 54 patients (59.3%) after resumed therapy at the end of follow-up (P = NS). The median near vision remained unchanged at 5 points from baseline to recurrence and after resumed therapy (P = NS).

Anatomic Parameters

Central retinal thickness increased from 220 ± 32 μm at baseline to 263 ± 47 μm at disease recurrence ($P < 0.001$). After resumed therapy, central retinal thickness decreased to 217 ± 32 μm (P = NS compared with baseline). Patients with a PED at baseline showed a 74% (14/19) recurrence rate compared with 48% (40/83) in patients without a PED ($P < 0.05$). Patients with GA of at least 2 disc diameters showed a 46% (21/46) recurrence rate compared with 58% (32/55) in patients without GA ($P = 0.21$). Patients with submacular fibrosis showed a 44% (4/9) recurrence rate compared with 54% (50/93) in patients without submacular fibrosis (P = NS). No lesion type was associated with an increased risk of reactivation, and no significant difference in time to recurrence was found among the different subtypes (Table 2).

Previous Injections and Earlier Recurrences

Eyes received a mean of 10.6 ± 4.4 injections before suspending therapy. Overall, we did not find an increased risk of relapse in patients with a previous recurrence or in patients who had received fewer injections. Significantly more patients with a type 3 MNV, 22 of 33 (66.7%), were rapid responders compared with patients with a type 1 or 2 lesion, 26 of 58 (44.8%; $P < 0.05$; Table 1). Twenty-nine rapid responders (51.8%) experienced a recurrence during the study compared with 25 of 46 patients (54.3%) who were not rapid responders (P = NS). In the subgroup of rapid responders, no significant differences were seen between the lesion types with regard to risk of reactivation. Of the patients with a previous recurrence before enrollment into the study, 19 of 29 patients (65.5%) experienced a relapse compared with 35 of 73 patients (47.9%) without an earlier episode ($P = 0.11$; Table 2).

Discussion

Since the introduction of anti-VEGF injections for nAMD some 15 years ago, a continuously growing patient population has needed active treatment.[10,11] This has caused an increasing logistic burden for an aging patient group but also for the health care services. Also, concerns have emerged that the prolonged use of anti-VEGF treatment exposes patients to endophthalmitis and macular atrophy.[12,13] These factors have increased the interest in

Table 2. Recurrences with Respect to Lesion Type, Age, Previous Recurrence, and Rapid Responders

Parameter	Recurrence
Lesion type	
Type 1 MNV	18/36 (50)
Type 2 MNV	13/22 (59)
Type 3 MNV	19/33 (48)
PCV	4/10 (40)
Age (yrs)	
≥80	31/54 (57)
<80	23/48 (48)
Previous recurrence	
Yes	19/29 (66)
No	35/73 (48)
Rapid responder	
Yes	29/56 (52)
No	25/46 (54)

MNV = macular neovascularization; PCV = polypoidal choroidal vasculopathy.
Data are presented as no./total no. (%). No significant differences were seen in recurrence rate in any parameter.

exploring the outcomes of suspending therapy in eyes that have shown inactive disease for a substantial period. We investigated the outcomes in a cohort of patients who had shown disease stability during 3 subsequent 12-week intervals in a TE regimen. We found that 53% of the patients showed evidence of recurrent macular edema within 12 months after discontinuation of injections. Information in the literature regarding patients who terminate therapy previously followed up in a TE protocol is sparse. Five-year data from the Comparison of Age-Related Macular Degeneration Treatments Trials showed that 15% of the patients did not receive any treatment at the end of follow-up.[14] In a retrospective single-center study, Adrean et al[7] noted a recurrence rate of 29% within 1 year after the treatment had been stopped at the third dry 12-week visit. In a recent study using data from the Fight Retinal Blindness! Registry, 41% of the patients showed disease reactivation in the first year of follow-up.[8] Wakazono et al[15] examined retrospectively the recurrence of MNV lesion activity after 1 year of fixed-regimen treatment with aflibercept. They found that 44% of the patients showed recurrent disease within 1 year after injections were suspended. We found a similar high recurrence rate in our study. The prospective design of our study with predetermined bimonthly control participants may explain the slightly higher incidence. This adds to the evidence that nAMD is a chronic disease that requires continuous and long-term follow-up.

The optimal exit strategy of suspending treatment in patients with inactive nAMD is unclear. In our study, we used 3 consecutive 12-week intervals as stability criteria. Given the high number of recurrences, it is possible that the intervals need to be extended longer before treatment can be terminated. A retrospective study using 3 consecutive injections with an interval of 16 weeks with stable findings as exit criteria showed a recurrence rate of only 13%.[16] However, a strong possibility exists that many cases were missed because the mean follow-up was only 9 months. Furthermore, in our study, signs of recurrent disease occurred in 76% of patients after more than 4 months and in 39% of patients after more than 6 months of follow-up. Extending intervals between treatments also increases the risk of recurrence. Essex et al[17] reported a reactivation of 37% at treatment intervals of 20 weeks or more using data from the Fight Retinal Blindness! Registry. However, our results also indicate that almost half the patients would have been overtreated if a TE regimen had been continued after the 3 consecutive 12-week intervals. This must be weighed against the risk of stopping treatment and a recurrence with visual impairment resulting. Unfortunately, an obvious and completely safe exit strategy when suspending therapy in nAMD does not seem to exist. This emphasizes the importance of frequent examinations during the first year after treatment has been terminated.

A close follow-up after treatment suspension also may increase the possibility of a good visual outcome. At the end of follow-up, 59% of eyes showed a BCVA of 20/40 or better, which was statistically unchanged compared with baseline. In our cohort with a bimonthly follow-up regimen, patients showed a recovery to baseline BCVA when the treatment was resumed. Similarly, Adrean et al[7] reported good visual recovery after treatment resumption when increasing follow-up intervals from 4 weeks in stepwise fashion up to 12-week intervals. In a retrospective analysis of data from the Fight Retinal Blindness! Registry, Nguyen et al[8] found significant vision loss after lesion reactivation that recovered only partly after resuming therapy. However, the regularity of patient monitoring and the assessment of lesion activity were at the discretion of the treating physician. Thus, it is possible that missed detection of lesion activity and delayed treatment caused a less favorable visual outcome. The Lucentis Compared to Avastin clinical trial showed that some patients following a TE regimen experienced irreversible visual deterioration when extended to 12 weeks even with ongoing treatment.[6] Hence, long intervals between disease monitoring may have a negative effect on the visual outcome.

A proactive follow-up approach is necessary in this patient group when treatment is suspended. Only 41% of the patients with recurrent disease showed symptoms of visual loss or metamorphopsia. Early signs of macular edema may not cause any visual symptoms but will be detected on an OCT scan. Spectral-domain OCT has been shown to have a sensitivity of fluid detection of more than 90% and remains the mainstay for nAMD detection.[18,19] However, a substantial proportion of patients without recurrent disease will report visual deterioration caused by GA, cataract progression, or other diseases. It is common that GA develops within an nAMD lesion in eyes receiving anti-VEGF therapy.[20,21] Forty-five percent of our cohort showed significant GA of at least 2 disc diameters when treatment was suspended. Hence, it is almost impossible to rely on patients' perceived visual deterioration when determining if it is caused by recurrent nAMD or advanced macular atrophy.

We found that 32% of the patients in the study demonstrated a type 3 MNV at the first diagnosis. This is a larger proportion than expected. Data from the Swedish Macula Registry, a nationwide database of patients treated for nAMD, showed that 14% of the patients harbored a type 3 MNV at diagnosis.[22] The higher representation of type 3 MNV in our study shows that these lesions respond well to TE follow-up and may reach 12-week intervals faster than other subtypes. This is consistent with the fact that patients with type 3 MNV lesions respond significantly more rapidly without any episodes of disease recurrence before the study baseline.

We did not find that any lesion subtype showed a higher risk of disease recurrence, but patients with a PED at baseline demonstrated a significantly higher risk of reactivation. Seventy-five percent of patients with a PED experienced disease recurrence within 1 year. This is consistent with previous observations that the presence of PED may indicate more active disease. The MONT BLANC study[23] reported that PED was associated with an increase in retreatment frequency, and Schmidt-Erfurth et al[24] showed that patients with baseline PED were more likely to experience recurrences when shifted to a variable-dosing regimen. Thus, it seems that PED can be a useful imaging marker for predicting risk for recurrent nAMD. The key strengths of this study are the prospective design, the very low dropout rate, and the strict bimonthly follow-up protocol. The size of the cohort could be a limitation of the study. Some potential risk factors for reactivation like previous recurrence of nAMD and absence of GA did not fully meet statistical significance. It is possible that the study did not have the power to expose these outcomes and that a larger sample size could have affected these results.

In conclusion, we found that disease recurrence is very common in patients with nAMD during the first year after treatment suspension. A close follow-up can preserve the visual gains previously obtained if treatment is resumed promptly. It is difficult to predict which patients will experience a recurrence, and most of these patients do not show symptoms in the early stages of reactivation. This necessitates continuous long-term monitoring for all patients with useful vision in the context of nAMD.

Footnotes and Disclosures

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HUMAN SUBJECTS: Human subjects were included in this study. The regional ethical review board in Stockholm approved the study. All research adhered to the tenets of the Declaration of Helsinki. All participants provided informed consent.

ANIMAL SUBJECTS: No animal subjects were included in this study.

Author Contributions:

Conception and design: Aslanis, Amrén, Lindberg, Epstein

Analysis and interpretation: Aslanis, Amrén, Lindberg, Epstein

Data collection: Aslanis, Amrén, Lindberg, Epstein

Obtained funding: N/A

Overall responsibility: Aslanis, Amrén, Lindberg, Epstein

Abbreviations and Acronyms:
BCVA = best-corrected visual acuity; **ETDRS** = Early Treatment Diabetic Retinopathy Study; **GA** = geographic atrophy; **MNV** = macular neovascularization; **nAMD** = neovascular age-related macular degeneration; **NS** = not significant; **PED** = pigment epithelial detachment; **TE** = treat-and-extend; **VEGF** = vascular endothelial growth factor.

Keywords:
Anti-VEGF, Neovascular age-related macular degeneration, Recurrence, Treat-and-extend regimen.

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