NATURAL COURSE OF PATIENTS DISCONTINUING TREATMENT FOR AGE-RELATED MACULAR DEGENERATION AND FACTORS ASSOCIATED WITH VISUAL PROGNOSIS

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Purpose: To evaluate the 24-month natural course of visual changes in patients discontinuing treatment despite persistent or recurrent fluid and factors predictive of visual prognosis.

Methods: This retrospective, observational study included 35 patients (35 eyes) who initially received anti-vascular endothelial growth factor treatment for neovascular age-related macular degeneration (AMD), but discontinued treatment despite persistent or recurrent fluid. The best-corrected visual acuity (BCVA) at treatment discontinuation was determined and compared with the 24-month BCVA, which was then compared between polypoidal choroidal vasculopathy and other neovascular age-related macular degeneration subtypes. Baseline characteristics predictive of visual outcome and the degree of visual change were also analyzed.

Results: The mean number of anti-vascular endothelial growth factor injections before treatment discontinuation was 4.0 ± 1.6. The mean logarithm of minimal angle of resolution of BCVA at treatment discontinuation and that at 24 months were 1.02 ± 0.20 (Snellen equivalents = 20/209) and 1.60 ± 0.56 (20/796), respectively ($P < 0.001$). The 24-month BCVA was not different between polypoidal choroidal vasculopathy and other neovascular age-related macular degeneration subtypes ($P = 0.803$). The type of fluid (intraretinal fluid vs. no intraretinal fluid) was predictive of 24-month BCVA ($P = 0.004$) and the degree of changes in BCVA ($P = 0.043$).

Conclusion: Marked deterioration in visual acuity was noted in patients discontinuing treatment, regardless of neovascular age-related macular degeneration subtypes. The presence of intraretinal fluid was associated with worse visual prognosis, suggesting that patients with intraretinal fluid should be strongly warned about their poor prognosis before they decide to discontinue treatment.

RETINA 37:2254–2261, 2017

Intravitreal anti-vascular endothelial growth factor (VEGF) therapy is an effective treatment for neovascular age-related macular degeneration (AMD).[1–3] Previous studies have shown that this treatment is also effective in polypoidal choroidal vasculopathy (PCV).[4–6] However, one limitation of anti-VEGF therapy was that the recurrence of fluid occurs in the majority of eyes.[7] Prompt additional injection is required to prevent visual deterioration of these eyes.

In clinical practice, we sometimes encounter patients who refuse additional anti-VEGF injections despite persistent or recurrent fluid.[8,9] The reasons for this reluctance may include economic burden, poor general condition, poor treatment outcome, or a fear of needles. Some patients are reluctant to undergo an invasive procedure unless there is a guarantee the treatment will improve their vision. Some of these

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Supported by Kim's Eye Hospital Research Center.

None of the authors has any conflicting interests to disclose.

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patients require answers to questions like "What happens next if I do not receive additional treatment?" or "How fast will my vision deteriorate?" before they decide to receive additional treatment, because they think this information is important in determining whether to receive additional treatment.

The natural history of neovascular AMD is generally unfavorable.[10] Thus, it seems obvious that the visual acuity of patients discontinuing treatment deteriorates over time. However, to the best of our knowledge, the speed and amount of visual deterioration following treatment discontinuation has not yet been reported. These data may provide useful information that can be used by clinicians when discussing treatment plans and visual prognosis with their patients.

The purpose of the present study was to evaluate the 24-month natural course of visual changes in patients who initially received anti-VEGF treatment for neovascular AMD, but discontinued treatment despite persistent or recurrent fluid. In addition, factors predictive of long-term visual prognosis were investigated.

Methods

This retrospective, observational case study was performed at a single center. The study was approved by the Institutional Review Board of Kim's Eye Hospital (Seoul, South Korea) and was conducted in accordance with the tenets of the Declaration of Helsinki.

Patients

The present study included patients who were diagnosed with treatment naive neovascular AMD between September 2009 and January 2014 at our institution. Additional inclusion criteria included 1) administration of anti-VEGF monotherapy using either ranibizumab (Lucentis; Genentech, Inc, South San Francisco, CA) or bevacizumab (Avastin; Genentech, Inc) before treatment discontinuation, 2) treatment discontinuation determined during the follow-up despite persistent or recurrent fluid on optical coherence tomography (OCT), and 3) a follow-up period of at least 24 months or longer without treatment.

All patients had undergone a comprehensive initial ophthalmologic examination, including measurement of best-corrected visual acuity (BCVA), 90-diopter (D) lens slit-lamp biomicroscopy, fundus photography, fluorescein angiography, spectral domain OCT (either Spectral OCT/SLO; OTI Ophthalmic Technologies Inc, Toronto, ON, Canada, or Spectralis; Heidelberg Engineering GmbH, Heidelberg, Germany). Indocyanine green angiography (ICGA) was performed at the discretion of the treating physician by using a confocal laser-scanning system (HRA-2; Heidelberg Engineering GmbH). The exclusion criteria included 1) disciform scar, fibrosis, or geographic atrophy, making up >50% of the total lesion or involving the center of the fovea; 2) severe media opacity; 3) −6.0 D or greater myopia or an axial length of 26.0 mm or greater; 4) concomitant retinal vascular disorders (e.g., macroaneurysms, proliferative diabetic retinopathy, or central retinal vascular occlusion); and 5) history of photodynamic therapy or intraocular surgery except cataract surgery.

Examination and Treatment

The included eyes were initially treated with intravitreal ranibizumab (0.5 mg/0.05 mL). Afterwards, patients were scheduled to visit the hospital every 1 month to 3 months at the discretion of the treating physician. Retreatment with intravitreal anti-VEGF—either ranibizumab (0.5 mg/0.05 mL) or bevacizumab (1.25 mg/0.05 mL)—was considered in cases with remaining intraretinal/subretinal fluid after initial treatment, reaccumulation of subretinal or intraretinal fluid after the fluid had completely resolved, or retinal/subretinal hemorrhage. The cost, benefit, and potential complications regarding the treatment were fully discussed with the patients. Additional treatment was not performed when the patient refused additional treatment despite sufficient explanation that their visual acuity can deteriorate and the chance to recover their vision may decrease if additional treatment is not performed. These patients were then followed-up every 2 months to 6 months at the discretion of the treating physician.

Two independent examiners (Y.S.C. and J.H.K.) analyzed the indocyanine green angiography, OCT, and fundus photography images. Polypoidal choroidal vasculopathy was diagnosed by the presence of polypoidal lesions with or without branching vascular networks.[11,12] As previously suggested,[13–15] Type 3 neovascularization was diagnosed on the basis of multi-modal imaging. Geographic atrophy was defined as round or ovular, well-demarcated areas with decreased pigmentation and increased visibility of the underlying choroid on fundus photographs, accompanied by increased choroidal penetration on OCT. Any disagreement between the examiners was settled by discussion.

Outcome Measures

The BCVA values measured when treatment discontinuation was determined (baseline BCVA),

at 6 months, 12 months, and 24 months after treatment discontinuation were recorded. If patient follow-up was not performed at the exact time point, the values measured at the closest follow-up were used. The BCVAs were compared among the four time points. The BCVAs were converted to the logarithm of the minimal angle of resolution (logMAR) value for analysis. As recommended by Holladay,[16] the counter finger and hand motion visual acuities were converted to logMAR values 2 and 3, respectively.

To evaluate baseline factors associated with final visual outcome, multivariate analysis was performed including the following factors: patients' age, sex, type of neovascularization, type of fluid, duration between diagnosis and treatment discontinuation, and number of anti-VEGF injections before treatment discontinuation. Baseline factors were measured when treatment discontinuation was determined. In the present study, mixed Type 1 and 2 lesions were determined as Type 2. In addition, mixed Type 1 and 3 lesions were determined as Type 3. Type of fluid was classified as follows: subretinal fluid only versus intraretinal fluid with or without subretinal fluid. Lesions mimicking intraretinal fluid, such as cystoid macular degeneration[17] or outer retinal tubulation,[18] were not considered to have intraretinal fluid. The diagnosis of cystoid macular degeneration was based on the morphologic finding on OCT using a previously suggested method.[17] Intraretinal cystic lesion with at least one concave or straight border was diagnosed as cystoid macular degeneration.

In patients with available indocyanine green angiography results, baseline BCVA, BCVA at 24 months, and degree of changes in BCVA were compared between PCV and other subtypes of neovascular AMD.

Statistics

Data are presented as mean ± SD, where applicable. Statistical analyses were performed using a commercially available software package (SPSS version 12.0 for Windows; SPSS Inc, Chicago, IL). Differences at various time points were analyzed using repeated-measures analysis of variances, and individual comparisons were made using Bonferroni's method. Difference between the two groups was analyzed using independent samples *t*-test or Mann–Whitney *U* test with or without Bonferroni's correction. The chi-square test was additionally used to compare categorical variables between the two groups. For multivariate analysis, stepwise linear regression was performed. A P value <0.05 was considered significant.

Results

Among the 64 patients who met the eligibility criteria, 29 (45.3%) were lost to follow-up before 24 months. As a result, 35 eyes (35 patients; 18 men, 17 women) were included in the study. Table 1 compares baseline characteristics of the patients that were included and those lost to follow-up. Table 2 summarizes the incidence of retinal pathologic lesions before and after treatment discontinuation.

Baseline BCVA, and BCVA at 6 months, 12 months, and 24 months after treatment discontinuation were 1.02 ± 0.20 (Snellen equivalents = 20/209), 1.16 ± 0.28 (20/289), 1.38 ± 0.35 (20/479), and 1.60 ± 0.56 (20/796), respectively (Figure 1A). When compared with the baseline BCVA, the BCVAs at 6 months ($P = 0.008$), 12 months ($P < 0.001$), and 24 months ($P < 0.001$) were significantly worse. At 24 months, deterioration of ≥3 lines of BCVA was noted in 28 eyes (80.0%), whereas deterioration of <3 lines of BCVA was noted in three eyes (8.6%). The remaining 4 eyes (11.4%) exhibited stable BCVA. When treatment discontinuation was determined, 6 eyes (17.1%) had BCVA 20/100; 19 (54.3%) had BCVA ≥20/200, <20/100; and 10 (28.6%) had BCVA ≥20/400, <20/200 (Figure 1B). None of the eyes had BCVA <20/400. At 24 months, 6 eyes (17.1%) had BCVA ≥20/200, <20/100; 13 (37.1%) had BCVA ≥20/400, <20/200; and 16 (45.7%) had BCVA <20/400 (Figure 1B). No eye had BCVA 20/100 or better. In 29 patients lost-to follow-up, the mean follow-up period after treatment discontinuation was 13.0 ± 5.1 months. The mean BCVA at baseline was 0.94 ± 0.22 (20/174), and the mean at the last visit was 1.27 ± 0.53 (20/372).

In multivariate analysis, one factor, i.e., the type of fluid, was found to be significantly associated with final visual acuity (Table 3) as well as the degree of visual deterioration during the follow-up period (Table 4). More specifically, eyes with subretinal fluid only showed better visual acuity at 24 months and lower degree of visual deterioration during the follow-up period than did eyes with intraretinal fluid with or without subretinal fluid. Figure 2 shows differences in BCVA outcomes between eyes with subretinal fluid only and those with intraretinal fluid only or a combination of intraretinal/subretinal fluid. The BCVA at baseline and at 24 months was 0.95 ± 0.23 (20/178) and 1.34 ± 0.38 (20/437), respectively, in eyes with subretinal fluid only. The values were 1.06 ± 0.19 (20/229) and 1.79 ± 0.60 (20/1,233) in eyes with intraretinal fluid only

Table 1. Results of Comparisons of Baseline Characteristics Between the Included Patients and Patients Lost to Follow-up

Characteristic	Included Patients (n = 35)	Patients Lost to Follow-up (n = 29)	*P*
Age, years	69.7 ± 9.8	72.0 ± 7.9	0.329*
Sex, n (%)			0.565†
Men	18 (51.4)	17 (58.6)	
Women	17 (48.6)	12 (41.4)	
Type of neovascularization, n (%)			1.000†
Type 1	23 (65.7)	18 (62.1)	
Type 2 with or without type 1	7 (20.0)	7 (24.1)	
Type 3	5 (14.3)	4 (13.8)	
ICGA-based classification,‡ n (%)			0.907†
Typical neovascular AMD	13 (44.8)	9 (39.1)	
Polypoidal choroidal vasculopathy	11 (37.9)	10 (43.5)	
Type 3 neovascularization	5 (17.2)	4 (17.4)	
Type of fluid, n (%)			0.348†
Subretinal fluid only	14 (40.0)	15 (51.7)	
Intraretinal fluid with or without subretinal fluid	21 (60.0)	14 (48.3)	
Duration between diagnosis and treatment discontinuation	7.4 ± 3.7	7.8 ± 3.4	0.694*
No. of anti-VEGF injections before treatment discontinuation	4.0 ± 1.6	4.3 ± 1.4	0.481*
BCVA when treatment discontinuation was determined, logMAR (Snellen equivalents)	1.02 ± 0.20 (20/209)	0.94 ± 0.22 (20/174)	0.174*

The data are presented as the mean ± SD where applicable.
*Statistical analysis was performed using independent samples *t*-test.
†Statistical analysis was performed using chi-square test.
‡Data from 52 patients (29 included patients and 23 excluded patients) with available indocyanine green angiography (ICGA) findings are presented.
AMD, age-related macular degeneration; BCVA, best-corrected visual acuity; logMAR, logarithm of the minimal angle of resolution; VEGF, vascular endothelial growth factor.

or a combination of intraretinal/subretinal fluid, respectively. There was no difference in baseline BCVA between eyes with subretinal fluid only and those with intraretinal fluid only or a combination of intraretinal/subretinal fluid (Figure 2A, $P = 0.276$). However, the BCVA at 24 months was significantly better in eyes with subretinal fluid only ($P = 0.030$).

In 11 eyes diagnosed as having PCV, the baseline BCVA and BCVA at 24 months were 0.91 ± 0.19 (20/162) and 1.52 ± 0.63 (20/662), respectively. In 18 eyes diagnosed as having either typical neovascular AMD or Type 3 neovascularization, the baseline BCVA and BCVA at 24 months were 1.09 ± 0.19 (20/246) and 1.47 ± 0.36 (20/590), respectively. The baseline BCVA was significantly better in PCV than in other subtypes of neovascular AMD ($P = 0.021$). However, there was no difference in the 24-month BCVAs between the two groups ($P = 0.803$). In addition, the degree of changes in BCVA during the 24-month follow-up was not different between the two groups ($P = 0.169$).

Discussion

In the present study, we first evaluated the long-term visual prognosis in patients with neovascular AMD who initially received anti-VEGF therapy, but discontinued

Table 2. Incidence of Retinal Pathologic Lesions When Treatment Discontinuation Was Determined and 24 Months After Treatment Discontinuation

Lesions	When Treatment Discontinuation Was Determined, No. of Eyes (%)	24 Months After Discontinuation, No. of Eyes (%)
Subretinal fluid only	14 (40.0)	7 (20.0)
Intraretinal fluid without subretinal fluid	9 (25.7)	12 (34.3)
Combination of intraretinal/subretinal fluid	12 (34.3)	9 (25.7)
Fovea-involving disciform scar	0	18 (51.4)
Fovea-involving geographic atrophy	0	9 (25.7)

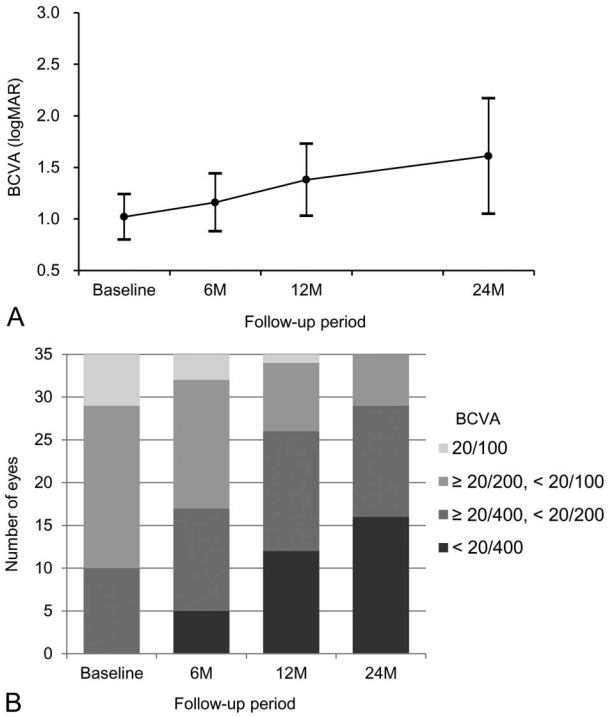

Fig. 1. A. Changes in best-corrected visual acuity (BCVA) in eyes discontinued treatment for neovascular age-related macular degeneration, according to the follow-up period (n = 35). B. Distribution of eyes according to the BCVA when treatment was discontinued (baseline) and at 6, 12, and 24 months (M) after the treatment discontinuation.

treatment thereafter. The visual prognosis was discouraging, with the majority of the patients showing deterioration of ≥3 lines of BCVA. At 24 months, only 17.1% of patients achieved 20/200 or better visual acuity, whereas the proportion was 71.4% when treatment discontinuation was determined. The poor prognosis was noted regardless of neovascular AMD subtypes. The presence of intraretinal fluid was strongly associated with worse visual prognosis.

The location of fluid is known to be associated with different visual outcomes in neovascular AMD. In a previous study based on CATT (Comparison of Age-related macular degeneration Treatment Trials) data, residual intraretinal fluid was associated with worse visual acuity,[19,20] whereas subretinal fluid was associated with better visual acuity.[20] In addition, Gianniou et al[21] reported that refractory intraretinal fluid (i.e., a refractory cyst) was associated with poorer anatomical and functional outcomes than was subretinal fluid. Compared with eyes without intraretinal fluid, eyes with intraretinal fluid started with a lower level of baseline BCVA and showed higher rate of loss of 10 Early Treatment Diabetic Retinopathy Study letters. In the study by Jang et al,[22] good and maintained visual improvement was noted in eyes with refractory subretinal fluid even if the fluid was located subfoveally. Schmidt-Erfurth and Waldstein[23] hypothesized that the presence of subretinal fluid without simultaneous manifestation of intraretinal fluid may be suggestive of a less aggressive or even supportive stage of choroidal neovascularization. The results of the present study are in line with these previous observations; the amount of visual deterioration was lower and the visual prognosis was less worse in eyes with subretinal fluid only than in eyes with intraretinal fluid even after treatment discontinuation. This result suggests that patients with intraretinal fluid should be more strongly warned of their poor prognosis before they decide to discontinue treatment.

One of the notable findings of the present study was the poor visual outcome in patients with PCV. Polypoidal choroidal vasculopathy is a distinct type of choroidal neovascularization that is characterized by polypoidal lesions on indocyanine green angiography with or without branching vascular networks.[11,12] One of the characteristics of PCV that is distinguished from other subtypes of neovascular AMD was that the natural course of PCV is relatively favorable.[24,25] In some patients with PCV, visual acuity remained stable or even improved

Table 3. Association Between Baseline Factors Measured When Treatment Discontinuation Was Determined and Best-Corrected Visual Acuity at 24 Months After Treatment Discontinuation

Factor	*P**	β	95% Confidence Intervals
Age, years	0.793		
Sex, male:female	0.235		
Type of neovascularization	0.991		
Type of fluid	0.004	0.470†	0.179–0.888
Duration between diagnosis and treatment discontinuation	0.459		
No. of anti-VEGF injections before treatment discontinuation	0.482		
BCVA when treatment discontinuation was determined	0.150		

*Statistical analysis with multivariate stepwise linear regression.

†A positive value indicates that the eyes with subretinal fluid only showed better visual acuity at 24 months than did eyes with intraretinal fluid with or without subretinal fluid.

BCVA, best-corrected visual acuity; VEGF, vascular endothelial growth factor.

Table 4. Association Between Baseline Factors Measured When Treatment Discontinuation Was Determined and Amount of Decrease in Best-Corrected Visual Acuity During 24 Months After Treatment Discontinuation

Factor	*P**	β	95% Confidence Intervals
Age, years	0.668		
Sex, male:female	0.178		
Type of neovascularization	0.792		
Type of fluid	0.043	−0.336†	−0.696 to −0.003
Duration between diagnosis and treatment discontinuation	0.539		
No. of anti-VEGF injections before treatment discontinuation	0.579		
BCVA when treatment discontinuation was determined	0.434		

*Statistical analysis with multivariate stepwise linear regression.
†A negative value indicates that the eyes with subretinal fluid only experienced lesser degree of visual deterioration than did eyes with intraretinal fluid with or without subretinal fluid.
BCVA, best-corrected visual acuity.

without any treatment.[24,25] However, this relatively favorable prognosis was not noted in our patients who discontinued treatment. One potential explanation is that only recurrent cases were included in the present study. Recently, Kuroda et al reported that 34.3% of the patients with neovascular AMD who were initially treated with three ranibizumab injections experienced no recurrence during the first year.[26] It is possible that recurrent cases may have a more aggressive disease activity. In the present study, the analysis was performed with only 11 PCV cases. Thus, the possibility of selection bias should be considered when interpreting the results. Further studies with a larger study population and consecutive series of patients are required to confirm our findings.

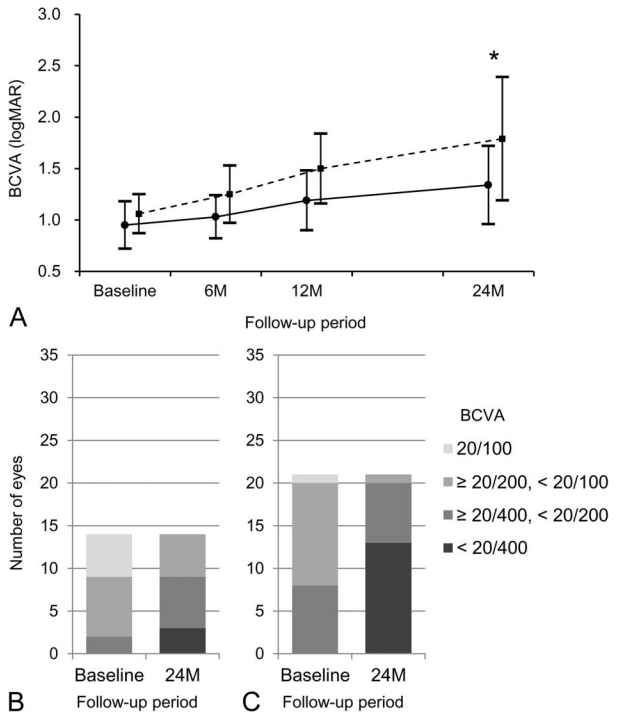

Fig. 2. A. Changes in best-corrected visual acuity (BCVA) in eyes that discontinued treatment for neovascular age-related macular degeneration, according to the follow-up period when divided into two groups based on the type of fluid. Closed circle (solid line) indicates eyes with subretinal fluid only, whereas a closed square (dashed line) indicates eyes with intraretinal fluid with or without subretinal fluid. *Statistically significant difference between the two groups. Distribution of eyes according to the BCVA when treatment was discontinued and at 24 months after the discontinuation in eyes with subretinal fluid only (**B**) and in eyes with intraretinal fluid with or without subretinal fluid (**C**).

It is well known that decreased visual acuity caused by AMD can lead to a decline in the quality of life.[27] In addition, poorer visual acuity was associated with greater restriction of participation in daily living.[28] Thus, visual rehabilitation is one of the important issues in treating patients with AMD. Previous studies have shown that patients with better residual visual function can have more benefit from visual rehabilitation.[29,30] In the study by Nguyen et al,[29] patients with 20/200 or better visual acuity showed significantly greater improvements in reading speed after the provision of low vision aid than did patients with worse visual acuity. In the other study of Wang et al,[30] greater improvement in visual function were noted for patients with visual acuity between 20/200 and 20/60 than in patients with worse visual acuity. In the present study, the proportion of eyes with 20/200 or better visual acuity markedly decreased from 71.4%, when treatment discontinuation was determined, to 17.1% at 24 months. This result suggests that the treatment discontinuation has a negative effect on visual rehabilitation and the visual prognosis itself.

This study has several limitations. The study was retrospective in nature and the sample size was small. Among the patients who met the eligibility criteria, 45.3% were lost to follow-up, and the analyses were performed only on the remaining 54.7% of patients. Oishi et al[31] reported that poor baseline visual acuity was observed in association with cessation of treatment for neovascular AMD. This suggests that baseline characteristics are associated with the patients'

behavior regarding treatment compliance. In the present study, the baseline characteristics were comparable in patients who were included and those lost to follow-up. In addition, the mean BCVA at the last visit (mean of 13 months) of the patients lost to follow-up was comparable to the BCVA of the included patients at 12 months. For this reason, we believe that selection bias may not significantly influence the study results. In this study, only patients treated with anti-VEGF monotherapy were included. Thus, the natural course of patients who received other treatments, such as photodynamic therapy, may differ from that of our patients. Lastly, all the included patients showed 20/100 or worse visual acuity when the treatment discontinuation was determined. Thus, our result may not be value for patients with better visual acuity.

In summary, we evaluated the long-term natural course of patients who discontinued treatment for neovascular AMD. During the 24-month follow-up period, marked deterioration in visual acuity was noted, regardless of subcategory of neovascular AMD. In addition, the visual deterioration was more prominent in eyes with intraretinal fluid. The results of the present study do not provide any guideline regarding which patients should be treated or not. The additional treatment should be encouraged for all patients with persistent or recurrent fluid. Our results may provide useful information to the clinician when patients want to discuss how their vision would change if they do not receive additional treatment.

Key words: age-related macular degeneration, natural course, polypoidal choroidal vasculopathy, anti-vascular endothelial growth factor, intraretinal fluid, subretinal fluid.

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