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Original Article

Intravitreal Anti-vascular Endothelial Growth Factor for Typical Exudative Age-related Macular Degeneration in Eyes with Good Baseline Visual Acuity

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Purpose: To investigate 12-month treatment outcomes of anti-vascular endothelial growth factor therapy in eyes with typical exudative age-related macular degeneration with good baseline visual acuity.

Methods: This retrospective observational case series included 18 eyes (18 patients) with typical exudative age-related macular degeneration with a baseline best-corrected visual acuity of 20 / 25 or better. Patients were treated with anti-vascular endothelial growth factor monotherapy during the 12-month follow-up period. Baseline visual acuity and central foveal thickness were compared to the values at 12 months.

Results: Patients received an average of 4.4 ± 1.3 intravitreal anti-vascular endothelial growth factor injections. The mean logarithm of minimum angle of resolution visual acuity was 0.08 ± 0.04, 0.08 ± 0.07, 0.12 ± 0.09, and 0.16 ± 0.11 at baseline, three months, six months, and 12 months, respectively. Visual acuity at 12 months was significantly worse than the baseline value at diagnosis (p = 0.017), and the mean central foveal thickness at the defined time points was 270.2 ± 55.6, 204.4 ± 25.4, 230.1 ± 56.3, and 216.8 ± 48.7 μm, respectively. The central foveal thickness at 12 months was significantly less than the baseline value at diagnosis (p = 0.042).

Conclusions: Deterioration in visual acuity was noted in eyes with typical exudative age-related macular degeneration with good baseline visual acuity, suggesting the need for close patient monitoring and prompt treatment even in patients with good baseline visual acuity.

Key Words: Anti-vascular endothelial growth factor, Bevacizumab, Good visual acuity, Macular degeneration, Ranibizumab

Intravitreal anti-vascular endothelial growth factor (VEGF) therapy has been extremely effective in maintaining or improving visual acuity in patients with exudative age-related macular degeneration (AMD) [1-3]. This therapy has also been shown to be effective in patients with good baseline visual acuity [4-7]. However, in most previous studies, treatment outcome in eyes with good baseline visual acuity were analyzed together, regardless of the exudative AMD subtype [4-6,8].

Treatment outcome may differ among exudative AMD subtypes [9,10]. One study examined 12-month visual outcomes in eyes with polypoidal choroidal vasculopathy (PCV) and good baseline visual acuity [7], but outcomes in eyes with typical exudative AMD and good baseline visual

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acuity remain to be elucidated.

The purpose of the present study was to evaluate the 12-month treatment outcome of intravitreal anti-VEGF therapy in eyes with typical exudative AMD and good baseline visual acuity (20 / 25 or better).

Materials and Methods

This retrospective, observational case series was performed at a single center and adhered to the tenets of the Declaration of Helsinki. The study was approved by our institutional review board. The medical records of patients with newly diagnosed exudative AMD between September 2009 and December 2012 were reviewed.

To be included in the study, subjects were required to have undergone a comprehensive initial ophthalmologic examination, including best-corrected visual acuity (BCVA) measurement, 90-diopter lens slit-lamp biomicroscopy, fundus photography, fluorescein angiography, spectral domain optical coherence tomography (OCT; Spectral OCT/SLO, OTI Ophthalmic Technologies Inc., Miami, FL, USA), and indocyanine green angiography (ICGA; HRA-2 confocal laser-scanning system, Heidelberg Engineering, Dossenheim, Germany). Eyes with branching vascular networks and/or terminating polypoidal lesions on ICGA were considered to have PCV and were excluded from analyses. All remaining eyes were diagnosed with typical exudative AMD. Patients diagnosed with typical exudative AMD and treated with intravitreal anti-VEGF for up to 12 months following diagnosis were included. Only eyes with baseline BCVA of 20 / 25 or better were included.

Exclusion criteria included less than 12 months of follow-up, severe media opacity, previous history of intraocular surgery (except cataract surgery), macroaneurysm, proliferative diabetic retinopathy, central retinal vascular occlusion, or any other retinal disorder that could influence macular microstructure and/or function. Eyes that had undergone other treatment for exudative AMD (e.g., photodynamic therapy) were also excluded so that only treatment-naïve eyes were included in our analyses.

All included eyes were treated with intravitreal ranibizumab for three consecutive months as an initial treatment. Afterward, patients were scheduled to visit the hospital once every one to three months, at clinician discretion. An OCT examination was also performed every one to three months, at the treating physician's discretion. Fluorescein angiography and ICGA were also performed after initial treatment, again at the treating physician's discretion. Re-treatment with intravitreal anti-VEGF (either ranibizumab or bevacizumab) was performed when intraretinal fluid, subretinal fluid, or retinal/subretinal hemorrhage developed accompanied by a central foveal thickness (CFT) exceeding approximately 300 μm. Re-treatment was also performed when visual acuity deteriorated, even if the CFT was less than 300 μm.

CFT was measured on OCT images and was defined as the distance between the internal limiting membrane and Bruch's membrane at the fovea; it was manually measured using the built-in calipers in the OCT software program. The BCVA was converted to logarithm of minimal angle of resolution (logMAR) scale for analyses. Baseline BCVA and CFT were compared with those measured three, six, and 12 months after treatment.

Data are presented as mean ± standard deviation, where applicable. Statistical analyses were performed using a commercially available software package (SPSS ver. 12.0; SPSS Inc., Chicago, IL, USA). Differences in values at various time points were analyzed using a repeated-measures analysis of variance with a Bonferroni correction. A p-value <0.05 was considered statistically significant.

Results

A total of 26 eyes (26 patients) were newly diagnosed with typical exudative AMD with an initial visual acuity of 20 / 25 or better. Eight of 26 eyes (30.7%) were excluded: five for a follow-up duration of less than 12 months and three for inadequate OCT images. Ultimately, 18 eyes from 18 patients (69.2%) were included in analyses (Table 1). Thirteen patients (72.2%) were men, and five (27.8%) were women. The mean patient age was 66.1 ± 7.3 years (range, 51 to 75 years). On fluorescein angiography, 11 (61.1%) and 7 (38.9%) eyes showed classic and occult-type choroidal neovascularization, respectively. The mean size of lesions on fluorescein angiography was measured as 1.0 ± 0.5 optic disc areas. Retinal cysts, subretinal fluid, and retinal pigment epithelial detachment were noted in 9 (50.0%), 16 (88.9%), and 14 (77.8%) eyes, respectively. The mean baseline BCVA was 0.08 ± 0.04 (Snellen equivalent, 20 / 24;

range, 20 / 25 to 20 / 20), and the mean baseline CFT was 270.2 ± 55.5 μm (range, 180 to 376 μm). Fluorescein angiography revealed subfoveal lesions in eight eyes (44.4%) and juxtafoveal lesions in the remaining ten eyes (55.6%).

Patients were treated with an average of 4.4 ± 1.3 intravitreal anti-VEGF injections (range; 3 to 7 injections, 3.9 ± 1.1 ranibizumab injections, 0.4 ± 0.9 bevacizumab injections) during the 12-month follow-up period. Fifteen eyes (83.3%) were treated with ranibizumab only, and the remaining three eyes (16.7%) were treated with both ranibizumab and bevacizumab. After the initial three monthly ranibizumab injections, patients were examined an average of 4.5 ± 0.9 times (range, 3 to 7) at our hospital during the 12-month follow-up period. The mean interval between each follow-up visit was 2.0 months.

Table 1. Baseline characteristics of eyes diagnosed with typical exudative age-related macular degeneration and good initial visual acuity (n = 18)

Variable	Value
Age (yr)	66.1 ± 7.3 (54 to 80)
Sex	
Male	13 (72.2)
Female	5 (27.8)
logMAR BCVA	0.08 ± 0.04 (20 / 25 to 20 / 20)
Central foveal thickness (μm)	270.2 ± 55.6 (180 to 376)
Location of lesion	
Subfoveal	8 (44.4)
Juxtafoveal	10 (55.6)
Type of lesion	
Classic	11 (61.1)
Occult	7 (38.9)
Size of lesion (disc areas)	1.0 ± 0.5

Data presented as mean ± standard deviation (range) or number (%).
logMAR = logarithm of minimum angle of resolution; BCVA = best-corrected visual acuity.

Fig. 1 shows changes in BCVA and CFT, according to the follow-up period. The BCVA was 0.08 ± 0.04, 0.08 ± 0.07, 0.12 ± 0.09, and 0.16 ± 0.11 at baseline, three months, six months, and 12 months, respectively (Fig. 1A) and significantly differed among the four time points (p = 0.009). The BCVA at diagnosis was not different from that measured at three or six months (p = 1.000 and p = 0.124, respectively). However, the BCVA at 12 months was significantly worse than that measured at baseline (p = 0.017). Deterioration in BCVA of 0.1 to 0.2 logMAR BCVA was noted in seven eyes (38.9%) and a ≥0.2 logMAR BCVA decrease was found in two eyes (11.1%) (Fig. 2). The remaining nine eyes (50.0%) had stable BCVA (Fig. 3).

The mean CFT at baseline, three months, six months, and 12 months was 270.2 ± 55.6, 204.4 ± 25.4, 230.1 ± 56.3, and 216.8 ± 48.7 μm, respectively (Fig. 1B). The CFT significantly differed among the four time points (p = 0.001) examined. Baseline CFT was significantly different from the CFT at 3 and 12 months (p < 0.001 and p = 0.042, respectively) but not at 6 months (p = 0.075).

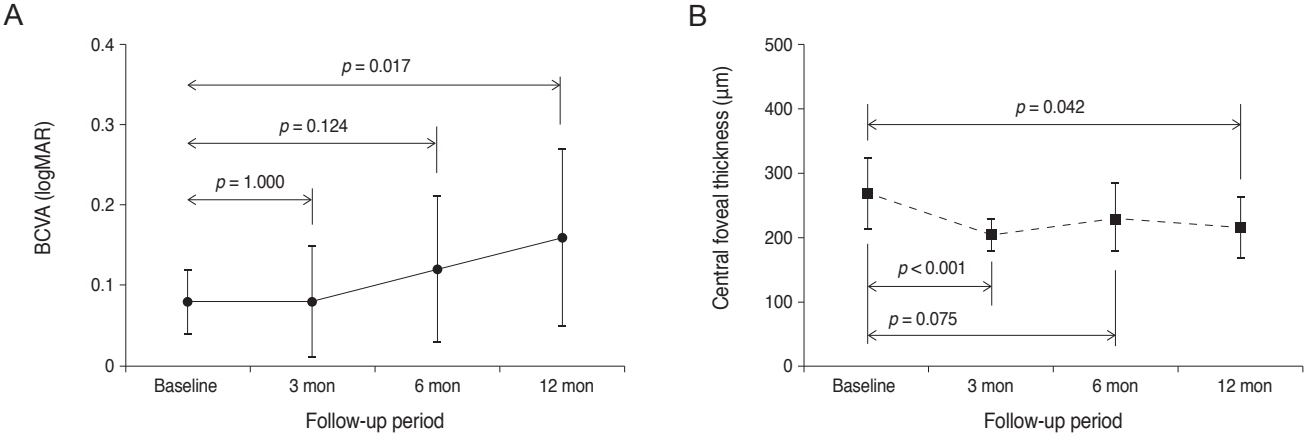

Fig. 1. Changes in mean logarithm of minimum angle of resolution (logMAR) best-corrected visual acuity (BCVA, A) and central foveal thickness (B) in eyes diagnosed with typical exudative age-related macular degeneration with good baseline visual acuity. Statistical analyses were performed using repeated measures analysis of variances with Bonferroni's correction.

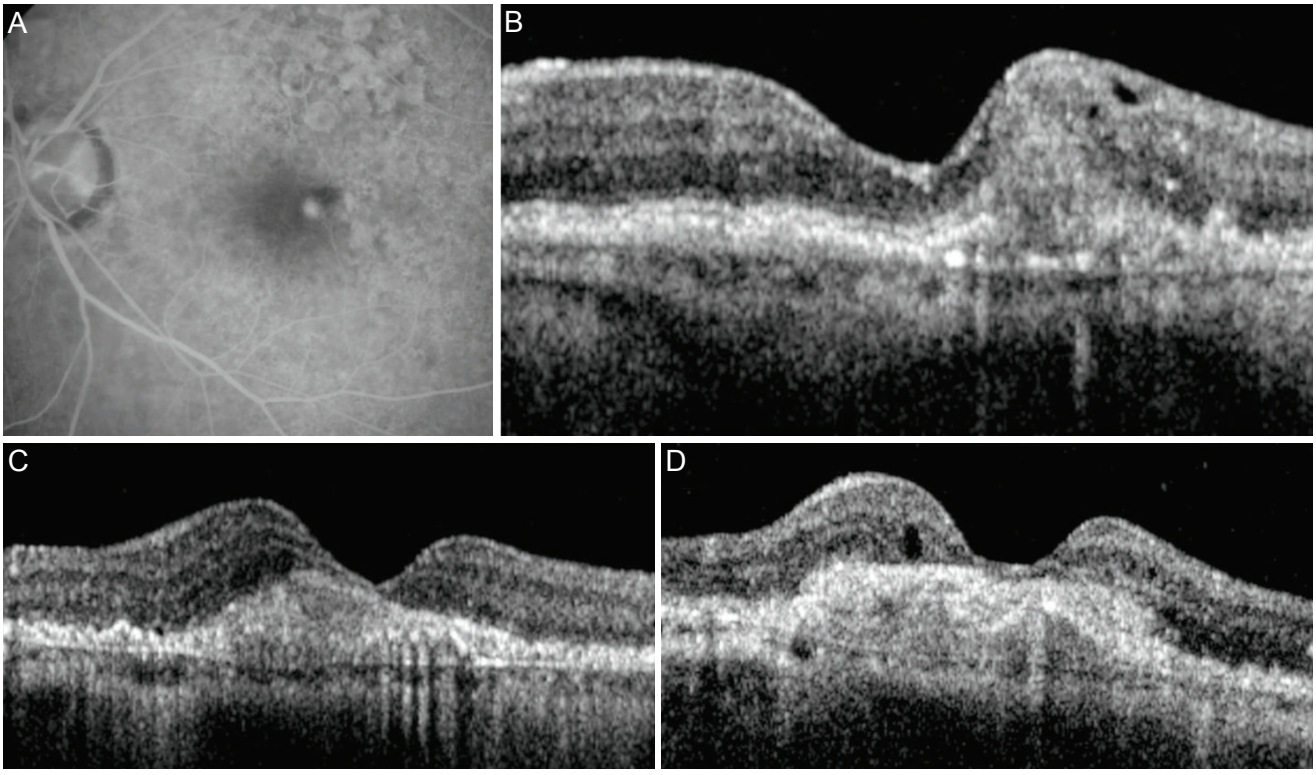

Fig. 2. Fluorescein angiography (A) and optical coherence tomography (B,C,D) findings in an eye with typical exudative age-related macular degeneration. The best-corrected visual acuity at the time of diagnosis was 20 / 25 (A,B). The eye received six ranibizumab injections during the 12-month follow-up period, but the subretinal lesion enlarged, as seen on optical coherence tomography at six (C) and 12 (D) months. A decrease in visual acuity to 20 / 50 was observed at 12 months.

Discussion

In the present study, we observed a relatively unfavorable outcome with intravitreal anti-VEGF therapy in eyes with typical exudative AMD with good baseline visual acuity. Twelve months into the follow-up, a significant deterioration in BCVA was noted, even though CFT had significantly decreased. Deterioration in visual acuity was noted in nine of 18 (50.0%) eyes.

The good initial visual acuity observed in our patients may be partially associated with the fact that the lesion sizes in the present study were relatively smaller than those in previous clinical trials [1,11]. In addition, retinal cysts were noted less frequently in our patients (50.0%) compared to those in a previous study (90.0%) [11]. It is notable that visual acuity remained stable during the first three months when ranibizumab injections were administered. Deterioration in visual acuity was only noted after this period, which may have been due to lesion progression. Lesion size generally increases in untreated exudative-AMD [12]. Although multiple anti-VEGF injections have been shown to prevent lesion progression [1,13,14], the efficacy of less frequent injections has not yet been studied. Because follow-up fluorescein angiography and ICGA were not routinely performed, we do not know for certain whether lesion progression occurred in our patient cohort. Further studies that include angiographic examination during the follow-up period are needed to verify whether lesion progression plays a role in vision loss.

Exudative AMD may have been undertreated because of treatment delays or an insufficient number of anti-VEGF injections. Because our study was retrospective, a strict uniform follow-up visit schedule was not employed. Thus, the monthly follow-up examination after initial treatment used in previous well-controlled clinical trials, all of which included OCT imaging [11,15], was not used in our study. Patients were followed up once every one to three months, and OCT examination was not routinely performed at each follow-up visit. It is possible that mild exudative recurrence occurred but was not detected due to omission of OCT. Therefore, prompt treatment may not have been performed in some cases. There is a close positive association

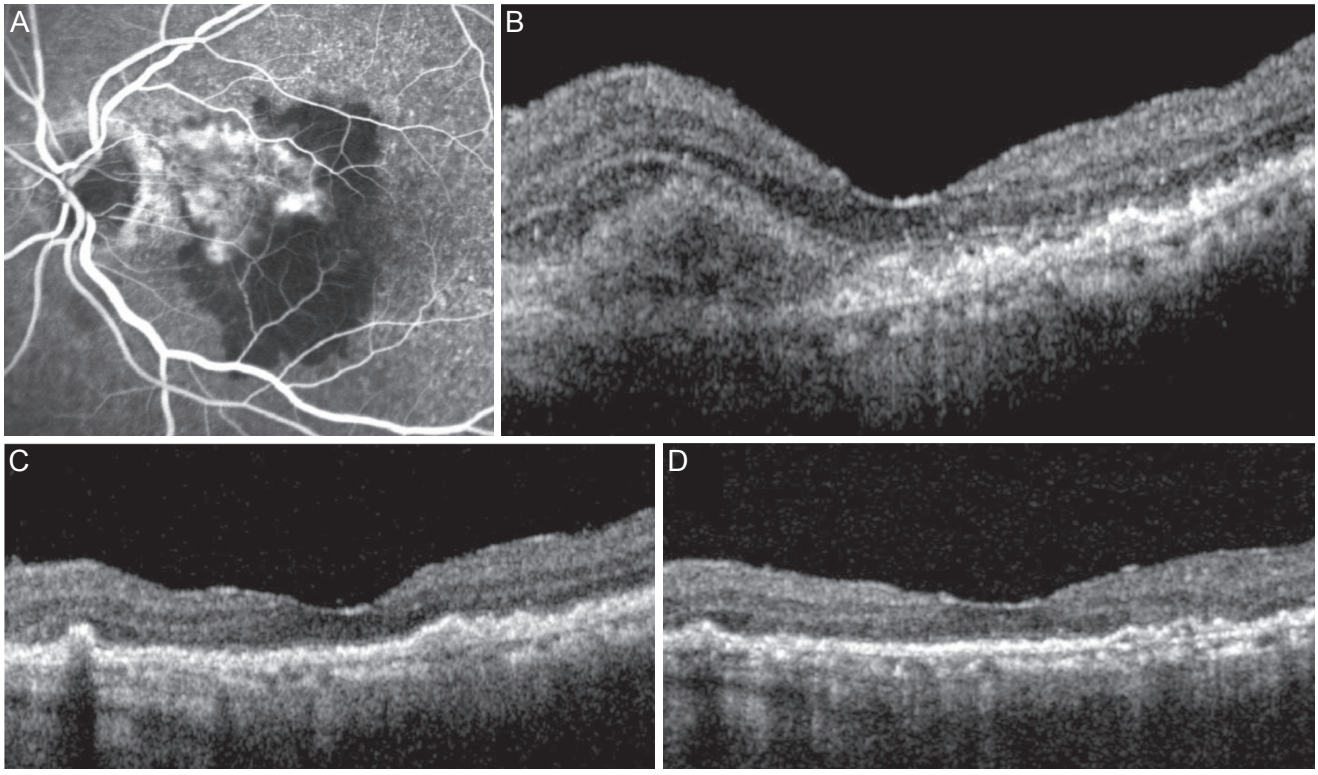

Fig. 3. Fluorescein angiography (A) and optical coherence tomography (B,C,D) findings of an eye diagnosed with typical exudative age-related macular degeneration. The best-corrected visual acuity at the time of diagnosis was 20 / 25 (A,B). After three consecutive ranibizumab injections, exudation recurrence was not noted during the 12-month follow-up period, as verified by optical coherence tomography at six (C) and 12 (D) months. The best-corrected visual acuity at 12 months was maintained at 20 / 25.

between frequency of anti-VEGF injections and visual improvement in exudative AMD [16]. Eyes receiving injections at least every two months regained more vision than eyes receiving injections less frequently [16]. In previous clinical trials that showed favorable visual outcome of anti-VEGF therapy in exudative AMD, a mean of 5.6 [11], 6.9 [15], and 7.7 injections [15] were administered during the 12-month follow-up period. However, in the present study, the mean number of anti-VEGF injection was only 4.4 during the same time period, with a mean interval between injections of 2.7 months. Thus, it is possible that our patients may have been undertreated. However, we postulate that the difference in the number of injections may also be influenced by differences in disease characteristics. For instance, the baseline lesion size in our patients was markedly smaller than that of previous clinical trials [1,11]. In addition, exudation recurrence was not noted in five of 18 eyes (27.8%) after the initial three monthly injections, whereas the proportion was approximately 18% in a previous clinical trial [11]. These results suggest that the exudative AMD patients included in the present study may have had a relatively favorable course.

Mori et al. [7] investigated the 12-month treatment outcome of eyes with PCV and a good baseline visual acuity. A favorable visual outcome was achieved with an average of 4.7 injections over 12 months, which is a comparable treatment frequency to that in our study. This outcome discrepancy may originate from the different natures of typical exudative AMD and PCV. In addition, their study was a prospective study with more frequent follow-ups, suggesting that prompt detection of exudation recurrence and subsequent prompt treatment may have been administered. Our study results suggest the need for intensive patient monitoring and treatment, including monthly follow-up examinations, for patients with typical exudative AMD and good baseline visual acuity, as in previous clinical trials.

In addition to its retrospective nature and small sample size, our study had some other limitations. Patient follow-up and re-treatment were conducted at the discretion of clinicians, rather than according to defined criteria. Moreover, a strict monthly follow-up schedule accompa-

nied by routine OCT examination, which allows prompt detection of exudation recurrence, was not required. Lastly, two different anti-VEGF agents (ranibizumab and bevacizumab) were used to treat patients. However, knowing that the two agents have comparable efficacies in treating exudative AMD [17], the influence of using different agents is likely minimal.

In conclusion, a significant deterioration in visual acuity was noted 12 months after anti-VEGF therapy initiation in eyes diagnosed with typical exudative AMD and good baseline visual acuity. We postulate that this unfavorable outcome is partially attributable to less frequent follow-up and treatment. Frequent follow-ups accompanied by OCT examination, which is generally recommended for exudative AMD treatment, may be required even in cases with typical exudative AMD showing good baseline visual acuity. Further prospective studies with a larger study population and more frequent follow-ups are required to demonstrate more accurate treatment outcomes for this condition.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Acknowledgements

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