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Switch to Aflibercept After Chronic Treatment With Bevacizumab for Choroidal Neovascularization With Age-Related Macular Degeneration

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Abstract

Purpose: To present the 5-year anatomic and functional outcomes in patients with choroidal neovascularization (CNV) and age-related macular degeneration (AMD) and determine whether late-onset intensification of treatment results in improved outcomes. **Methods:** This retrospective interventional study analyzed spectral-domain optical coherence tomography data and visual acuity (VA) in eyes in which treatment intensification was implemented after a mean of 39 months. Data collected included age, sex, injection frequency, central retinal thickness, type of CNV, and VA. Patients were evaluated every 4 to 10 weeks, depending on the disease activity. **Results:** Fifty eyes of 50 patients with CNV were evaluated. The mean initial VA was 0.37 Snellen (0.58 logMAR), which improved to 0.44 Snellen (0.47 logMAR) after the first bevacizumab injection. Six months after bevacizumab was switched to aflibercept, the improvement in VA was significant in all groups ($P < .05$). The VA improved throughout the 6-year observation period, with the greatest improvement in VA after the switch in patients who received the most injections ($P < .05$), who had the best initial VA ($P < .05$), and who experienced a significantly greater improvement in VA after the first bevacizumab injection ($P = .01$). **Conclusions:** Increasing the treatment frequency, even after several years of treatment, improved visual outcomes in patients with CNV and AMD who switched from bevacizumab to aflibercept.

Keywords

age-related macular degeneration, aflibercept, AMD, bevacizumab, CNV, vascular endothelial growth factor, anti-VEGF

Introduction

Choroidal neovascularization (CNV) concurrent with age-related macular degeneration (AMD) is routinely treated with intravitreal (IVT) antivascular endothelial growth factor (anti-VEGF) injections. Numerous clinical studies have shown excellent improvements in vision during the first 2 years of treatment, with monthly ranibizumab or bimonthly aflibercept injections.[1–3] Because the most frequently used treatment approaches are as-needed or, more recently treat-and-extend, most patients tend to receive fewer injections in subsequent years. This is justified by decreased amounts of subretinal fluid (SRF), which is usually taken as a sign of disease activity.

Decreasing the frequency of injections is more convenient for patients and more cost-effective. According to some studies, it may also reduce the potential risk for developing geographic atrophy (GA),[4] although the results are conflicting. However, emerging real-world data have shown that visual acuity (VA) differs from that observed in clinical trials. Despite optical coherence tomography (OCT)-based treatment schemes, less frequent injections in real-world clinical settings lead to worse long-term outcomes.[5–7] Long-term data from clinical studies have also shown that with time and fewer injections, VA tends to deteriorate.[8,9]

In Poland, anti-VEGF treatment costs were borne by patients for many years. When reimbursement was introduced a few years ago, patients included in the program were obligated to take 3 loading doses of bevacizumab followed by a bimonthly

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dose of aflibercept, regardless of whether they were treatment-naïve. The aim of this study was to evaluate the anatomic and functional outcomes in a series of patients who had initially received as-needed or treat-and-extend regimens for a minimum of 24 months and were subsequently transitioned to an intensified treatment regimen.

Methods

This retrospective interventional study was conducted in accordance with the principles of the Declaration of Helsinki. The Ophthalmic Clinic's Jasne Blonia Institutional Review Board Ethics Committee approved the study (#8/JB/2022).

Medical records were reviewed to locate patients treated with bevacizumab in the as-needed or treat-and-extend format (self-funded) for approximately 3 years (±3 months) before they were selected for the government reimbursement program and subsequently switched to aflibercept for at least 36 months. After the switch, patients received 3 monthly aflibercept injections and were further treated at varying intervals as follows: monthly, every 6 weeks, bimonthly, or after the treat-and-extend regimen. The determination of treatment frequency was made at the discretion of the retina specialist. The eligibility criteria for selection for reimbursement included CNV concurrent with AMD confirmed with OCT and fluorescein angiography.

Patients in the reimbursement program are obligated to attend a scheduled monthly visit for the initial 2 months followed by visits at least every 8 weeks thereafter. The injection is administered at the discretion of the treating ophthalmologist and may be performed as often as monthly, if required. Noncompliance with 4 consecutive monthly appointments resulted in the cancellation of reimbursement.

As a rule, during each visit/injection, the VA was measured using Early Treatment Diabetic Retinopathy Study (ETDRS) charts, tonometry was performed, and spectral-domain OCT images were obtained. A B-scan centered on the fovea was performed, and a 3-dimensional scan (7.0 mm × 7.0 mm) was done using the follow-up mode (Spectralis, Heidelberg Engineering). A comprehensive ophthalmic examination was performed at the initiation of the program, every 6 months, or at the discretion of the retina specialist.

The analysis included the following data: age, treatment duration in months, number of injections before inclusion in the reimbursement program, type of CNV, VA, and central retinal thickness (CRT) at the initiation of bevacizumab treatment, 1 month later, 1 year later, before the first aflibercept injection, 1 month later, 1 year later, 2 years later, and at the final assessment. The primary endpoints were the VA and CRT 1 month after administration of aflibercept. The secondary endpoints were the VA and CRT 36 months after the first administration of aflibercept.

Injection Procedure

IVT bevacizumab (Avastin, Roche Pharma) or IVT aflibercept (Eylea, Bayer Vital GmbH) injections were administered under topical anesthesia to all patients as a 1-day surgery in the operating room. After the conjunctival sac was cleaned with 5% povidone–iodine solution for 30 seconds, the conjunctiva was repositioned and an IVT injection of bevacizumab 0.05 mL or aflibercept 0.05 mL was administered through a scleral tunnel through the pars plana 3.5 to 4.0 mm posterior to the limbus.

Patient Analysis

The patients' age, VA at each analyzed timepoint, gain in VA, CNV type, CRT at each analyzed timepoint, number of injections, GA, and vitreomacular interface abnormalities were evaluated. The OCT images were analyzed by 2 experienced examiners (K.D.C., M.T.), and the images were discussed with the senior author in case of disagreement.

Statistical Analysis

Statistical analysis was performed using SigmaStat software for Windows (version 3.5, Grafiti LLC). A paired *t* test and Wilcoxon signed rank test were performed, and $P < .05$ was considered statistically significant. One-way analysis of variance was used to compare groups or an analysis of variance on ranks when normality test failure was noted. Mean values are ± SD.

Results

The study included 50 eyes of 50 patients (29 women, 21 men) who had been treated with anti-VEGF for at least 6 years. The mean age was 76.9 ± 7.9 years. Patients were treated with bevacizumab for a mean duration of 39 months. During this period, patients received a mean of 13.3 injections (range, 1-37; median, 11.5) (Tables 1 and 2). The mean initial Snellen VA was 0.37 ± 0.28 (0.58 logMAR) (range, 0.02-1.0 and 0.1-1.69, respectively). The initial VA improved to 0.44 ± 0.28 Snellen (0.47 logMAR) (range, 0.02-1.00 and 0.1-1.69, respectively) after the first bevacizumab injection ($P = .003$). The improvement in VA was statistically significant after the first bevacizumab dose for all CNV types ($P < .05$).

During the 3 years of treatment with aflibercept, patients received a mean of 24 injections (range, 11-35; median, 24). Twenty-three eyes had type 1 CNV, 17 had type 2 CNV, 8 had type 3 CNV, and 2 eyes had mixed-type CNV (1/2). At the time of the first aflibercept injection, the mean Snellen VA was 0.37 ± 0.23 (0.52 logMAR) (range, 0.04-0.9 and 0.1-1.0, respectively), which improved to 0.39 ± 0.22 Snellen (0.48 logMAR) (range, 0.15-0.9 and 0.1-1.0, respectively) after 1 month and to 0.44 ± 0.22 Snellen (0.41 logMAR) after 12 months (range, 0.04-0.9 and 0.1-1.3, respectively). The VA was maintained for 36 months after treatment initiation for all types of CNV (Table 3 and Figure 1A).

After switching to aflibercept, patients experienced a significant improvement in VA at 6 months ($P < .05$), without significant differences between the groups (Table 3 and Figure 1A). The VA improved throughout the 6-year observation period, from 0.37 ± 0.22 Snellen (0.52 logMAR) to 0.45 ± 0.24 Snellen (0.44

Table 1. Baseline Data: Day Treatment Was Switched to Aflibercept.

Parameter	CNV 1	CNV 2	CNV 3	CNV 1/ CNV2
Mean age (y) ± SD	75 ± 8.10	77 ± 6.41	80 ± 8.57	71 ± 7.00
Sex (n)				
Male	8	11	2	2
Female	15	6	6	0
Injections (n)	12	14	15	9, 5
Months (n)	40	39	37	19
Visual acuity				
Mean Snellen ± SD	0.39 ± 0.2	0.35 ± 0.2	0.44 ± 0.2	.040 ± 0.15
LogMAR	0.48	0.60	0.43	0.41

Abbreviation: CNV, choroidal neovascularization.

Table 2. Mean Number of Injections Each Year of Treatment by Type of CNV.

	Injections (n)			
Time	CNV 1	CNV 2	CNV 3	CNV 1/ CNV 2
Day treatment was switched to aflibercept	12	14	15	9, 5
1st year of aflibercept treatment	8	8	8	13, 5
2nd year of aflibercept treatment	7	8	6	3
3rd year of aflibercept treatment	7	8	6	3
4th year of aflibercept treatment	4	5	5	0

Abbreviation: CNV, choroidal neovascularization.

logMAR) ($P = .03$). Patients who received the most injections and those with the best initial VA had the greatest improvement in VA after changing to aflibercept (both $P < .05$). Multiple linear regression analysis showed that the VA 1 month after the transition to aflibercept appeared to predict the final VA ($P < .05$).

Patients were categorized as switch gainers when there was an improvement in VA of more than 10 ETDRS letters (2 Snellen lines) after 1 year of intensification of therapy and a switch to aflibercept. The switch gainers initially had significantly greater improvements in VA after the first bevacizumab injection ($P = .01$). However, in addition to the substantial gain in VA at the initiation of therapy, this group also experienced a greater loss of vision than the rest of the patients in the months leading up to the switch ($P = .01$), which was often accompanied by recurrent SRF. Switch gainers were not different from the rest of the patients in terms of age, sex, initial VA, initial CRT, number of previous injections, and type of CNV.

Switch gainers had a greater reduction in CRT during the first year of bevacizumab treatment than the rest of the patients (−91 μm vs −17 μm; $P = .03$). The mean CRT decreased in all patients after the first bevacizumab injection ($P = .04$) (Figure 1B). The final CRT was dependent on the measurement 1 month after the switch to aflibercept ($P < .001$) and patient age ($P = .06$).

SRF was present in 31 eyes on the day of the switch and in 7 eyes after 3 months. Intraretinal fluid (IRF) was observed in 12 eyes on the day of the switch and in 4 eyes 3 months later. Patients with CNV 1 (Figure 2) were most likely to benefit from the switch in regard to the disappearance of SRF, and eyes with CNV 2 (Figure 3) were most likely to benefit from the switch in regard to the disappearance of IRF.

Serous pigment epithelium detachment (PED) was noted in 8 eyes; however, this did not influence the visual outcome. Similarly, vascularized PED was observed in 10 patients and had no impact on the final vision. Throughout the observation period, 3 eyes experienced a submacular hemorrhage. As a result of immediate treatment (IVT bevacizumab, recombinant tissue plasminogen activator, and 0.5 cm^3 sulfur hexafluoride), the VA of these patients was maintained and further continuous anti-VEGF treatment was administered.

GA coexisting with a neovascular membrane was identified in 19 eyes at the initial visit, and the VA of these patients was significantly worse than in eyes without GA ($P = .01$), although no differences in the CRT were observed. At the end of the observation period, 34 eyes had GA, and their VA was significantly worse (0.38 Snellen [0.42 logMAR] vs 0.59 Snellen [0.22 logMAR]; $P = .003$). During treatment, 15 eyes had newly developed GA, 12 eyes had growth of the existing GA, and the extent of the GA remained unchanged in 7 eyes. The number of injections administered did not correlate with the development of GA.

Vitreomacular traction (VMT) was noted in 22 eyes, 19 of which experienced spontaneous release during the observation period. Patients with VMT had statistically similar VAs as eyes without traction ($P = .34$); however, in the final control group, eyes that experienced spontaneous release of VMT had significantly better VA than those without spontaneous release and those in which VMT was never observed ($P = .03$). During the observation period, 1 eye developed a lamellar macular hole and another eye experienced a tear in the retinal pigment epithelium after the spontaneous relief of traction. The CRT was similar in eyes with spontaneous release of traction and in the remaining

Table 3. Visual Acuity and CRT by CNV Type.

Parameter	CNV 1	CNV 2	CNV 3	CNV 1/CNV 2
Visual acuity				
Initial				
Mean Snellen ± SD	0.42 ± 0.27	0.25 ± 0.25	0.46 ± 0.24	0.65 ± 0.20
LogMAR	0.50	0.78	0.46	0.22
Day treatment was switched to aflibercept				
Mean Snellen ± SD	0.39 ± 0.20	0.35 ± 0.20	0.44 ± 0.20	0.40 ± 0.15
LogMAR	0.48	0.60	0.43	0.41
After 1 year of aflibercept treatment				
Mean Snellen ± SD	0.45 ± 0.20	0.36 ± 0.19	0.54 ± 0.20	0.60 ± 0.30
LogMAR	0.40	0.53	0.30	0.20
After 2 years of aflibercept treatment				
Mean Snellen ± SD	0.46 ± 0.20	0.38 ± 0.20	0.46 ± 0.23	0.80 ± 0.40
LogMAR	0.44	0.51	0.40	0.10
After 3 years of aflibercept treatment				
Mean Snellen ± SD	0.36 ± 0.20	0.43 ± 0.25	0.30 ± 0.17	0.80 ± 0.40
LogMAR	0.54	0.47	0.58	0.10
Final				
Mean Snellen ± SD	0.45 ± 0.21	0.42 ± 0.25	0.48 ± 0.23	0.48 ± 0.075
LogMAR	0.44	0.46	0.38	0.45
Mean CRT (μm) ± SD				
Initial	377 ± 179	465 ± 200	338 ± 84	256 ± 110
Before aflibercept treatment	321 ± 130	405 ± 159	277 ± 125	469 ± 65
After 1 year of aflibercept treatment	268 ± 95	314 ± 125	239 ± 96	205 ± 71
After 2 years of aflibercept treatment	263 ± 50	299 ± 118	225 ± 76	239 ± 79
After 3 years of aflibercept treatment	255 ± 65	312 ± 155	193 ± 75	216 ± 67
Final	245 ± 60	282 ± 105	219 ± 100	286 ± 100

Abbreviations: CNV, choroidal neovascularization; CRT, central retinal thickness.

cases ($P = .14$). In addition, 1 eye developed a spontaneous release of the epiretinal membrane.

Conclusions

This study showed that patients with CNV, even those undergoing treatment for many years with bevacizumab, benefited from the intensification of treatment with a switch to aflibercept. The gain may be associated with the change in treatment frequency and the change in drug. In these patients, the VA improved and the CRT decreased significantly. The best results were in patients with the best initial VA, a greater total number of injections, and the greatest increase in VA in the first month of switching.

Bevacizumab is a recombinant humanized monoclonal antibody that neutralizes all active forms of VEGF-A. Aflibercept is a soluble fusion protein of key domains from human VEGF receptors 1 and 2 with a constant region of human immunoglobulin G, which binds VEGF-A, VEGF-B, and placental growth factor. Both are considered standard treatment for neovascular AMD.

Randomized clinical trials have shown that anti-VEGF agents improved VA by an average of 1 to 2 lines within the first 12 months and maintained it until month 24.[1–3,10–12] However, 5-year data usually showed a decline in VA. The CATT study showed a decline of 11 letters from year 2 to year 5.[8] Real-world clinical settings usually resulted in worse outcomes than controlled clinical studies,[9] a phenomenon that is less pronounced in individuals treated with aflibercept.[13] Gillies et al[14] published a loss of 2.6 letters at 7 years when compared with baseline. The SEVEN-UP study reported a loss of 8.6 letters 7 years after initiation of therapy.[15] Interestingly, the VA improved in our group throughout the 6-year observation period (from 0.57 logMAR to 0.44 logMAR at year 6) ($P = .03$).

Furthermore, 10% to 30% of patients are nonresponders to anti-VEGF, the reason for which may be tachyphylaxis, among others.[16–18] Switching these patients to even a single dose of aflibercept could result in an improvement in VA in approximately 30% of them.[19] A prolonged switch to aflibercept was previously reported to decrease SRF and IRF in one half of patients who switched.[19–23] In those eyes, PEDs tended to diminish.[24]

The CATT study reported that the VA at 5 years declined by 3 letters compared with baseline and 11 letters compared with month 24 of treatment.[8] Similar results were obtained in the current study, where the VA improved by a mean of 8 ETDRS letters (1.5 Snellen) after the first bevacizumab injection. However, this improvement continued to decrease to reach baseline VA after 12 months and then stabilized until the initiation of aflibercept treatment. After the switch, a strict dosing regimen was introduced with 3 loading doses, which was followed by bimonthly treatment. This resulted in an improvement in VA up to the level obtained 1 year after the initiation of treatment.

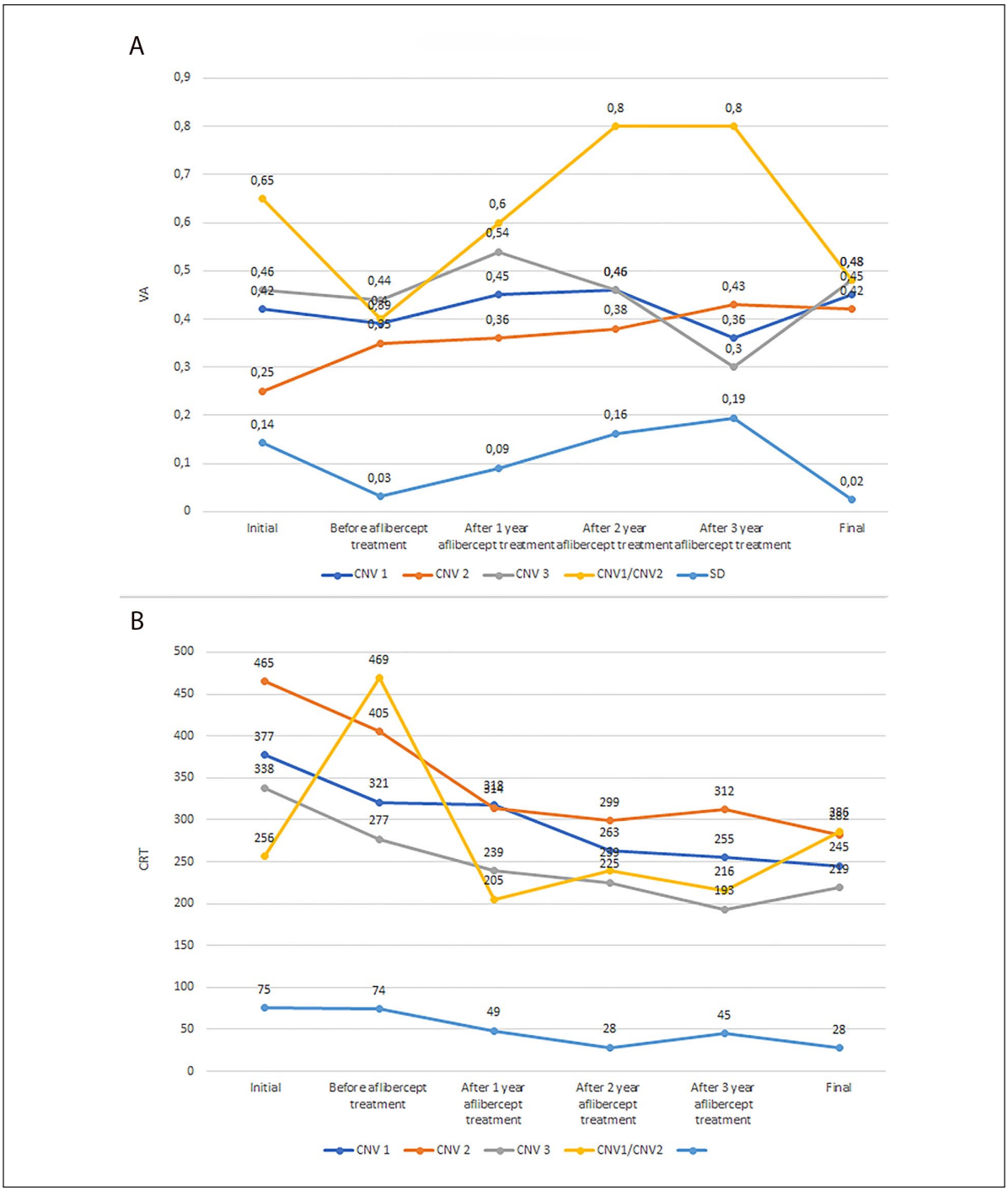

Figure 1. (A) Mean change in Snellen VA. (B) Mean change in CRT.
Abbreviations: CNV, choroidal neovascularization; CRT, central retinal thickness; VA, visual acuity.

Notably, the VA improved and the CRT decreased, with results maintained until 36 months after switching. The best results were seen in patients who received the most injections, had the best initial VA, and showed the greatest improvement in VA after the first aflibercept injection.

The SEVEN-UP study found that in a clinical study setting, the only factor responsible for significant long-term visual loss was the development of GA.[25] Subsequent studies found that GA more often developed in eyes requiring fewer injections as a result of milder disease activity.[26] Because there is a general tendency to reduce the number of anti-VEGF treatments over the years, it is not surprising that the frequency of GA increases. In real-life settings, the most important factors responsible for a decrease in vision are nonadherence and a limited number of injections.

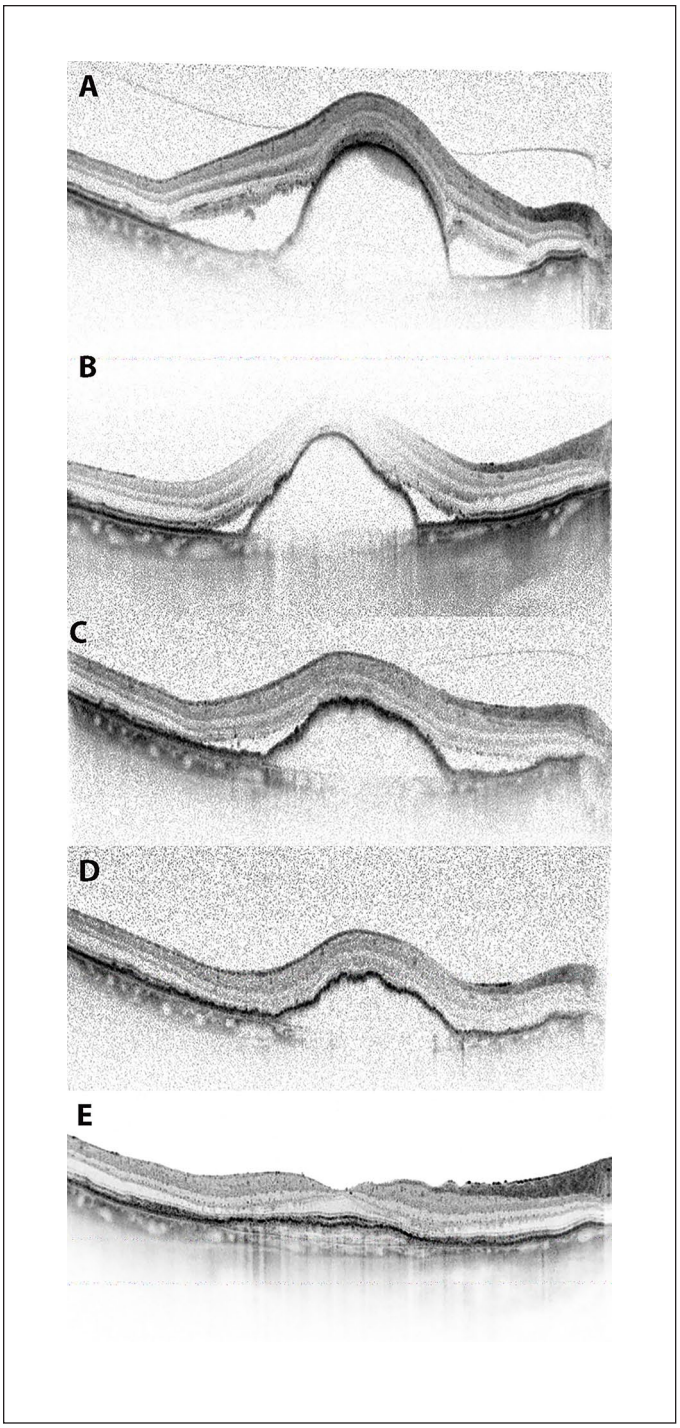

Figure 2. Swept-source optical coherence tomography in an 80-year-old woman with a pigment epithelium detachment and type 1 choroidal neovascularization. (A) Initial visual acuity (VA): 0.25 Snellen (0.6 logMAR); central retinal thickness (CRT): 909 μm. (B) VA after the first injection of bevacizumab: 0.1 Snellen (1.0 logMAR); CRT: 802 μm. (C) VA on the day treatment was switched to aflibercept: 0.6 Snellen (0.2 logMAR); CRT: 590 μm. (D) VA after the first injection of aflibercept: 0.6 Snellen (0.2 logMAR); CRT: 478 μm. (E) Final VA: 0.8 Snellen (0.1 logMAR); final CRT: 275 μm.

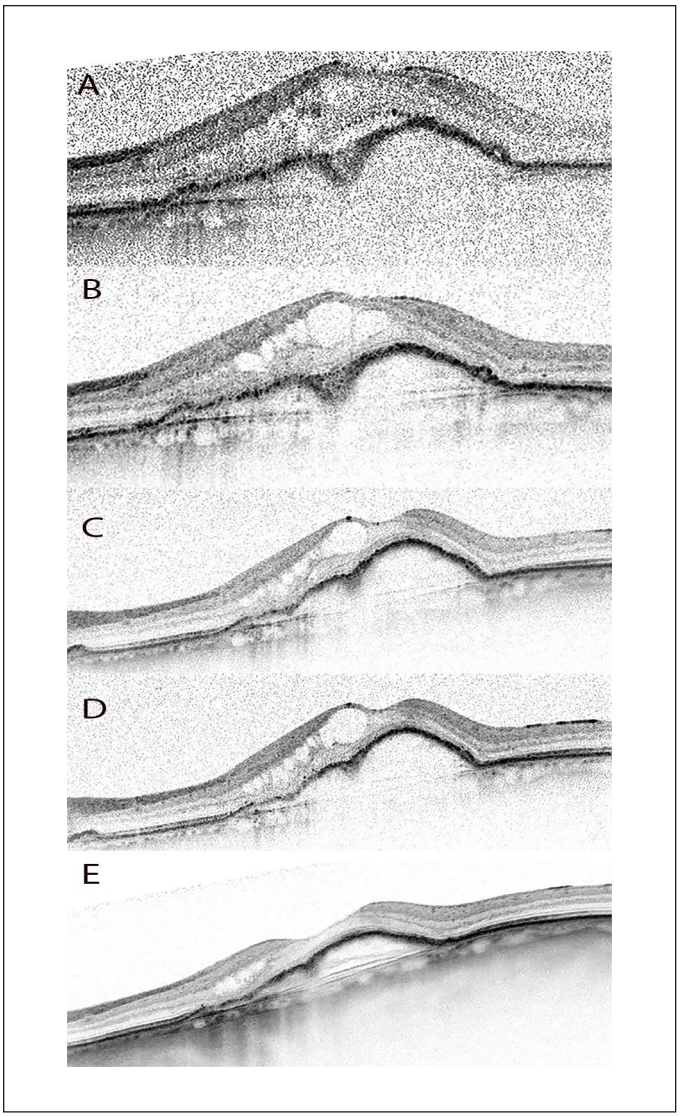

Figure 3. Swept-source optical coherence tomography in an 84-year-old woman with type 2 CNV. (A) Initial visual acuity (VA): 0.10 Snellen (1.0 logMAR); central retinal thickness (CRT): 651 μm. (B) VA after the first injection of bevacizumab: 0.1 Snellen (1.0 logMAR); CRT: 517 μm. (C) VA on the day treatment was switched to aflibercept: 0.3 Snellen (0.52 logMAR); CRT: 467 μm. (D) VA after the first injection of aflibercept: 0.6 Snellen (0.2 logMAR); CRT: 416 μm. (E) Final VA: 0.3 Snellen (0.52 logMAR); final CRT: 338 μm.

Patient comfort is also an important issue. Besides fear of pain and the need for frequent controls, the fear of the unknown is an important consideration for patients treated with anti-VEGF. This constant process of decision-making regarding whether to inject is stressful for patients.[27] Thus, determining whether it is more reasonable to treat based on clinical findings than to adhere to strict dosing regimens requires reevaluation. In addition, improvement in vision remains the most important factor for enhancing patients' quality of life.[28] It is possible that in the

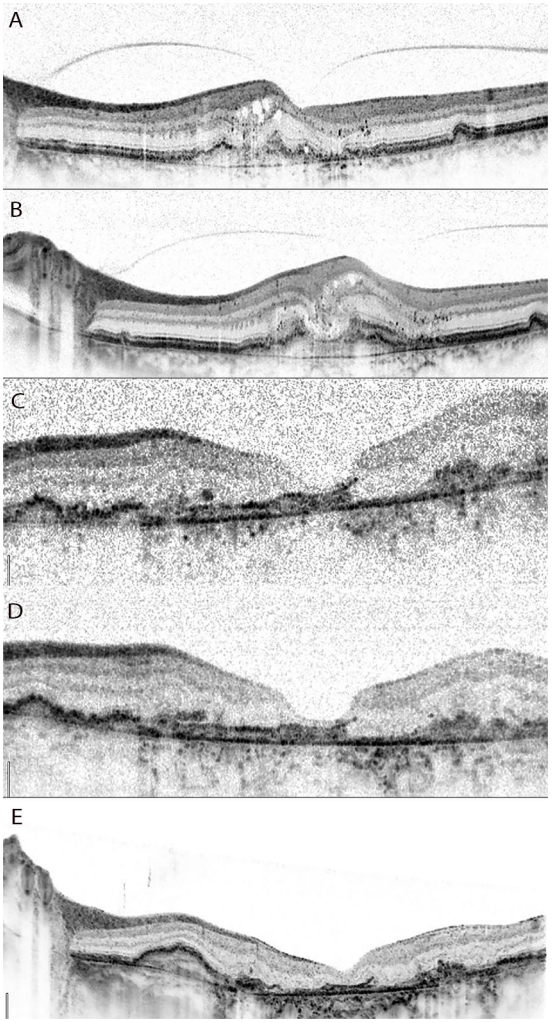

Figure 4. Swept-source optical coherence tomography in a 75-year-old man with type 3 CNV. (A) Initial visual acuity (VA): 0.10 Snellen (1.0 logMAR); CRT: 258 μm. (B) VA after the first injection of bevacizumab: 0.2 Snellen (0.7 logMAR); CRT: 518 μm. (C) VA on the day treatment was switched to aflibercept: 0.1 Snellen (1.0 logMAR); CRT: 130 μm. (D) VA after the first injection of aflibercept: 0.1 Snellen (1.0 logMAR); CRT: 87 μm. (E) Final VA: 0.2 Snellen (0.7 logMAR); final CRT: CRT 64 μm.

future, sustained drug delivery devices will be able to overcome these challenges.

Another issue is that our treatment is based on the analysis of OCT scans, which estimate IRF and SRF as markers of disease activity. With the advancement of OCT angiography (OCTA), different questions have been raised, including whether treatment should be administered when an increase of visible vessels is seen on OCTA and whether treatment should continue until these vessels disappear. Further prospective studies are required to answer these questions and to enhance our treatment regimens.

A flaw of the current study is the lack of a control group and the small number of cases with type 3 CNV (Figure 4), which might have influenced statistical analysis. Moreover, it may be difficult to extrapolate results to different healthcare systems. However, the main outcome of the study is that intense treatment, even many years after treatment initiation, is associated with a good outcome. Interestingly, better VA was observed in eyes with spontaneous release of traction in the final control. Vitreous detachment may lower VEGF levels near the retina and improve oxygenation.

In conclusion, the best results were achieved when more injections were used. Intense treatment should be considered, even in cases that are apparently well controlled with as-needed and treat-and-extend protocols but still had a decline of some ETDRS letters. Initiating intense treatment with aflibercept in patients previously treated with bevacizumab, even after several years of injections, could result in an improvement in VA.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Ophthalmic Clinic's Jasne Blonia Institutional Review Board Ethics Committee retrospectively approved the study (#8/JB/2022).

Statement of Informed Consent

Informed consent was waived for the present study because inclusion in the study posed no substantial risk to participants and data analysis consisted of de-identified data obtained through retrospective chart review.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of the article

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