# Seven-year outcome after 1-year fixed regimen of intravitreal aflibercept injections followed by pro re nata treatment for neovascular age-related macular degeneration

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**Competing Interest:**

All authors attest that they meet the current ICMJE criteria for authorship.

## KEY MESSAGES

### What is known

- Anti-vascular endothelial growth factor therapy is the current standard of care for neovascular age-related macular degeneration; however, the long-term outcome of 1-year fixed regimen of intravitreal aflibercept injections followed by pro re nata treatment has not been demonstrated.

### New information

- Best-corrected visual acuity in neovascular age-related macular degeneration eyes remained stable for 7 years after 1-year fixed regimen of intravitreal aflibercept injection, followed by pro re nata treatment, without drug-induced severe complications.

- Baseline best-corrected visual acuity in neovascular age-related macular degeneration eyes positively correlated with that at 7 years.

- Therefore, early diagnosis and treatment of neovascular age-related macular degeneration are essential for maintaining good long-term visual acuity, even in eyes with relatively poor vision at first visit.

**ABSTRACT**

**Purpose:** To investigate the 7-year best-corrected visual acuity (BCVA) course after 1-year fixed regimen of intravitreal aflibercept injection (IVA) for neovascular age-related macular degeneration (nAMD) and to identify factors affecting this BCVA.

**Methods:** This longitudinal, observational study included 63 treatment-naïve eyes (61 patients) with nAMD, treated with 1-year fixed regimen of IVA—3 monthly injections and 4 subsequent bimonthly injections—essentially followed by PRN regimen of IVA but sometimes followed by agent switching, photodynamic therapy (PDT), or vitrectomy, as needed. We assessed BCVA changes over a 7-year period. Morphologically, we assessed central retinal thickness (CRT), central choroidal thickness (CCT), subfoveal pigment epithelial detachment (PED) height, vitreomacular traction/adhesion (VMT/VMA), epiretinal membrane (ERM), and macular atrophy involving the fovea.

**Results:** Logarithm of the minimum angle of resolution (logMAR) BCVA changed from 0.20±0.24 to 0.29±0.45 over 7 years. BCVA improved significantly after years 1 and 2 ($P$=0.002 and 0.001, respectively) and then slowly decreased. BCVA after years 3–7 did not significantly differ from baseline. CRT and CCT decreased significantly during follow-up, while PED height did not. VMT/VMA decreased significantly, whereas ERM and macular atrophy increased significantly. Seven-year and baseline BCVA positively correlated ($P$=0.007, β=0.35).

**Conclusions:** BCVA was maintained for 7 years in nAMD eyes after 1-year fixed regimen of IVA, essentially followed by PRN regimen, but sometimes followed by agent switching, PDT, or vitrectomy, without severe drug-induced complications. Thus, early diagnosis and treatment of nAMD are essential for maintaining good long-term BCVA, even in eyes with relatively poor baseline vision.

**KEYWORDS**

age-related macular degeneration; injection frequency; intravitreal aflibercept injection; macular atrophy; long-term observation

## INTRODUCTION

Neovascular age-related macular degeneration (nAMD) is a progressive disease of the macula with a poor long-term visual prognosis [1]. The three subtypes of neovascular degeneration are classified as polypoidal choroidal vasculopathy (PCV), retinal angiomatous proliferation (RAP), and typical nAMD (tAMD; i.e., nAMD excluding PCV and RAP) [2]. The clinical characteristics of these subtypes differ [3].

Anti-vascular endothelial growth factor (VEGF) therapy is the current standard of care for nAMD. Clinical trials have demonstrated the effectiveness of anti-VEGF therapy—including ranibizumab, aflibercept, and brolucizumab—1 or 2 years after treatment [4-6]. However, aside from being scarce, studies investigating long-term visual outcomes after anti-VEGF therapy have used various agents and treatment regimens [7, 8]. The SEVEN-UP Study assessed the 7-year outcome of intravitreal injections of ranibizumab (IVR), administered as a fixed regimen over 2 years, followed by pro re nata (PRN) regimen, and showed a decrease in 7-year best-corrected visual acuity (BCVA) [7].

Differences in the anti-VEGF agent used, treatment regimen (injection frequency), or nAMD subtype may affect the long-term outcomes. The VIEW I/II Studies showed similar efficacy of aflibercept and ranibizumab in terms of BCVA gain 2 years after treatment [5]. Furthermore, there were no differences reported in visual improvement among the three subtypes of nAMD at both 1 year and 4 years after 1-year fixed regimen of intravitreal injections of aflibercept (IVA) [9, 10]; however, the difference at 7 years after treatment remains unclear.

A meta-analysis study showed a small difference in 1-year effectiveness between monthly fixed regimen and PRN regimen, but reported that endophthalmitis was more common with monthly injections than with PRN regimen [11]. Furthermore, the PRN regimen can lead to cessation of anti-VEGF therapy, and fewer anti-VEGF injections lead to lower healthcare costs, reducing the burden on patients [11].

This study investigated the 7-year course of BCVA, morphological changes, and frequency of injections after 1-year fixed regimen of IVA, essentially followed by PRN regimen, and sometimes followed by agent switching, photodynamic therapy (PDT), or vitrectomy as needed, and sought to identify factors correlated with the 7-year BCVA in nAMD.

## MATERIALS AND METHODS

The ethics committee of Kyoto University Graduate School of Medicine (Kyoto, Japan) approved this prospective cohort study. All study protocols adhered to the tenets of the Declaration of Helsinki. We explained the nature of the study and the

possible risks and benefits of participation to all study candidates. Those who agreed to participate by providing written informed consent were enrolled.

**Participants**

This prospective cohort study included treatment-naïve eyes with nAMD in consecutive patients who visited Kyoto University Hospital. Prior to the initial treatment, all eyes underwent a comprehensive ophthalmological examination, including autorefractometry, BCVA measurements using a Landolt chart, measurement of intraocular pressure, indirect ophthalmoscopy, slit-lamp biomicroscopy with a contact lens, colour fundus photography, spectral domain optical coherence tomography (OCT), and fundus fluorescein and indocyanine angiography. Most eyes also underwent axial length (AL) measurement using partial coherence interferometry. Retinal specialists diagnosed nAMD based on the above multimodal imaging techniques and determined the relevant subtype (PCV, RAP, or tAMD) [2]. During the follow-up period, the measurement of BCVA and intraocular pressure, indirect ophthalmoscopy, slit-lamp biomicroscopy, colour fundus photography, and spectral domain OCT were performed.

We retrospectively analysed the eyes that met the following inclusion and exclusion criteria among the prospectively included cohort observed over 7 years. The inclusion criteria were: (1) diagnosis of nAMD; (2) age ≥50 years; and (3) 1-year fixed regimen of 2 mg IVA (Eylea®, Bayer, Leverkusen, Germany) for retinal exudate, including subretinal and intraretinal fluid/haemorrhage, at Kyoto University Hospital between December 2012 and July 2014. The fixed regimen included 3 monthly injections and 4 consequent bimonthly injections. After the fixed regimen, we essentially provided "intensive" PRN regimen of IVA, i.e., our retreatment policy was to maintain a status of no retinal exudate, as far as possible. When alternate treatment was deemed necessary, we switched to PDT using verteporfin (Visudyne®, Novartis AG, Basel, Switzerland), 0.5 mg IVR (Lucentis®, Novartis AG), or intravitreal injections of 6 mg brolucizumab (Beovu®, Novartis AG). At times, PDT was used to decrease the treatment burden in older patients [12]. When massive submacular haemorrhage (SMH) developed, we performed vitrectomy with subretinal tissue plasminogen activator injection, starting in July 2018.

The exclusion criteria were as follows: (1) pre-treatment BCVA <20/200 (legal blindness) [1] on a Landolt chart; and (2) other macular abnormalities, including moderate or severe epiretinal membrane (ERM) with loss of the foveal pit (stage 2–4 as classified by a previous report) [13], retinal vein occlusion, and diabetic retinopathy.

**Morphological Analysis**

Central retinal thickness (CRT), central choroidal thickness (CCT), and subfoveal pigment epithelial detachment (PED) height were calculated by averaging values measured on vertical and horizontal OCT B-scans through the fovea, at baseline and 7 years, by a single investigator (YH), using the device's built-in software. CRT was defined as the distance between the vitreoretinal surface and the inner surface of the retinal pigment epithelium (RPE). CCT was defined as the distance between the outer surface of Bruch's membrane and the chorioscleral interface. Subfoveal PED height was defined as the distance between the outer surface of the RPE and the inner surface of Bruch's membrane.

Vitreomacular traction or adhesion (VMT/VMA) involving the fovea, ERM, and macular atrophy involving the fovea were assessed at baseline and 7 years after treatment. Furthermore, massive SMH (>4-disc diameter) involving the fovea was assessed during the observational period, including at baseline. These assessments were performed by a single investigator (YH). VMT/VMA involving the fovea was defined as posterior vitreous detachment (PVD) around the fovea and no PVD at the fovea, while ERM was defined as a highly reflective membrane at the vitreomacular interface on an OCT image [14]. ERM was classified as stage 1–4, as previously reported [13]. Macular atrophy involving the fovea was assessed using colour fundus photograph and OCT and infrared images, as previously reported (Figure 1) [12]. Cataract surgeries were recorded over the 7-year observational period.

**Statistical Analysis**

Data are presented as means±standard deviations, where applicable. We converted BCVA into logarithm of the minimum angle of resolution (logMAR) values for statistical analysis. To compare our results with those of a previous report that used 15 letters on an ETDRS chart as the cut-off value of change in BCVA [7], we used a corresponding cut-off value of a change of 0.30 logMAR. We performed comparative analyses among the three subtypes of nAMD using one-way analysis of variance (ANOVA), or the chi-square trend test where applicable. We analysed the change in logMAR BCVA over 7 years using repeated measures ANOVA and post hoc analysis with Bonferroni correction. Morphological changes between baseline and 7-year measurements were compared using a paired *t*-test or chi-square test, where applicable. We compared parameters between eyes with and without newly developed macular atrophy over the 7 years using an unpaired *t*-test or chi-square test, where applicable. We performed correlation analyses of the 7-year logMAR BCVA with baseline, treatment-associated, and 7-year parameters using Spearman's correlation coefficient. Multivariable correlation analyses were

performed using 7-year logMAR BCVA as the dependent variable and baseline parameters with $P<0.10$ on Spearman's correlation test as independent variables. We conducted all statistical analyses using IBM SPSS Statistics, Version 27.0 (IBM Corp, Armonk, NY, USA). Statistical significance was set at $P<0.05$.

## RESULTS

In total, 154 eyes of 149 patients met the inclusion criteria; however, 77 eyes of 76 patients were lost to follow-up over the 7-year observational period. Among the remaining eyes, 7 had a worse baseline BCVA than 20/200, 4 had diabetic retinopathy, and 3 had retinal vein occlusion (Supplementary Figure 1). Thus, 63 eyes of 61 consecutive patients were included in the analysis (mean age, 73.2±7.4 years, Table 1). Regarding the subtypes of nAMD, 31 eyes were diagnosed with tAMD, 27 with PCV, and 5 with RAP. LogMAR BCVA changed during 7-year observation period from 0.20±0.24 to 0.29±0.45 in the whole cohort (from 0.19±0.24 to 0.29±0.44 in tAMD, from 0.17±0.21 to 0.19±0.32 in PCV, and from 0.34±0.38 to 0.76±0.79 in RAP). There was no significant difference in logMAR BCVA among the three groups at any time-point (Table 2). In the analysis of all 63 eyes using repeated measures ANOVA, BCVA was significantly changed during 7 years ($P<0.001$). Furthermore, using post hoc analysis, BCVA significantly improved at the 1-year (logMAR BCVA, 0.10±0.24) and 2-year (0.09±0.22) time-points as compared with baseline ($P=0.002$ and 0.001, respectively); however, at the 3-, 4-, 5-, 6-, and 7-year time-points ($P=0.30$, >0.999, >0.999, >0.999, >0.999, and >0.999, respectively), BCVA did not significantly differ from baseline (Figure 2A). Taken together, BCVA initially improved after year 1 and 2, and then slowly decreased back to baseline BCVA. In the analysis of each nAMD subtype, BCVA changed in PCV ($P<0.001$), whereas there were no significant changes in the tAMD and RAP subtypes (Figure 2B). In PCV, BCVA at the 1-year ($P<0.001$) and 2-year ($P=0.001$) time-points was significantly better than that at baseline. Compared with baseline, the 7-year BCVA improved in 8 eyes (13%) and declined in 12 eyes (19%) by more than 0.30 logMAR (corresponding to 15 letters) and was stable (within 0.30 logMAR) in 43 eyes (68%). No severe drug-induced complications occurred during the 7-year observation period.

The median annual number of anti-VEGF injections after the 1-year fixed regimen (7/year) were 3, 3, 3, 3, 2, and 2 at the 2-, 3-, 4-, 5-, 6-, and 7-year time-points, respectively (means are presented in Table 1). Although eyes with RAP required more IVA than did those with other nAMD subtypes, there was no significant difference in the number of annual injections among the three subtypes. Regarding additional treatment using PDT, 5 eyes underwent combination therapy of

IVR and PDT (1–3 sessions), and 2 eyes underwent simple PDT (1 session). The median of combined or simple PDT sessions during the 7 years was 0. Regarding the use of other additional agents, 2 eyes were administered 1 and 4 brolucizumab injections, and 1 eye was administered 2 IVR and 4 brolucizumab injections.

The CRT and CCT at the 7-year time-point significantly decreased as compared with baseline ($P$<0.001 for both, Table 3), whereas the subfoveal PED height remained unchanged ($P$=0.92). Moreover, the rate of VMT/VMA involving the fovea significantly decreased ($P$=0.01). Vitrectomy was not performed for VMT/VMA. Spontaneous complete and macular PVD occurred in 7 and 1 eyes, respectively. Additionally, the rate of ERM significantly increased ($P$=0.04)—1 eye was in stage 2 (new development), whereas the remaining eyes (12 eyes) were in stage 1. The rate of macular atrophy involving the fovea significantly increased from baseline ($P$=0.002); 10 eyes (17%) of 59 eyes without macular atrophy at the baseline newly developed macular atrophy at 7 years. There were no differences in any studied parameters between eyes with and without new macular atrophy (Supplementary Table 1). Massive SMH was observed in 3 eyes at baseline and in 5 eyes at 2–6 years after therapy; thus, the new development rate of massive SMH was 8% (5/60). One surgeon (M. Miyata) performed vitrectomy using subretinal tissue plasminogen activator injection in 2 eyes, and IVA in 6 eyes.

The parameters that significantly correlated with 7-year logMAR BCVA (Table 4) were baseline logMAR BCVA ($P$<0.001, r=0.45), 7-year ERM ($P$=0.002, r=0.38), 7-year macular atrophy involving the fovea ($P$=0.004, r = 0.36), and the total number of PDT sessions ($P$=0.04, r=0.26). On multivariable analysis, among baseline parameters, 7-year logMAR BCVA correlated with only baseline logMAR BCVA ($P$=0.007, β=0.35).

Based on the baseline age, patients that were lost to follow-up (n=77) were significantly older than the patients that were not lost to follow-up (n=77) after 7 years (77.4±8.3 years vs. 73.4±7.3 years, $P$=0.002). However, there were no differences in sex (female sex, 26 for both, $P$>0.999) or nAMD subtype (tAMD, 39 vs. 37; PCV, 31 vs. 26; RAP, 7 vs. 14; $P$=0.42) between those that were lost to follow-up and those that were not.

## DISCUSSION

In this study, we showed that BCVA in nAMD was maintained for 7 years after 1-year fixed regimen of IVA—essentially followed by PRN regimen of IVA but sometimes followed by agent switching or PDT, as needed—and macular surgery, without drug-induced severe complications. With 0.30 logMAR BCVA (corresponding to 15 letters) as the cut-off value, 7-year BCVA improved in 13% of eyes, declined in 19% of eyes,

and was stable in 68% of eyes. In the SEVEN-UP Study, 7-year BCVA declined by an average of 8.6 letters as compared to baseline, and in 34% of the eyes, it declined by more than 15 letters [7]. Another retrospective study reported that the 7-year BCVA declined by an average of 9 letters. The former study involved a 2-year fixed regimen of IVR, followed by PRN regimen, while the latter involved PRN regimen of various anti-VEGF therapies, including aflibercept, bevacizumab, and ranibizumab. The difference between our results and those of the two abovementioned reports may be due to differences in agents as well as in the retreatment criteria for the PRN regimen. We used aflibercept in all eyes from baseline. Furthermore, our retreatment policy was to maintain a status of no retinal exudate, as far as possible. Therefore, the annual number of retreatments was higher (mean, 2.8) than that in the SEVEN-UP Study (mean, 2.0). The FLUID Study with a treat-and-extend (TAE) regimen found that 2-year BCVA in the relaxed arm (subretinal fluid-tolerant, except subfoveal fluid height >200 μm) was similar to that in the intensive arm (complete resolution of subretinal and intraretinal fluid) [15]. Our retreatment criteria were similar to the latter arm. In terms of long-term observation, treatment aimed at maintaining complete resolution of retinal exudate may maintain BCVA more stably when using the PRN treatment.

In the present study, for all nAMD subtypes, 7-year BCVA did not significantly decrease from baseline. The course of BCVA in eyes with PCV and those with tAMD was similar over 7 years, corresponding to previous reports involving 1-year and 4-year observations after 1-year fixed regimen of IVA, followed by PRN regimen [9, 10]. A previous report showed that 3-year BCVA in eyes with RAP that received IVR and/or intravitreal injection of bevacizumab did not change (baseline, 0.79±0.56 logMAR; 3-year, 0.75±0.41 logMAR) [16]. Another previous report showed a gradual decrease (mean logMAR: baseline, 0.58; 3-year, 0.70; 4-year, 0.82; 9-year, 0.92) after IVR or IVA [17]. In the present study, the mean logMAR BCVA in eyes with RAP remained unchanged from baseline (0.34) to 5 years (0.34) after treatment, although the sample size of eyes with RAP (n=5) was too small to allow analysis. The favourable results in this study may be because of better baseline BCVA than that in the previous reports. Early detection and prompt treatment of RAP may maintain BCVA.

A meta-analysis of real-world outcomes after IVR treatment showed that the change in BCVA after a TAE regimen was better than that after the PRN regimen; however, the annual injection frequency was higher with the TAE regimen than the PRN regimen during the 3-year observational period (6.9 vs. 4.7) [18]. The RPN regimen can lead to the end of anti-VEGF therapy. More anti-VEGF injections lead to higher costs, given the expensive drugs and an increased physical burden on

patients. The economic burden on the community increases concurrently with the rate of nAMD and its chronicity [19]. Furthermore, endophthalmitis as a severe side effect of IVA or IVR occurs in the case of 0.100% and 0.056% of injections, respectively [20]. A meta-analysis study showed a high risk of endophthalmitis in fixed regimen 8 times than in PRN regimen [11]. Given that our 1-year fixed regimen of IVA, followed by PRN treatment, only required 2.8 additional injections per year and maintained BCVA over 7 years, it can be considered as an option for treatment-naïve eyes with nAMD.

In terms of the morphological changes over 7 years in the present study, the CRT, CCT, and prevalence of VMT/VMA decreased, while the prevalence of EMR increased. Since retinal exudate, which was included in the CRT, resolved in most cases and macular atrophy newly developed in some cases, the mean 7-year CRT decreased from 334.7 μm at baseline to 182.1 μm (54%; 7-year value per baseline value). Similarly, the CATT Study reported that the mean CRT decreased from 464 μm at baseline to 278 μm (60%) at the 5-year time-point [21]. In the present study, the mean 7-year CCT decreased from 234.7 μm to 186.1 μm (79%). Although long-term changes in CCT have not been reported, to the best of our knowledge, the choroid becomes thinner with increasing age, even in healthy eyes [22]. The prevalence of VMT/VMA decreased due to spontaneous PVD occurrence in 8 out of 9 eyes (89%) over our 7-year observational period. A previous study showed that PVD occurred in 70% (7/10) of eyes 21 months after anti-VEGF therapy for nAMD [23]. ERM newly developed in 17% (10/60) of eyes that had no ERM at baseline over our 7-year observational period. A previous 3-year observation study showed that ERM newly developed in 43% (13/30) of eyes [24]. The higher prevalence of ERM in AMD has been proposed to be caused by inflammation or more preretinal glial cells compared with healthy eyes [25].

Macular atrophy involving the fovea increased and correlated with 7-year BCVA in the present study. Previous studies demonstrated that the rate of new development of macular atrophy involving the fovea was 22% and 17% over a 5-year and 2-year observational period following anti-VEGF therapy, respectively [12, 26]. In the present study, the rate of new macular atrophy development was 17% (10/59) over 7 years. The HARBOR Study suggested that monthly injections may involve a higher risk than PRN regimen over 2 years [27]. Recently, subfoveal choroidal thinning at baseline correlated with an increased risk of macular atrophy over 2 years [28]. In the present study, there were no differences in baseline parameters or treatment frequency between eyes with and without new macular atrophy over the 7-year observational period. The cause of macular atrophy after anti-VEGF treatment for nAMD over the long-term is unclear.

Among the baseline parameters, only baseline BCVA correlated with 7-year BCVA. Therefore, early diagnosis and treatment of nAMD is essential for maintaining good BCVA over the long-term. Baseline CRT did not correlated with 7-year BCVA ($P$=0.92), which is similar to the results of the SEVEN-UP Study ($P$<0.80) [7]. Eyes requiring PDT induced a poor course of 7-year BCVA. Recent 5-year studies reported that BCVA was maintained in PCV with a pachychoroid phenotype but not in PCV with a nonpachychoroid phenotype after PDT [29], whereas it did not differ after anti-VEGF monotherapy between the two phenotypes [30]. We did not assess phenotypes before PDT; however, when PDT is considered, it may be better to investigate whether a pachychoroid or nonpachychoroid phenotype is involved. Furthermore, cataract surgery during the observation period marginally significantly correlated with 7-year logMAR BCVA ($P$=0.06) but the correlation was weak (r=−0.24).

This study had certain limitations. First, the sample size was small. It was challenging to conduct a complete 7-year observation in older patients with nAMD; therefore, the number of eyes that were lost to follow-up was relatively large (77/154; 50%). The age of eyes that were lost to follow-up was significantly higher than that of the eyes that completed the 7-year follow-up. Since the mean 7-year logMAR BCVA was lower than that at baseline, a larger sample size might reveal significant difference. Second, there was an interracial difference in the nAMD subtype ratio. A previous binational study using the same diagnostic criteria showed that the rate of PCV was lower in the Caucasian than in the Asian population (9% vs. 48%) [31]. However, the 7-year visual outcomes of tAMD (higher in the Caucasian population) were similar to that of PCV (higher in the Asian population) in the present study. Although we presented the outcome of eyes with RAP, the sample size was too small to be appropriately analysed. Third, each retinal specialist decided retreatments. However, the treatment policy for each patient was discussed in a weekly conference. Fourth, available agents changed over time. Brolucizumab has only been available for use in Japan since May 2020.

In conclusion, BCVA in nAMD eyes remained stable for 7 years after 1-year fixed regimen of IVA, essentially followed by PRN regimen of IVA, and sometimes followed by agents switching, PDT, or vitrectomy as needed, without drug-induced severe complications. Given that baseline BCVA positively correlated with the 7-year BCVA, early diagnosis and treatment of nAMD are essential to maintain good BCVA over the long term, even in eyes with relatively poor vision at the first visit.

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**Compliance with Ethical Standards**

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**Conflict of Interest:**

Manabu Miyata has received research grants from Alcon Japan, Novartis Pharma, and Santen Pharmaceutical; and a speaker honorarium from HOYA, Santen Pharmaceutical, Bayer Yakuhin, Senju Pharmaceutical, and Kowa Pharmaceutical. Sotaro Ooto has received a speaker honorarium from Bayer Yakuhin, Kowa Pharmaceutical, Janssen Pharmaceutical, Novartis Pharma, AMO Japan, Santen Pharmaceutical, Alcon Japan, and Senju Pharmaceutical. Hiroshi Tamura has received a grant from Findex; and a speaker honorarium from Bayer Yakuhin, Novartis Pharma, Santen Pharmaceutical, SUNTORY, and Otsuka Pharmaceutical. Naoko Ueda-Arakawa has received a speaker honorarium from Santen Pharmaceutical, Novartis Pharma, and Chugai Pharmaceutical. Yuki Muraoka has received grants from Bayer Yakuhin, Novartis Pharma, and Alcon Japan; and a speaker honorarium from Canon, Santen Pharmaceutical, Senju Pharmaceutical, Bayer Yakuhin, Novartis Pharma, AMO Japan, HOYA, and Johnson & Johnson. Masahiro Miyake has received a grant from Novartis Pharma; and a speaker honorarium from Bayer Yakuhin, Kowa Pharmaceutical, Alcon Japan, HOYA, Novartis Pharma, AMO Japan, Santen Pharmaceutical, Senju Pharmaceutical, Johnson & Johnson, and Chugai Pharmaceutical. Ayako Takahashi has a speaker honorarium from Bayer Yakuhin, Novartis Pharma, Santen Pharmaceutical, and MSD. Akihito Uji has received a speaker honorarium from Canon, Bayer Yakuhin, Novartis Pharma, Santen Pharmaceutical, Senju Pharmaceutical, and HOYA. Kenji Yamashiro has received a speaker honorarium from Novartis Pharma, Bayer Yakuhin, Santen Pharmaceutical, Alcon Pharma, Senju Pharmaceutical, Kowa Pharmaceutical, and Chugai Pharmaceutical. Akitaka Tsujikawa has received grants from Canon, Findex, Santen Pharmaceutical, Kowa Pharmaceutical, Pfizer, AMO Japan, Senju Pharmaceutical, Wakamoto Pharmaceutical, Alcon Japan, Novartis Pharma, Otsuka Pharmaceutical, Bayer Yakuhin, and Nitten Pharmaceutical; a speaker honorarium from Bayer Yakuhin, Senju Pharmaceutical, Novartis Pharma, Santen Pharmaceutical, Alcon Pharma, Alcon Japan, AbbVie GK, AMO Japan, Kowa Pharmaceutical, Canon Otsuka Pharmaceutical, and Wakamoto Pharmaceutical; and consultant fee from Senju Pharmaceutical, Bayer Yakuhin,

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**Ethical approval:**
All procedures performed in studies involving human participants were in accordance with the ethical standards of the ethics committee of Kyoto University Graduate School of Medicine (Kyoto, Japan) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Informed consent:**
Informed consent was obtained from all individual participants included in the study.

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**Table 1. Comparison of baseline parameters, treatment frequency, and submacular haemorrhage during the observational period for each subtype of neovascular age-related macular degeneration**

| | | Whole Cohort | Typical Neovascular AMD | PCV | RAP | *P*-value |
|---|---|---|---|---|---|---|
| Eyes, n (%) | | 63 | 31 (49) | 27 (43) | 5 (8) | |
| Age, years (range) | | 73.2±7.4 (56–88) | 73.6±7.5 (58–88) | 71.4±6.7 (56–83) | 80.0±7.7 (69–87) | 0.052 |
| Male sex, n (eyes, %) | | 44 (70) | 24 (77) | 18 (56) | 2 (40) | 0.12† |
| LogMAR BCVA | | 0.20±0.24 | 0.19±0.24 | 0.17±0.21 | 0.34±0.38 | 0.34 |
| AL, mm | | 23.38±1.03[a] | 23.36±1.10[b] | 23.41±0.98[c] | 23.28±1.08 | 0.96 |
| Refractive errors (spherical equivalent), dioptres | | +0.49±1.93 | +0.52±1.87 | +0.63±2.01 | −0.53±2.01 | 0.47 |
| IOP, mmHg | | 14.0±3.4 | 14.5±3.9 | 13.8±3.0 | 12.3±1.9 | 0.42 |
| OCT-derived parameter | CRT, µm | 334.7±141.8 | 350.6±155.9 | 311.1±121.2 | 363.7±164.5 | 0.52 |
| | CCT, µm | 234.7±85.0 | 236.4±83.2 | 242.4±82.2 | 183.5±111.4 | 0.35 |
| | Subfoveal PED height, µm | 56.7±97.6 | 37.8±49.2 | 51.7±69.8 | 201.3±262.4 | 0.34 |
| | VMT/VMA involving the fovea, n (%) | 9 (14) | 6 (19) | 3 (11) | 0 (0) | 0.21† |
| | ERM, n (%) | 3 (5) | 2 (6) | 1 (4) | 0 (0) | 0.49† |
| | Macular atrophy involving the fovea, n (%) | 4 (6) | 2 (6) | 2 (7) | 0 (40) | 0.85† |
| Anti-VEGF injections, n | Total (0–7) | 24.0±13.3 | 23.4±13.6 | 23.1±13.0 | 32.0±13.2 | 0.38 |
| | 1-year (0–1) | 7 | 7 | 7 | 7 | |
| | 2-year (1–2) | 2.9±3.0 | 2.9±2.8 | 2.7±3.2 | 4.4±2.9 | 0.51 |
| | 3-year (2–3) | 3.0±2.8 | 3.2±2.7 | 2.5±2.8 | 4.4±2.9 | 0.33 |
| | 4-year (3–4) | 2.9±2.7 | 3.0±2.9 | 2.5±2.6 | 4.4±1.8 | 0.36 |
| | 5-year (4–5) | 3.0±2.5 | 2.7±2.6 | 3.0±2.3 | 4.2±2.1 | 0.48 |
| | 6-year (5–6) | 2.5±2.5 | 2.2±2.5 | 2.7±2.4 | 3.8±2.4 | 0.41 |
| | 7-year (6–7) | 2.6±2.5 | 2.4±2.5 | 2.7±2.6 | 3.8±2.4 | 0.49 |
| | Additional injections (1–7) | 17.0±13.3 | 16.4±13.6 | 16.1±13.0 | 25.0±13.2 | 0.38 |
| PDT sessions over the 7 years, n | | 0.2±0.6 | 0 | 0.2±0.8 | 1.0±1.7 | 0.44 |
| Cataract surgery over the 7 years, n | | 25 (40) | 15 (48) | 10 (37) | 0 (0) | 0.08† |
| Massive SMH over the 7 years including baseline, n (%) | | 8 (13) | 3 (10) | 5 (19) | 0 (0) | 0.70† |

Data are presented as means ± standard deviations where applicable.

AMD = age-related macular degeneration; PCV = polypoidal choroidal vasculopathy; RAP = retinal angiomatous proliferation; logMAR BCVA = logarithm of the minimal angle of resolution best-corrected visual acuity; AL = axial length; IOP = intraocular pressure; OCT = optical coherence

tomography; CRT = central retinal thickness; CCT = central choroidal thickness; PED = pigment epithelial detachment; VMT = vitreomacular traction; VMA = vitreomacular adhesion; ERM = epiretinal membrane; VEGF = vascular endothelial growth factor; PDT = photodynamic therapy; SMH = submacular haemorrhage

Displacement grading at 1 week after treatment: 0, almost no displacement; 1, displacement beyond the arcade but residual at the fovea; 2, displacement outside the fovea

The data for [a, b,] and [c] are missing in 8, 6, and 2 eyes, respectively.

[†]Chi-square trend test was performed. Other tests for comparison of the three groups using analysis of variance.

*Statistically significant ($P$<0.05)

**Table 2. Comparison of logMAR best-corrected visual acuity among the three groups at each observational time point**

| | | Whole Cohort | Typical Neovascular AMD | PCV | RAP | *P*-values Among the 3 Groups |
|---|---|---|---|---|---|---|
| LogMAR BCVA | Baseline | 0.20±0.24 | 0.19±0.24 | 0.17±0.21 | 0.34±0.38 | 0.34 |
| | 1-year | 0.10±0.24 | 0.13±0.24 | 0.02±0.17 | 0.35±0.43 | 0.10 |
| | 2-year | 0.09±0.22 | 0.13±0.20 | 0.02±0.18 | 0.28±0.38 | 0.09 |
| | 3-year | 0.13±0.24 | 0.15±0.22 | 0.08±0.21 | 0.31±0.41 | 0.12 |
| | 4-year | 0.15±0.25 | 0.15±0.22 | 0.12±0.24 | 0.32±0.41 | 0.26 |
| | 5-year | 0.16±0.23 | 0.17±0.22 | 0.12±0.23 | 0.34±0.27 | 0.12 |
| | 6-year | 0.20±0.31 | 0.19±0.29 | 0.16±0.28 | 0.52±0.52 | 0.39 |
| | 7-year | 0.29±0.45 | 0.29±0.44 | 0.19±0.32 | 0.76±0.79 | 0.26 |

Data are presented as means ± standard deviations

logMAR BCVA = logarithm of the minimum angle of resolution of best-corrected visual acuity; AMD = age-related macular degeneration; PCV = polypoidal choroidal vasculopathy; RAP = retinal angiomatous proliferation.

**Table 3. Morphological parameter changes between baseline and the 7-year time point**

| | Baseline | After 7 Years | *P*-value |
|---|---|---|---|
| CRT, µm | 334.7±141.8 | 182.1±56.4 | <0.001* |
| CCT, µm | 234.7±85.0 | 186.1±79.5 | <0.001* |
| Subfoveal PED height, µm | 56.7±97.6 | 58.7±111.7 | 0.92 |
| VMT/VMA involving the fovea, n (%) | 9 (14) | 1 (2) | 0.01*[#] |
| ERM, n (%) | 3 (5) | 13 (21) | 0.04*[#] |
| Macular atrophy involving the fovea, n (%) | 4 (6) | 14 (22) | 0.002*[#] |

Data are presented as means ± standard deviations where applicable.

CRT = central retinal thickness; CCT = central choroidal thickness; PED = pigment epithelial detachment; VMT = vitreomacular traction; VMA = vitreomacular adhesion; ERM = epiretinal membrane

[#]Chi-square test; alternatively, the *t*-test was used. *Statistically significant (*P*<0.05)

**Table 4. Correlation between 7-year logarithm of the minimal angle of resolution best-corrected visual acuity and studied parameters**

| | | Univariable analysis | | Multivariable analysis | |
|---|---|---|---|---|---|
| | | *P* | r | *P* | β |
| Baseline parameters | Age | 0.06 | 0.24 | 0.42 | 0.10 |
| | Sex (1, male; 2, female) | 0.68 | −0.05 | - | - |
| | LogMAR BCVA | <0.001* | 0.45 | 0.007 | 0.35 |
| | AL | 0.30 | 0.14 | - | - |
| | Refractive errors | 0.38 | −0.11 | - | - |
| | IOP | 0.57 | 0.08 | - | - |
| | CRT | 0.92 | 0.01 | - | - |
| | CCT | 0.92 | 0.01 | - | - |
| | Subfoveal PED height | 0.49 | 0.09 | - | - |
| | VMT/VMA involving the fovea | 0.83 | −0.03 | - | - |
| | ERM | 0.59 | −0.07 | - | - |
| | Macular atrophy involving the fovea | 0.11 | 0.21 | - | - |
| | Massive SMH | 0.74 | 0.04 | - | - |
| Seven-year parameters | CRT | 0.23 | 0.15 | | |
| | CCT | 0.52 | −0.08 | | |
| | Subfoveal PED height | 0.31 | 0.13 | | |
| | VMT/VMA involving the fovea | 0.96 | 0.007 | | |
| | ERM | 0.002* | 0.38 | | |
| | Macular atrophy involving the fovea | 0.004* | 0.36 | | |
| Treatment-associated parameters | Total number of anti-VEGF injections | 0.68 | 0.05 | | |
| | Additional number of anti-VEGF injections | 0.68 | 0.05 | | |
| | PDT sessions over the 7 years | 0.04* | 0.26 | | |
| | Cataract surgery over the 7 years | 0.06 | −0.24 | | |

logMAR BCVA = logarithm of the minimal angle of resolution best-corrected visual acuity; AL = axial length; IOP = intraocular pressure; CRT = central retinal thickness; CCT = central choroidal thickness; PED = pigment epithelial detachment; VMT = vitreomacular traction; VMA = vitreomacular adhesion; ERM = epiretinal membrane; SMH = submacular haemorrhage; VEGF = vascular endothelial growth factor; PDT = photodynamic therapy

Multivariable regression analysis was performed among baseline parameters.

*Statistically significant (*P*<0.05)

**Supplementary Table 1. Differences in baseline parameters, treatment frequency, and submacular haemorrhage over the observational period between eyes with and without new macular atrophy involving the fovea**

| | New Macular Atrophy Involving the Fovea | No Macular Atrophy Involving the Fovea at 7 Years | *P*-value |
|---|---|---|---|
| Eyes, n | 10 | 49 | |
| Age, years | 74.0±10.0 | 72.9±6.9 | 0.66 |
| Male sex, n (%) | 7 (70) | 35 (71) | 0.93[#] |
| LogMAR BCVA | 0.22±0.24 | 0.17±0.21 | 0.46 |
| AL, mm | 23.14±0.85[a] | 23.45±1.07[b] | 0.44 |
| Refractive errors, dioptres | +0.28±1.74 | +0.38±1.96 | 0.88 |
| IOP, mmHg | 12.4±2.5 | 14.3±3.4 | 0.11 |
| CRT, µm | 369.5±158.1 | 322.4±128.6 | 0.32 |
| CCT, µm | 210.6±97.8 | 237.9±78.5 | 0.34 |
| Subfoveal PED, µm | 86.2±137.1 | 50.3±90.3 | 0.30 |
| VMT/VMA involving the fovea, n (%) | 2 (20) | 6 (12) | 0.51[#] |
| ERM, n (%) | 0 (0) | 3 (6) | 0.42[#] |
| Total anti-VEGF therapy, n | 22.0±13.3 | 25.0±13.7 | 0.52 |
| Additional anti-VEGF therapy, n | 15.0±13.3 | 18.0±13.7 | 0.52 |
| PDT sessions over the 7 years, n | 0.2±0.4 | 0.2±0.7 | 0.91 |
| Massive SMH over the 7 years, n | 2 (20) | 6 (12) | 0.51[#] |

Data are presented as means ± standard deviations where applicable.

LogMAR BCVA = logarithm of the minimal angle of resolution best-corrected visual acuity; AL = axial length; IOP = intraocular pressure; CRT = central retinal thickness; CCT = central choroidal thickness; PED = pigment epithelial detachment; VMT = vitreomacular traction; VMA = vitreomacular adhesion; ERM = epiretinal membrane; VEGF = vascular endothelial growth factor; PDT = photodynamic therapy; SMH = submacular haemorrhage

The data for [a] and [b] are missing in 2 and 5 eyes, respectively.

[#]Chi-square test; alternatively, the *t*-test was used. *Statistically significant (*P*<0.05)

## FIGURE LEGENDS

Figure 1. Representative images of eyes with a good and poor 7-year visual course
(A–D) Images of eyes with a good 7-year visual course in a 60s female patient with polypoidal choroidal neovasculopathy. Baseline and 7-year BCVAs were 1.2 (20/17) and 1.5 (20/13), respectively.
(A) An optical coherence tomography (OCT) image with a near-infrared fundus image at baseline. Subretinal fluid, serous pigment epithelial detachment, and choroidal neovascularization are observed. (B) A colour fundus photograph at baseline. Many drusen are observed. (C) An OCT image with a near-infrared fundus image 7 years after the initial treatment. No retinal exudates are observed. Macular atrophy is observed nasal to the fovea; however, it does not involve the fovea. Furthermore, there is increased signal transmission in the choroid on OCT and hyper-refractivity on the near-infrared fundus image at the site of macular atrophy. (D) A colour fundus photograph taken 7 years after the initial treatment. The choroidal vessels are clearly visible, and hypopigmentation is observed at the site of macular atrophy.
(E–H) Images of eyes with a poor 7-year visual course in a 70s male patient with typical neovascular age-related macular degeneration. Baseline and 7-year BCVAs were 0.7 (20/29) and 0.2 (20/100), respectively.
(E) An OCT image with a near-infrared fundus image at baseline. Subretinal fluid, choroidal neovascularization, and vitreomacular adhesion at the fovea are observed. (F) A colour fundus photograph at baseline. Drusen or fundus tessellation is not observed. (G) An OCT image with a near-infrared fundus image taken 7 years after the initial treatment. No retinal exudates are observed. Macular atrophy involving the fovea is observed. Signal transmission in the choroid is increased on OCT and hyper-refractivity appears on the near-infrared fundus image at the site of macular atrophy. Posterior vitreous detachment occurred and vitreomacular adhesion was relieved. (H) A colour fundus photograph taken 7 years after the initial treatment—no contradictory findings to macular atrophy are observed. Fundus tessellation is increased.

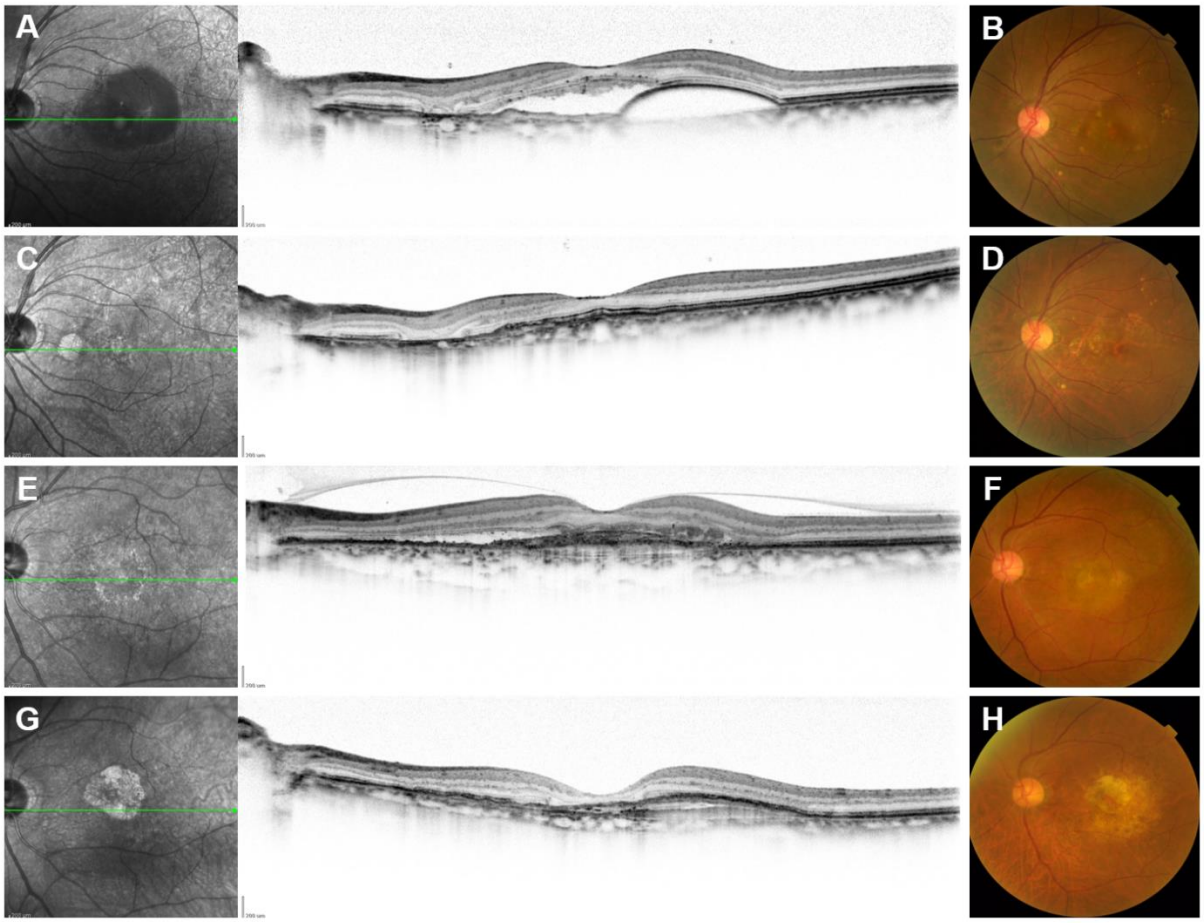
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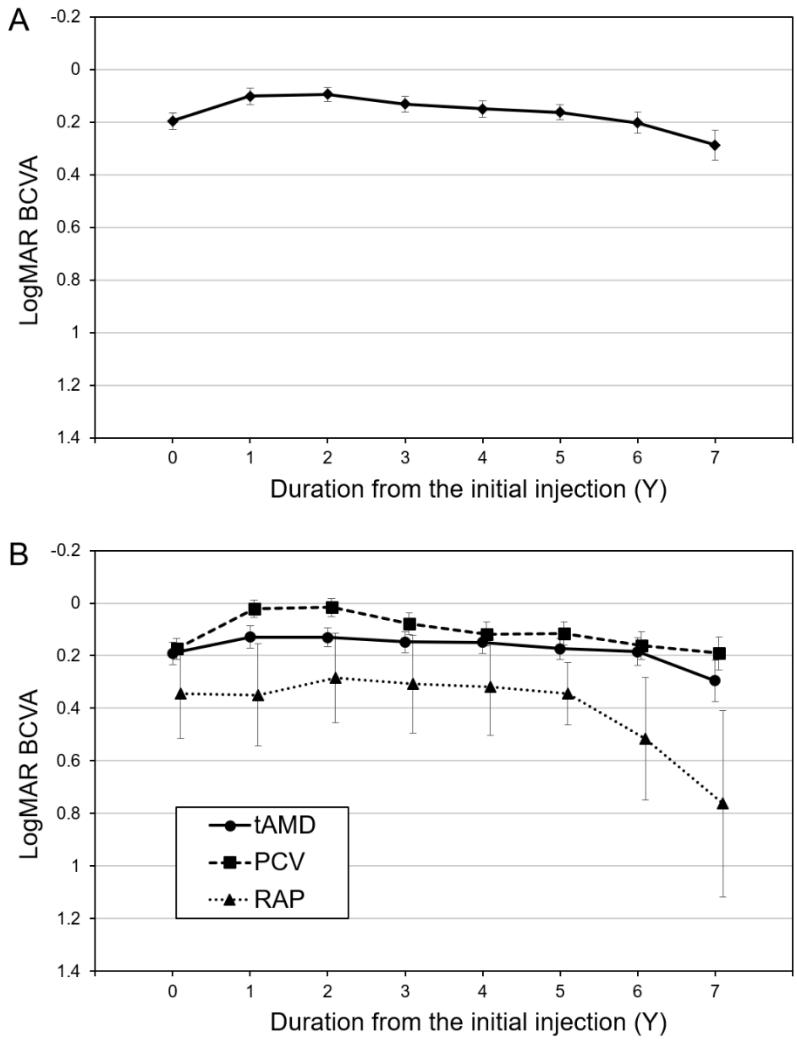
Figure 2. Seven-year course of best-corrected visual acuity
(A) In the analysis of the 63 eyes using repeated measures analysis of variance, best-corrected visual acuity (BCVA) significantly changed (*P*<0.001), and 1-year and 2-year BCVA significantly increased as compared with baseline BCVA (*P*=0.002 and 0.001, respectively) when assessed using post hoc analysis. However, 3-, 4-, 5-, 6-, and 7-year BCVA were not significantly different from baseline BCVA (*P*=0.30, >0.999, >0.999, >0.999, and >0.999, respectively). Taken together, BCVA significantly improved after year 1 and 2, and then slowly decreased back to baseline BCVA.
(B) In the analysis of each neovascular age-related macular degeneration (nAMD) subtype, BCVA changed in polypoidal choroidal vasculopathy (PCV; *P*<0.001), but not in typical nAMD (tAMD) or retinal angiomatous proliferation (RAP; *P*=0.13 and 0.25, respectively). In PCV, 1-year (*P*<0.001) and 2-year (*P*=0.001) BCVA was significantly better than at baseline, whereas 3-, 4-, 5-, 6-, and 7-year BCVA did not significantly differ from baseline.



Supplementary Figure. Flow chart of the study population selection process
In total, 154 eyes met the inclusion criteria; however, 77 eyes were lost to follow-up over the 7-year observational period. Among the remaining eyes, 7 had a worse baseline best-corrected visual acuity than 20/200, 4 had diabetic retinopathy, and 3 had retinal vein occlusion. Thus, 63 eyes were included in the analysis.