One-year outcomes of fixed treatment of intravitreal aflibercept for exudative age-related macular degeneration and the factor of visual prognosis

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Abstract
The aim of this study was to investigate the efficacy of periodic intravitreal aflibercept (IVA) in exudative age-related macular degeneration, and to explore the predictive factors for visual outcome.

This is a prospective interventional case series.

Fifty-two eyes of 52 treatment-naïve age-related-macula-degeneration patients were enrolled. All participants received IVA bimonthly following 3 monthly loading dose. The primary endpoint was change in best corrected visual acuity (BCVA) and central retinal thickness (CRT), and the secondary outcomes included changes in subfoveal choroidal thickness (SCT), macular atrophy (MA), and retinal average sensitivity (AS) determined by microperimetry at 12 months compared with baseline. The predictive factors for the change of BCVA were examined.

Of 52 enrolled patients, 4 patients were drop out. Remaining 48 patients were examined. Mean logMAR BCVA significantly improved from 0.42 ± 0.37 at baseline to 0.29 ± 0.34 at 12 months (P = .008). Mean CRT and SCT significant reduced from 285.6 ± 135.2 \( \mu \)m, 247.9 ± 96.7 \( \mu \)m at baseline to 233.4 ± 98.0 \( \mu \)m, 208.1 ± 94.6 \( \mu \)m at 12 months, respectively (P < .001). At 12 months, 35 eyes of 48 eyes (72.3%) were archived dry macula. MA occurred in 7 eyes of 35 eyes with dry macula at 12 months (20.0%). AS was significant improved (P = .027) between baseline (median: 15.7 dB) and 12 months (median: 19.5 dB). The BCVA of the cases with MA-involved fovea was significant worse. Age was significantly predicted for the BCVA for the BOCA at 12 months.

IVA administered over 1 year improved BCVA, AS, and morphological findings, and the predictive factors for BCVA were age and MA-involved fovea.

Abbreviations: AMD = age-related-macula-degeneration, BCVA = best-corrected visual acuity, CNV = choroidal neovascularization, CRT = central retinal thickness, FAF = fundus autofluorescence, ICGA = indocyanine green angiography, IVA = intravitreal aflibercept, IVR = intravitreal ranibizumab, logMAR = logarithm of the minimum angle of resolution, MA = macular atrophy, OCT = optical coherence tomography, PCV = polypoidal choroidopathy, PRN = pro re nata, RAP = retinal angiomatous proliferation, RPE = retinal pigment epithelium, SCT = subfoveal choroidal thickness, t-AMD = typical AMD, VEGF = vascular endothelial growth factor.

Keywords: aflibercept, central retinal thickness, exudative age-related macular degeneration, macular atrophy, microperimetry, retinal sensitivity, subfoveal choroidal thickness

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1. Introduction

Exudative age-related-macula-degeneration (AMD) is the significant damage of visual function, and it can cause severe visual loss. The management of AMD has been revolutionized by the introduction of anti-vascular endothelial growth factor (VEGF) agents, with pivotal clinical trials demonstrating efficacy in visual outcomes for ranibizumab (Lucentis; Novartis Pharma AG, Basel, Switzerland)[12,13] and aflibercept (Eylea; Bayer HealthCare, Berlin, Germany)[14] using fixed treatment regimens. The development of anti-VEGF agents changed AMD treatment and anti-VEGF therapy become a main therapy for AMD presently. There are also several dosing regimens such as pro re nata (PRN), fixed[15] and treat and extend. There are many discussions about the treatment regime of AMD. In the VEGF Trap-Eye, investigation of efficacy and safety in wet AMD (VIEW) 1,[16] VIEW 2 trials[17] and the report of the VEGF Trap-Eye, investigation of efficacy and safety in wet AMD (VIEW) 1,[18] VIEW 2 trials[19] and the report by Yamamoto et al.[20] intravitreal aflibercept (IVA) injections dosed monthly or every 2 months after 3 initial monthly doses demonstrated noninferiority and safety when compared with monthly intravitreal ranibizumab injections.

Macular atrophy (MA) is the late-stage, atrophic manifestation of exudative AMD.[8–10] The appearance of MA is an important indicator of poor visual prognosis in eyes with AMD.[11–13] Although, anti-VEGF therapy was a major breakthrough in treating exudative AMD, a treatment protocol that halts or reverses MA progression has not yet been developed. Protein complex formation, retinal pigment epithelial (RPE) hypertrophy, and cell death, the first events in MA, have been observed after anti-VEGF treatment.[11,14] Two previous studies evaluated intravitreal ranibizumab (IVR) monotherapy during a 2-year period and reported MA incidences of 23.8% and 71.4%.[15] Moreover, there is a report about MA development after aflibercept therapy for exudative AMD.[9]

Koizumi et al.[16] reported that mean subfoveal choroidal thickness (SCT) decreased in eyes with exudative AMD treated with aflibercept therapy during 12 months, whereas the relationship between SCT and visual prognosis was unknown.

The Macular Integrity Assessment Device system (MAIA; Centerveue, Padova, Italy),[17] a novel device that utilizes scanning laser ophthalmoscopy technology, is an advancement on the MP-1 device (Nidek Instruments Inc, Padova, Italy). MAIA is a third-generation microperimetry system that measures visual sensitivity using Goldmann style stimulus points. It is fast, can be customized, and allows follow-up assessments. The purpose of this examination is to evaluate the maintenance retinal sensitivity during follow-up period.

The purpose of this study was to evaluate 1-year visual acuity, visual field, and morphologic outcomes of IVA for treatment-naive AMD. And, the predicted factors for visual outcome were examined. Therefore, we investigated the 1-year results of fixed-dose regimen with aflibercept for AMD, respectively.

2. Methods

2.1. Study design and participants

This was a prospective, interventional, uncontrolled, pilot study conducted in an institutional setting. The institutional review board/ethics committee of the Kagawa university, faculty of medicine approved this study, which was registered in the university hospital medical information network clinical trials registry (ID: UMIN 000010171). This study was conducted between March 13, 2013 and July 8, 2014 in the department of ophthalmology of Kagawa university hospital. Written informed consent was obtained from each participant before any study procedures or examinations were performed and study conduct adhered to the tenets of the Declaration of Helsinki.

All participants were diagnosed with exudative AMD and met all of the following criteria: age >45 years, neovascular AMD with presence of subfoveal exudative change, best-corrected visual acuity (BCVA) better than <1 logarithm of the minimum angle of resolution (logMAR) and >0 logMAR, and agree with participants in the study. The exclusion criteria included the following: the total lesion area on fluorescein angiography >12 Macular Photocoagulation Study disc area, any previous treatment to choroidal neovascularization (CNV), the presence of other retinal diseases (e.g., angioid streaks, myopic CNV, retinal vein or artery occlusion), the presence of subretinal hematoma, scar, or macular fibrosis (>50% lesion area), active intraocular inflammation, allergy to fluorescein sodium or indocyanine green dye. In addition, the patients who dropped out from the study were excluded from the analysis.

2.2. Intervention and observation procedure

![](http://example.com/image1)

During the study period, a total of 52 patients with treatment-naive AMD were scheduled to receive bi-monthly IVA injections followed by 3 consecutive monthly IVA during 1 year. Of the 52 patients, 4 were lost to follow-up. They received a total of 7 injections in the study period of 12 months.

Patients underwent comprehensive examinations including visual acuity measurement, fundus photography, spectral-domain optical coherence tomography (OCT, Spectralis; Heidelberg Engineering, Heidelberg, Germany), fluorescein angiography, indocyanine green angiography (ICGA), and fundus autofluorescence imaging (FAF, HRA2; Heidelberg Engineering, Germany) at baseline under sufficient pupillary dilation. Visual acuity was measured using Landolt C charts (Takagi Seiko, Nakano, Japan), and the BCVA was calculated using the logMAR scale. SCT was measured in enhanced depth imaging, which was defined as the distance between the outer border of the Bruch membrane and outer border of the choroid. All OCT measurements were performed by 2 independent well-trained retinal specialists (A.O., S.M.). The average of the values measured by the 2 investigators was used for analysis. A macula status was judged to be dry when there was complete resolution of subretinal and intraretinal fluid on OCT.

The MA was defined as a hypofluorescent area detected by FAF imaging, which included, such as, fibrovascular scarring, drusen, and surrounding RPE atrophy in this study. When the exudative changes were remaining, it was confused to estimate the MA area, according to a block of subretinal material or increased FAF signal (e.g., retinal hemorrhage, subretinal fluid, lipid deposit, and fibrin). So that, MA areas were estimated only in eyes with dry macula at 12 months.

Macular retinal sensitivity was measured by MAIA microperimetry. The following parameters were used in the present study: a 68-stimuli grid covering the central 10 degree of the retina, a fixation target that consisted of a red circle with 18 diameter stimulus size, Goldmann III, background luminance set at 4 apostilb (asb), maximum luminance of 1000 asb, and a stimulus dynamic range of 36 dB.

2.3. Outcome measure

The primary treatment outcomes of this study included change in BCVA and central retinal thickness (CRT) at 12 months.
compared with baseline. The secondary outcomes included changes in SCT, MA area on FAF, macular retinal sensitivity with microperimetry between baseline and 12 months. And, the influenced factors for visual outcome were examined.

2.4. Statistical analyses

Statistical analysis was carried out using SPSS version 21.0 (International Business Machines Corp, Armonk, NY), except for the generalized estimating equation, which was performed using software R (ver. 3.0.2 R Foundation for Statistical Computing, Vienna, Austria).

Visual acuity was measured with Landolt C and converted to logMAR to perform statistical analysis. Paired t test was used to assess changes in BCVA from baseline to 12 months. Correction of repeated measurements was used for Bonferroni correction. Changes in CRT, SCT, and average macular retinal sensitivity from baseline were assessed using Wilcoxon signed-rank test with Bonferroni correction. Comparison of BCVA change, and presence or absence of MA at fovea, was assessed using student t-test. Statistical significance was defined as \( P < .05 \).

3. Results

3.1. Patients

Fifty-two eyes of 52 patients were included in the study. During the study period, 4 patients were dropped out. These 4 patients chose to withdraw from the study for personal reasons. Because the reason for the missingness was unrelated to the response, we did not employ the imputation analyses to avoid the bias generated by imputation. Therefore, 48 eyes of 48 patients were completed this study.

Patients’ background is shown in Table 1. Thirty-five patients were men and 13 patients were women. The mean age of patients was 75.0 ± 8.2 (mean ± SD) years’ old. In terms of subtype, 11 patients with typical AMD (t-AMD), 31 patients with polypoidal choroidopathy (PCV) and 6 patients with retinal angiomatous proliferation (RAP) of 48 patients. All patients received 7 times injections of a...}

### Table 1

Baseline Characteristics of 48 eyes with age-related macular degeneration, and statistical analysis of the amount of BCVA change between baseline and 12 months in each category.

|                        | Baseline         | Analysis of BCVA change |
|------------------------|------------------|-------------------------|
| Age, y (mean±SD)       | 75.0±8.2         | .023                    |
| Sex (%)                |                  |                         |
| - Men                  | 35 (72.9)        | .064                    |
| - Woman                | 13 (27.1)        |                         |
| AMD phenotype (%)      |                  |                         |
| - Typical AMD          | 11 (22.9)        |                         |
| - Polypoidal choroidal vasculopathy | 31 (64.6) | .264                   |
| - Retinal angiomatous proliferation | 6 (12.5) | .942                   |
| logMAR BCVA (mean±SD)  | 0.20±0.19        | .001                    |
| Central retinal thickness, mm (mean±SD) | 375.0±94.5 | .202                   |
| Subfoveal choroidal thickness, mm (mean±SD) | 247.3±96.7 | .164                   |
| Average retinal sensitivity, dB (mean±SD) | 15.4±5.4 |                         |
| Fluorescein angiographic finding (%) |                  |                         |
| - Predominantly classic CNV | 6 (12.5) |                         |
| - Minimally classic CNV | 5 (10.4) | .423                   |
| - Occult CNV           | 24 (77.1)        | .455                    |
| Presence of PED (%)    |                  |                         |
| - Exist                | 24 (50)          | .217                    |
| - Absent               | 24 (50)          |                         |
| Presence of CME (%)    |                  |                         |
| - Exist                | 11 (22.9)        | .108                    |
| - Absent               | 37 (77.1)        |                         |

BCVA=best-corrected visual acuity, CME=cystoid macular edema, CNV=choroidal neovascularization, dB=decibel, logMAR=logarithm of the minimum angle of resolution, PED=pigment epithelial detachment, SD=standard deviation.

BCVA was not signiﬁcantly improved by in 1 eye (2.1%) (Fig. 1).

3.2. Change in the logarithm of the minimum angle of resolution (logMAR) visual acuity

Mean BCVA at the baseline was 0.35 ± 0.34 in PCV, 0.54 ± 0.37 in t-AMD and 0.50 ± 0.48 in RAP. The mean logMAR BCVA signiﬁcant improved in all 48 eyes, and was 0.42 ± 0.37 (\( P = .002 \)), 0.33 ± 0.37 (\( P = .001 \)), 0.29 ± 0.34 (\( P = .008 \)) at 3, 6, and 12 months, respectively. In each subtype, mean logMAR BCVA was not signiﬁcant but gradually improved in each subtype of AMD for 12 months. LogMAR BCVA at 12 months was improved by ≥ 0.3 in 9 eyes (18.7%), and stable in 38 eyes (79.2%) and worsened by in 1 eye (2.1%) (Fig. 1).

3.3. Change in CRT

CRT at baseline was 420.1 ± 152.5 μm. After the treatment with aflibercept retinal thickness promptly reduced at 3 months and maintained until 12 months by continue bimonthly injection after loading treatment. In all subtypes pattern, CRT was reduced signiﬁcantly. Patients with PCV (\( P < .001 \)) and t-AMD (\( P = .08 \)) showed signiﬁcant reduction from baseline. The changes of CRT

with RAP (\( P = .19 \)) were not signiﬁcant between baseline and 12 months. The CRT decreased to nearly the minimum amount by 3 months, then essentially keeping unchanged thereafter (Fig. 2).

3.4. Change in SCT

The mean SCT decreased from 247.9 ± 95.7 μm at baseline to 226.8 ± 96.1 μm at 3 months, 224.0 ± 95.4 μm at 6 months, and 208.1 ± 94.6 μm at 12 months (\( P < .001 \)) signiﬁcantly. SCT decreased statistically signiﬁcant in t-AMD (\( P = .006 \)) and PCV (\( P = .001 \)), but not in RAP (\( P = 1.00 \)). The SCT seemed to decrease to nearly the minimum amount by 3 months, then decreased moderately thereafter (Fig. 3).

3.5. Change in retinal sensitivity

Change in the retinal sensitivity of macular area as 68-stimuli grid covering the central 10 degree of the retina was statistically signiﬁcantly improved between baseline and 12 months (\( P = .027 \)). Baseline median sensitivity of macular area was 15.72 dB (first quartile: third quartile = 11.45:20.20), at 3 months, 14.65 dB (first quartile: third quartile = 12.68:21.50), and at 12 months, 19.49 dB (first quartile: third quartile = 13.41:22.39) (Fig. 4).

3.6. Achievement rate of dry macula

At 12 months, 35 eyes of 48 eyes (72.9%) archived dry macula, and remaining 13 eyes (27.1%) maintained exudative lesion. Of 35 eyes with dry macula at 12 months, t-AMD was 72.7% (8/11...
eyes), PCV was 73.3% (22/30 eyes), and RAP was 66.7% (4/6 eyes). Achievement rate of dry macula was not significant differences among 3 phenotypes.

3.7. Incident rate of MA

In 35 eyes with dry macula at 12 months, MA was occurred in 7 eyes (20.0%). Eyes with MA including the fovea were significantly lower visual acuity compared with eyes with MA existing extrafovea, or absence ($P = .032$, student $t$ test) (Fig. 5).

3.8. Factors related to visual acuity changes

Single regression analyses of the amount of BCVA change between baseline and 12 months were indicated in Table 1. Multiple regression analysis for potential confounders with the amount of BCVA change between baseline and 12 months are summarized in Table 2. LogMAR BCVA at baseline ($P < .001$) and age ($P = .001$) were significantly associated with improvement of BCVA at 12 months, indicating that poor vision at baseline and younger patients impacted improvement of BCVA changes. And another factor, such as phenotype, fluorescein angiographic findings, baseline CRT, SCT, average retinal sensitivity, and incident of MA (including extrafovea) were no correlation with the BCVA change.

4. Discussion

In the present study, 1-year visual and morphological outcomes of IVA therapy were investigated. The study included 48 eyes of 48 patients with exudative AMD administered 3 monthly IVA injections followed by injections every 2 months, similar to the 2q8 regimen of the VIEW 1 and VIEW 2 studies[6] and the report by Yamamoto et al for PCV.[7] At the end of 1 year, BCVA and CRT had improved significantly. Significant vision gains were observed, and these were largely stable throughout the study. There was a slight trend toward maintained BCVA at 12 months.
In the VIEW study,[5] it was suggested that although CRT is an important parameter for anti-VEGF therapies, it has limitations as a parameter for individual retreatment decisions aimed at optimizing visual acuity outcomes.

In the present study, the proportion of patients who achieved a dry macula at 12 months was 35/48 (72.9%), and the results indicated that the treatment performance was good with regard to maintaining visual acuity and reducing CRT. Although aflibercept treatment was effective in most patients in the present study, changes in CRT were not correlated with changes in BCVA. The mean CRT was reduced rapidly during the loading dose period, whereas the mean BCVA either improved gradually over the 12-month observation period or was maintained. MA influenced the outcome in some cases (20%). In addition, the presence of MA involving the fovea was associated with a higher risk of sustained visual acuity disturbance.[18]

In a previous study, a thicker SCT at baseline was related to better visual outcomes and better treatment responses to ranibizumab therapy for 6 months in eyes with exudative AMD.[19] Conversely, Koizumi et al[16] reported that, in their study, they did not identify a role of SCT in making detailed predictions of the effect of aflibercept. However, the possibility that excessive reduction in choroidal thickness resulted in an adverse effect in some eyes with exudative AMD was considered because the choroid plays an important role in supplying nutrients and oxygen to the outer retinal layers. Further investigation, including evaluation of additional clinical characteristics, is required in this regard.

According to a study in mice, anti-VEGF therapies can interfere with the maintenance of the ocular vasculature,[20] and may be associated with RPE damage and choroidal atrophy.[21–23] Therefore, it is possible that medications that block VEGF...
may play a role in the development of MA. Somewhat surprisingly, in the present study, there were no significant differences in MA development between subjects treated monthly and subjects treated via the 2q8 regimen. However, proactive abrcept treatment may be associated with higher MA incidence over longer periods of observation.

This study differs from other reports in several ways. We examined the 3 AMD subtypes in Japanese patients. In addition, we investigated retinal sensitivity from baseline to 12 months. Retinal sensitivity as measured by microperimetry may be more sensitive to changes in macular function because it assesses a larger retinal area than conventional distance visual acuity. Preservation of the central visual field is very important for activities of daily living. Therefore, retinal sensitivity should be a better indicator of practical visual capabilities in patients with AMD.

Bolz et al.[24] conducted a prospective study evaluating CRT. Changes in retinal sensitivity with CRT, and the functional and morphological effects of 3 loading doses of IVR, were investigated in 29 patients with previously untreated exudative AMD. They observed improvements in BCVA, CRT, and central retinal sensitivity after 1 month. However, in patients who were unstable and therefore required additional ranibizumab injections during the course of their study, retinal sensitivity as measured via the MAIA was unchanged from baseline to the end of the study period. In contrast, Okada et al.[25] reported that the retinal sensitivity measured by microperimetry may be a better way to assess the efficacy of photodynamic therapy for AMD.

Angiographic characteristics such as classic CNV on fluorescein angiography, blocked fluorescence, and large CNV lesions at baseline, and OCT characteristics such as thickened retina, subretinal fibrovascular tissue complex, and subretinal fibrotic tissue predict an increased risk of MA.[26,27]

The present study yielded novel information on relationships between macular sensitivity, retinal thickness, and BCVA in the maintenance phase of abrcept therapy for AMD. Patients could have stable BCVA and retinal thickness, yet still exhibit deteriorating retinal sensitivity, suggesting that this is a late-stage manifestation of the disease. Further studies on microperimetry in wet AMD are needed to determine whether repeated abrcept injections can help to prevent the deterioration of macular retinal sensitivity.[28] This may lead to new treatments that target the prevention of scarring or MA formation.

In conclusion, although mean CRT reduced rapidly during the loading dose period, mean BCVA and mean retinal sensitivity improved slowly or were maintained. The predictive factors for BCVA were age, CRT at baseline, and MA involving the fovea. Notably, given the heterogeneity of the patients included in the present study, the small sample size was suboptimal. Therefore, the effects of abrcept should be further investigated in larger trials with longer follow-up periods.

**Table 2**

| Variables             | Estimated β | Standard error | P     |
|-----------------------|-------------|----------------|-------|
| Baseline logMAR BCVA  | −.903       | .002           |       |
| Patient age           | −.352       | −.507          | <.001 |
| Sex                   | .013        | .409           |       |
|                       | −.107       | −.189          | .113  |

BCVA = best-corrected visual acuity.

**Author contributions**

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