

Two-year outcome of treat-and-extend aflibercept after ranibizumab in age-related macular degeneration and polypoidal choroidal vasculopathy patients

Keiko Azuma¹
Ryo Asaoka¹
Aya Matsuda²
Jihee Lee³
Kimiko Shimizu¹
Hiroko Inui¹
Hiroshi Murata¹
Asako Ogawa¹
Motoshi Yamamoto¹
Tatsuya Inoue¹
Ryo Obata¹

¹Department of Ophthalmology, Graduate School of Medicine and Faculty of Medicine, The University of Tokyo, Tokyo, Japan; ²Department of Ophthalmology, Toranomon Byoin, Tokyo, Japan; ³Department of Ophthalmology, Miyata Eye Hospital, Miyakonojo, Japan

Background: The purpose of the study was to evaluate the 2-year outcome and predictive factors of treat-and-extend aflibercept in patients with eyes affected by typical neovascular age-related macula degeneration (t-AMD) or polypoidal choroidal vasculopathy (PCV), who were switched from ranibizumab.

Patients and methods: The patients underwent three monthly aflibercept injections and subsequent administration following the treat-and-extend protocol. Sixty-two eyes of 62 patients were reviewed retrospectively. R statistical software was used for statistical analysis.

Results: Twenty-two eyes were t-AMD and the remaining 40 eyes were PCV. There was no significant difference in the logarithm of the minimal angle of resolution visual acuity (VA) between baseline and 2 years after switching to aflibercept (0.40 vs 0.40; $P=0.99$). Multivariate analyses suggested that the following factors were significantly correlated with better VA at 2 years after switching to aflibercept: patients with PCV, the absence of intraretinal fluid at baseline, and better VA at baseline.

Conclusion: In conclusion, VA was maintained and there was an anatomical improvement at 2 years in patients with t-AMD and PCV who were switched from ranibizumab to treat-and-extend aflibercept. PCV patients showed more favorable visual outcomes and less injections at 2 years compared to t-AMD patients. Intraretinal fluid and VA at baseline were predictors of VA at 2 years.

Keywords: typical neovascular age-related macular degeneration, polypoidal choroidal vasculopathy, persistent exudative changes with ranibizumab, aflibercept, 2-year outcome

Background

Age-related macular degeneration (AMD) is a leading cause of blindness in the elderly population.¹⁻⁵ Polypoidal choroidal vasculopathy (PCV) is a subtype of neovascular AMD commonly seen in Asians and thought to have distinct characteristics and treatment responses when compared to typical neovascular age-related macula degeneration (t-AMD).⁶ Severe visual loss or blindness is caused by hemorrhage, atrophy, or exudative changes both in t-AMD and PCV.⁷ Anti-vascular endothelial growth factor (anti-VEGF) agents with intravitreal injections have dramatically improved visual outcomes and reduced the incidence of legal blindness resulting from AMD.⁵ It was reported that ranibizumab (Lucentis[®]; Novartis Pharma AG, Basel, Switzerland), an anti-VEGF drug approved for AMD treatment, was superior to all previously available treatments for AMD.^{8,9} However, a certain proportion of patients are refractory to this

Correspondence: Ryo Obata
Department of Ophthalmology, Graduate School of Medicine and Faculty of Medicine, The University of Tokyo, Tokyo 113-8655, Japan
Tel +81 35 800 8660
Fax +81 33 817 0798
Email robata-tky@umin.ac.jp

treatment or exhibit frequent recurrences.¹⁰ Approximately 14% of patients with AMD treated with either ranibizumab or bevasizumab were identified as non-responders.^{11,12} Moreover, 2% of the patients with AMD developed tachyphylaxis during ranibizumab treatment, though the precise mechanism has not been demonstrated.^{11,12} Aflibercept (Eylea®; Regeneron Pharmaceuticals, Tarrytown, NY, USA) is one of the anti-VEGF agents that have a higher affinity to vascular endothelial growth factor (VEGF), a longer half-life, and the capability of inhibiting not only VEGF-A, which ranibizumab also inhibits, but also VEGF-B and placental growth factor.^{13,14} Therefore, switching to aflibercept has been considered a reasonable strategy in patients with AMD resistant to other anti-VEGF agents.

Regarding the treatment regimens, multiple clinical trials have demonstrated the beneficial effect of fixed-dosing anti-VEGF treatments.^{9,15–18} In real-world practice, the majority of patients with AMD are given pro re nata or treat-and-extend (TAE) regimens to reduce various physical and financial burdens on both the patients and physicians,^{19–22} and a TAE dosing regimen showed similar visual outcomes with less injection numbers compared to fixed-dosing regimens.²³

In patients with AMD refractory to ranibizumab or bevacizumab, switching to aflibercept has been reported to be effective in improving anatomical changes and in maintaining visual acuity (VA) in short-term studies,^{19–21,24–26} in particular, with the TAE regimen.^{19,26} However, these studies are the results of a relatively short follow-up period (4 months–1 year^{19,27–29}); therefore, the outcome in a longer follow-up period is still unclear. This is clinically very important because a short follow-up period is often not long enough to conclude the patients' prognoses. Furthermore, patients with PCV show different responses to anti-VEGF treatments compared to the t-AMD patients.^{30,31} Although there were several investigations regarding the efficacy of switching to aflibercept for patients with PCV,^{19,27–29} these studies had small sample sizes and were treated with a fixed-dosing procedure. Thus, the outcome of TAE aflibercept therapy for patients with PCV has not been investigated in detail.

In the present study, we measured the visual and anatomical outcomes of switching from ranibizumab to TAE aflibercept therapy for patients with t-AMD and PCV over 2 years. In addition, we analyzed the relationship between factors at the time point of aflibercept switch and the visual outcomes at 2 years.

Patients and methods

Ranibizumab treatment and switching to aflibercept

We retrospectively reviewed the charts of 73 patients with t-AMD and PCV who were switched from ranibizumab to aflibercept (2 mg/0.05 mL) from February 2013 to August 2014 at the outpatient clinic of Tokyo University Hospital. Seven patients were excluded because they were lost to follow-up until 2 years. Additionally, we excluded four patients who received cataract surgery during aflibercept therapy. Remaining 62 patients were included. Only one eye was investigated in each patient. All patients were switched from ranibizumab to aflibercept. The study was conducted in accordance with the tenets of the Declaration of Helsinki, and was approved by the institutional review board (IRB) of the University of Tokyo as a retrospective review of the patients' medical records. All data were fully anonymized before we accessed them. Written informed consent was not required by the IRB, but participants who did not grant authorization to use their medical records for the research were excluded from analyses. All patients provided written informed consent before treatment.

During ranibizumab administration, all patients were treated following the pro re nata protocol with monthly monitoring. Resistance to ranibizumab was defined as follows: after three consecutive monthly ranibizumab injections, the patients showed persistent subretinal fluid (SRF)/intraretinal fluid (IRF) on optical coherence tomography (OCT) examination or clinically recognized new hemorrhage.^{32,33} We excluded four patients who received cataract surgery during aflibercept therapy.

TAE aflibercept

After switching to aflibercept, all patients received three consecutive monthly injections. Then, aflibercept was administered in a TAE protocol. In the maintenance phase, if persistent or new hemorrhage was found on slit-lamp biomicroscopy, or a fluid was observed on OCT (IRF and/or SRF) at the time of injection, the treatment was continued at 4-week intervals. When these findings continued to be absent twice at the same interval, the next injection was extended by 2 weeks, with a maximal treatment interval of 12 weeks. When these findings of recurrence were observed at the time of any visit, the next injection was shortened by 2 weeks. If a dry macula was maintained two times at a certain interval, the next injection was extended by 2 weeks again.^{32,33} Minimum intervals for the injection were 4 weeks.

Baseline and follow-up examinations

All patients underwent a standard examination that included measurement of best-corrected visual acuity (BCVA), slit-lamp biomicroscopy, funduscopy, and spectral domain OCT (Heidelberg Spectralis, Heidelberg, Germany) at each visit. BCVA was measured using the Landolt C chart and was converted to the logarithm of minimal angle of resolution (LogMAR). OCT was used to measure central retinal thickness (CRT) and central choroidal thickness (CCT), and to assess the presence or absence of IRF or SRF. CRT was defined as the distance between the internal limiting membrane and the presumed retinal pigment epithelium (RPE) at the fovea. CCT was defined as the distance between the hyper-reflective line corresponding to the Bruch's membrane beneath the RPE and the inner surface of the sclera. CRT and CCT were measured by two independent investigators and the mean values were used for analyses. The fluid status was judged by two independent investigators in a blinded manner. If their judgments differed, they reexamined the data together to reach a consensus.

All patients underwent fluorescein angiography and indocyanine-green angiography (ICGA) at the time point of aflibercept switch unless contraindicated. Choroidal vascular hyperpermeability (CVH) was assessed using ICGA. Similar to previous reports,^{34–37} CVH was defined as the presence within the choroid of multifocal areas of hyperfluorescence with blurred margins identified in the late phase of ICGA. Two independent investigators judged the cases in a blinded manner. If their judgments differed, they reexamined the images together to reach a consensus. The diagnosis of PCV was mainly based on the angiographic findings at the time point of aflibercept switch, according to the previous reports;^{28,33,38,39} a PCV diagnosis was made if at least one subretinal focal hyperfluorescence was observed on ICGA.³⁸ The greatest linear dimension (GLD) at the time point of aflibercept switch was measured based on FA.

Statistical analysis

The baseline (switched to aflibercept) characteristics were summarized and the difference between the PCV and t-AMD eyes was analyzed using the chi-squared test for categorical variables and Wilcoxon signed-rank test for continuous variables. The mean LogMAR VA, CRT, and CCT at baseline, 1 year, and 2 years were calculated. The change from the baseline was analyzed using repeated measures analysis of variance with Dunnett's post hoc test. Also, using all eyes, the relationship between the LogMAR VA at 2 years and

the ten explanatory variables (age, sex, LogMAR VA at baseline, CRT at baseline, CCT at baseline, GLD at baseline, presence of SRF or IRF at baseline, history of photodynamic therapy [PDT], and CVH at baseline) was calculated using a linear model. Then, the optimal linear model was calculated among all possible combinations of predictors: 2^{10} patterns, based on the second-order bias-corrected Akaike Information Criterion (AICc) index (denotes optimal model). The AIC is a well-known statistical measure used in model selection, and the AICc is a corrected version of the AIC, which provides an accurate estimation when the sample size is finite.⁴⁰ The degrees of freedom in a multivariate regression model decreases with a large number of variables. It is, therefore, recommended that clinicians use the model selection method to improve the model fit by removing redundant variables.^{41,42} These processes were iterated only in PCV and t-AMD patients.

Ethics approval and consent to participate

The study was in accordance with the tenets of the Declaration of Helsinki and was approved by the ethical committee of the coordinating center of the University of Tokyo. All data were fully anonymized before we accessed them. Written informed consent was not required by the IRB, but participants who did not grant authorization to use their medical records for the research were excluded from analyses. All patients provided written informed consent before treatment.

Results

We retrospectively reviewed 62 eyes of 62 patients with ranibizumab-resistant AMD (43 males and 19 females; age range, 58–91 years; mean age \pm SD, 74.9 \pm 6.7 years). No patients in the present study had both eyes treated. There were 40 cases with PCV and the remaining 22 cases were t-AMD (all were type 1 choroidal neovascularization [CNV]). The baseline characteristics of the patients who switched to aflibercept are shown in Table 1.

The visual and anatomical outcomes from baseline to 2 years in all patients (N=62) are shown in Table 2. The outcomes in PCV patients (n=40) and t-AMD patients (n=22) are shown in Tables 3 and 4, respectively. The *P*-value is calculated is always at the baseline. In all patients, the BCVA improved significantly at 1 year, while BCVA at 2 years was not significantly different from that at baseline (Table 2). Similarly, in PCV patients (n=40), BCVA significantly

Table 1 Baseline characteristics of 62 Japanese patients with t-AMD and PCV when the patients were switched to aflibercept

Variables	Total	t-AMD	PCV	P-value
Number of eyes	62	22	40	
Age (mean±SD, years)	74.9±6.7	76.4±6.6	74.0±6.8	0.36
LogMAR VA (years, mean±SD)	0.40±0.34	0.40±0.38	0.41±0.33	0.68
CRT (μm, mean±SD)	364±187	361±151	376±206	0.61
CCT (μm, mean±SD)	216±87	218±84	215±89	0.72
GLD (μm, mean±SD)	4,486±1,847	4,165±1,476	4,661±1,985	0.52
Sex/male (%)	43 (69%)	13 (21%)	30 (48%)	0.25
History of PDT (%)	25 (40%)	5 (8%)	20 (32%)	0.039
Number of previous ranibizumab injections (times, mean±SD)	9.9±4.4	10.3±4.9	10±4.2	0.72
Days of previous ranibizumab treatment (days, mean±SD)	718±464	626±467	768±460	0.23

Abbreviations: CCT, central choroidal thickness; CRT, central retinal thickness; GLD, greatest linear dimension; LogMAR, logarithm of the minimal angle of resolution; PCV, polypoidal choroidal vasculopathy; PDT, photodynamic therapy; t-AMD, typical neovascular age-related macula degeneration; VA, visual acuity.

improved from baseline to 1 year, and there was no significant difference between BCVA at 2 years and baseline (Table 3). In t-AMD patients (n=22), BCVA at 1 year also significantly improved from that at baseline; however, BCVA at 2 years was significantly worse compared to that at baseline (Table 4). The CRT and CCT significantly decreased from baseline both at 1 and at 2 years in all (Table 2), PCV (Table 3), and t-AMD (Table 4) patients. Both CRT and CCT were unchanged at 1 and 2 years. Moreover, there was no statistical difference in the CRT or CCT between PCV and t-AMD patients. The dry macula rates in all, PCV, and t-AMD patients were 77%, 82%, and 64% at 1 year and 60%, 62%, and 55% at 2 years, respectively (Tables 2–4).

The mean numbers of injections in PCV patients were 9.1±2.0 in the first year and 6.6±2.5 in the second year. In t-AMD patients, there were 9.8±1.8 injections in the first year and 7.7±2.6 in the second year. The PCV patients had significantly less injections at 2 years than the t-AMD patients (15.6±0.6 vs 17.5±0.9, $P=0.042$).

As shown in Table 5, the optimal model for LogMAR at 2 years was $0.17-0.13 \times \text{PCV (yes)} + 0.64 \times \text{baseline LogMAR VA} + 0.17 \times \text{baseline IRF (yes)}$ ($\text{AICc}=-20.95$). Thus, age,

sex, CRT, CCT, GLD, SRF at baseline, number of previous ranibizumab treatments, days of previous ranibizumab treatment, history of PDT, and CVH at baseline were not included. Also, as shown in Table 5, the optimal model for PCV was $\text{LogMAR at 2 years} = 0.033 + 0.60 \times \text{LogMAR at baseline} + 0.25 \times \text{IRF (yes) at baseline}$ ($\text{AICc}=-9.29$). Thus, age, sex, CRT, CCT, GLD, SRF at baseline, number of previous ranibizumab treatment, days of previous ranibizumab treatment, history of PDT, and CVH at baseline were not included. As also shown in Table 5, the optimal model for t-AMD was $\text{LogMAR at 2 years} = 0.17 + 0.77 \times \text{LogMAR at baseline}$ ($\text{AICc}=-9.59$). Thus age, sex, CRT, CCT, GLD, SRF, IRF at baseline, number of previous ranibizumab treatment, days of previous ranibizumab treatment, history of PDT, and CVH at baseline were not included.

Discussion

The present study demonstrated that 1) VA significantly improved at 1 year, but was similar to baseline at 2 years after switching to TEA aflibercept, although CRT significantly decreased at 3 months, 1 year, and 2 years after switching to aflibercept and 2) patients with PCV, the absence of IRF at

Table 2 Visual and anatomical outcomes in all patients at baseline, 1 year, and 2 years (N=62)

Variables	Baseline (95% CI)	3 months (95% CI)	P-value	1 year (95% CI)	P-value	2 years (95% CI)	P-value
LogMAR	0.40 (0.31–0.49)	0.33 (0.24–0.42)	0.0042	0.34 (0.25–0.44)	0.028	0.40 (0.31–0.49)	0.99
CRT (μm)	364 (316–411)	225 (194–256)	<0.0001	199 (174–224)	<0.0001	228 (188–267)	<0.0001
CCT (μm)	216 (194–238)	194 (171–217)	<0.0001	196 (172–219)	<0.0001	192 (169–215)	<0.0001
IRF (%)	31 (19–42)	3 (–1 to 8)		10 (2–17)		18 (7–28)	
SRF (%)	87 (79–96)	19 (9–29)		15 (5–24)		26 (15–37)	
Either SRF or IRF (%)	100	19 (9–29)		23 (13–35)		40 (27–53)	

Note: Values are shown as the mean and 95% CI.

Abbreviations: CCT, central choroidal thickness; CRT, central retinal thickness; IRF, intraretinal fluid; LogMAR, logarithm of the minimal angle of resolution; SRF, subretinal fluid.

Table 3 Visual and anatomical outcomes in PCV patients at baseline, 1 year, and 2 years (PCV only: N=40)

Variables	Baseline (95% CI)	3 months (95% CI)	P-value	1 year (95% CI)	P-value	2 years (95% CI)	P-value
LogMAR	0.41 (0.30–0.51)	0.32 (0.21–0.43)	0.0072	0.33 (0.20–0.45)	0.016	0.35 (0.24–0.46)	0.12
CRT (μm)	366 (300–432)	214 (176–252)	<0.0001	186 (162–211)	<0.0001	219 (166–271)	<0.0001
CCT (μm)	215 (187–244)	195 (168–225)	0.0006	198 (167–229)	0.0032	196 (166–225)	0.0007
IRF (%)	30 (15–45)	3 (–2 to 8)		10 (0.3–20)		15 (3–27)	
SRF (%)	86 (77–98)	5 (–2 to 12)		8 (–1 to 16)		25 (11–39)	
Either SRF or IRF (%)	100	5 (–2 to 12)		18 (5–30)		38 (22–53)	

Note: Values are shown as mean and 95% CI.

Abbreviations: CCT, central choroidal thickness; CRT, central retinal thickness; IRF, intraretinal fluid; LogMAR, logarithm of the minimal angle of resolution; PCV, polypoidal choroidal vasculopathy; SRF, subretinal fluid.

baseline, and better VA at baseline were significant predictive factors for better VA at 2 years.

There are some studies that evaluated the 1-year outcomes after switching to aflibercept for patients with refractory AMD and compared them to other anti-VEGF agents.^{19,20,25,43,44} Some of the studies showed visual improvements,^{19,20,44} but others failed to include this information.^{21,25,43} The difference in treatment protocols may be one of the reasons for the different visual outcomes among the studies.^{45,46} The studies that showed visual improvements used a monthly dosing regimen or TAE regimen. However, a recent study reported the visual outcome in patients with t-AMD who were switched from ranibizumab or bevacizumab to aflibercept using a TAE regimen. The VA at 2 years was worse by 0.07 LogMAR than that at baseline.³² The same results were obtained in the present study. Furthermore, we found that PCV patients have better visual prognosis. In previous studies with relatively small numbers of patients, visual outcomes at 1 year after switching to aflibercept were suggested to be more favorable in PCV patients than in t-AMD patients.^{19,28} To the best of our knowledge, there have been no reports that analyzed the difference in the treatment outcome between PCV and t-AMD patients in a longer-term follow-up than 1 year. In the present study, VA at 2 years in patients with t-AMD was worse than at baseline, while in those with PCV, VA was maintained at 2 years. Some studies^{47,48} that evaluated the effects of

aflibercept therapy using TAE regimen on treatment-naïve AMD suggested fewer injections as compared to the present study. It was because of the difference in how the patients were selected. Since all the patients included in the present study were refractory to ranibizumab, their CNV should have higher activity that required more injections than that of treatment-naïve patients as a whole. Moreover, multivariate analyses showed that after adjusting patient demographic data, VA, or morphologic factors, PCV was a predictive factor for better VA at 2 years. Although some studies suggested that PCV patients may poorly respond to anti-VEGF therapy,^{31,49} other more recent studies revealed beneficial effects of ranibizumab or aflibercept in PCV.^{50–53} In the present study, the dry macula rate in patients with PCV tended to be better than those of the t-AMD patients at 3 months–2 years. These data indicated that switching to aflibercept might suppress the activity of the disease in patients with PCV more efficiently than in patients with t-AMD, leading to a more favorable visual outcome.

Considering that the response to anti-VEGF is different in each individual, it is essential to elucidate predictive factors of treatment outcomes. In previous reports, some baseline characteristics might have been predictive of the treatment outcome,^{25,53} but it still remains to be elucidated. In the present study, BCVA at baseline was associated with BCVA at 2 years, and was similar to the 2-year outcome of

Table 4 Visual and anatomical outcomes in t-AMD patients at baseline, 1 year, and 2 years (t-AMD only; n=22)

Variables	Baseline (95% CI)	3 months (95% CI)	P-value	1 year (95% CI)	P-value	2 years (95% CI)	P-value
LogMAR	0.40 (0.23–0.57)	0.35 (0.19–0.52)	0.41	0.38 (0.22–0.45)	<0.001	0.48 (0.24–0.54)	0.047
CRT (μm)	361 (294–428)	245 (188–302)	<0.0001	221 (165–278)	<0.0001	245 (182–307)	<0.0001
CCT (μm)	218 (181–256)	190 (148–233)	0.0013	191 (152–231)	0.0019	185 (144–226)	0.0001
IRF (%)	32 (11–53)	5 (–5 to 14)		9 (–4 to 22)		23 (4–42)	
SRF (%)	86 (71–102)	45 (23–68)		27 (7–47)		27 (7–47)	
Either SRF or IRF (%)	100	45 (23–68)		36 (14–58)		45 (23–68)	

Note: Values are shown as the mean and 95% CI.

Abbreviations: CCT, central choroidal thickness; CRT, central retinal thickness; IRF, intraretinal fluid; LogMAR, logarithm of the minimal angle of resolution; SRF, subretinal fluid; t-AMD, typical neovascular age-related macula degeneration.

Table 5 Baseline parameters included in the optimal model for LogMAR visual acuity at 2 years

Parameters	All eyes, N=62			PCV eyes, n=40			t-AMD eyes, n=22		
	Coefficient	SE	P-value	Coefficient	SE	P-value	Coefficient	SE	P-value
Age (years)		NS			NS			NS	
PCV (yes)	-0.13	0.051	0.012	-			-		
Sex (male)		NS			NS			NS	
Baseline LogMAR	0.64	0.11	<0.0001	0.60	0.13	0.00011	0.77	0.10	<0.0001
Baseline CRT (μm)		NS			NS			NS	
Baseline CCT (μm)		NS			NS			NS	
Baseline GLD (μm)		NS			NS			NS	
Baseline SRF (yes)		NS			NS			NS	
Baseline IRF (yes)	0.17	0.078	0.031	0.25	0.098	0.014		NS	
Baseline CVH (yes)		NS			NS			NS	
Number of ranibizumab treatment		NS			NS			NS	
Days of ranibizumab treatment		NS			NS			NS	

Abbreviations: CCT, central choroidal thickness; CRT, central retinal thickness; CVH, choroidal vascular hyperpermeability; GLD, greatest linear dimension; IRF, intraretinal fluid; LogMAR, logarithm of the minimal angle of resolution; NS, not selected in the optimal model; PCV, polypoidal choroidal vasculopathy; PDT, photodynamic therapy; SE, standard error; SRF, subretinal fluid; t-AMD, typical neovascular age-related macula degeneration.

afibercept or ranibizumab therapy in patients with treatment-naïve AMD.^{18,54,55} Moreover, IRF at baseline was associated with BCVA at 2 years. The presence of IRF is a hallmark of more advanced or perhaps chronic disease, indicating possible irreversible neurosensory damage.⁵⁶ Indeed, the presence of IRF at baseline was associated with worse VA at 2 years in the Comparison of AMD Treatment Trial (CATT) study.⁵⁷ Similarly, the VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD (VIEW 1 and VIEW 2) data suggested that eyes with baseline IRF had worse VA at week 52 than those without IRF.^{18,55} However, the significance of IRF as a biomarker in patients with PCV has not been reported. In the present study, IRF at baseline was still a predictor of poor visual prognosis when multivariate analyses were conducted in the subset of PCV patients.

The CCTs from 3 months to 2 years were significantly decreased compared to those at baseline in all patients. The results were consistent with the previous studies in patients treated with aflibercept for AMD.^{36,58–60} However, the effect of switching to aflibercept from ranibizumab on CCT remains unknown. The present study showed that the CCT was decreased between the period of baseline and at 3 months, even though repeated injection of ranibizumab had been administered before switching to aflibercept. This may have been because switching to aflibercept prevented the CNV and suppressed VEGF secretion due to CNV. This mechanism can be explained by the higher VEGF-binding affinity of aflibercept and its longer intravitreal half-life when compared with ranibizumab.⁶¹ Additionally, VEGF is physiologically produced in the RPE-choroid to maintain the permeability of the choroidal vasculature.^{62,63} Because the binding affinity

of aflibercept is higher than that of ranibizumab, aflibercept binding might block the physiological secretion of VEGF, leading to thinning of the choroidal vasculature.^{59,62–64}

Limitations

The current study has several limitations. This study was a retrospective study of a relatively small number of patients, which may have led to selection bias. Additionally, this was a single-armed study. The clinical data on the patients who had been treated otherwise were not available. Therefore, the benefit of switching was likely to be overestimated, because there might be patients who did not improve with three consecutive ranibizumab but could have responded with further frequent ranibizumab. Furthermore, there were seven patients who were switched but lost to follow-up until 2 years. Although our findings have potentially important clinical implications for patients with t-AMD and PCV who responded poorly to ranibizumab, randomized controlled trials are needed to verify our results.

Conclusion

This study investigated the 2-year visual and anatomical outcomes of intravitreal aflibercept using a TAE protocol in cases with t-AMD and PCV who responded poorly to ranibizumab. There was no statistically significant difference in VA between baseline and 2 years after switching to aflibercept, while anatomical responses were maintained. Multivariate analyses showed that PCV, better LogMAR VA at baseline, and IRF at baseline were predictive factors for better LogMAR VA at 2 years. This is the first report investigating the long-term outcome of the TAE regimen

of aflibercept switched from ranibizumab in patients with t-AMD and PCV. Switching to TAE aflibercept could be an alternative treatment to expect anatomical improvement in patients with neovascular AMD who are refractory to the other anti-VEGF drugs. Several predictors of visual outcome shown in the present study should be of value when clinicians consider switching to TAE aflibercept.

Availability of data and materials

The datasets generated and/or analyzed during this study are available from the corresponding author on reasonable request.

Acknowledgment

This study was conducted under JSPS KAKENHI Grant Number JP16K11260. The organization had no role in the study design, collection, analysis, and interpretation of data, writing of the report, or in the decision to submit the article for publication.

Author contributions

KA and RO designed the study. KA, AM, JL, KS, HI, AO, MY, and TI collected the data. KA, RA, and HM analyzed the data. KA and RO wrote the paper. KA, RA, AM, JL, KS, HM, AO, TI, and RO reviewed the paper. All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Kawasaki R, Yasuda M, Song SJ, et al. The prevalence of age-related macular degeneration in Asians: a systematic review and meta-analysis. *Ophthalmology*. 2010;117(5):921–927.
2. Klaver CC, Assink JJ, van Leeuwen R, et al. Incidence and progression rates of age-related maculopathy: the Rotterdam Study. *Invest Ophthalmol Vis Sci*. 2001;42(10):2237–2241.
3. Klein R, Klein BE, Cruickshanks KJ. The prevalence of age-related maculopathy by geographic region and ethnicity. *Prog Retin Eye Res*. 1999;18(3):371–389.
4. Klein R, Peto T, Bird A, Vannewkirk MR. The epidemiology of age-related macular degeneration. *Am J Ophthalmol*. 2004;137(3):486–495.
5. Wong TY, Wong T, Chakravarthy U, et al. The natural history and prognosis of neovascular age-related macular degeneration: a systematic review of the literature and meta-analysis. *Ophthalmology*. 2008;115(1):116–126.
6. Wong CW, Yanagi Y, Lee WK, et al. Age-related macular degeneration and polypoidal choroidal vasculopathy in Asians. *Prog Retin Eye Res*. 2016;53:107–139.
7. Ferris FL, Fine SL, Hyman L. Age-related macular degeneration and blindness due to neovascular maculopathy. *Arch Ophthalmol*. 1984;102(11):1640–1642.
8. Brown DM, Kaiser PK, Michels M, et al. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. *N Engl J Med*. 2006;355(14):1432–1444.
9. Rosenfeld PJ, Brown DM, Heier JS, et al. Ranibizumab for neovascular age-related macular degeneration. *N Engl J Med*. 2006;355(14):1419–1431.
10. Gasperini JL, Fawzi AA, Khondkaryan A, et al. Bevacizumab and ranibizumab tachyphylaxis in the treatment of choroidal neovascularization. *Br J Ophthalmol*. 2012;96(1):14–20.
11. Eghøj MS, Sørensen TL. Tachyphylaxis during treatment of exudative age-related macular degeneration with ranibizumab. *Br J Ophthalmol*. 2012;96(1):21–23.
12. Krebs I, Glittenberg C, Ansari-Shahrezaei S, Hagen S, Steiner I, Binder S. Non-responders to treatment with antagonists of vascular endothelial growth factor in age-related macular degeneration. *Br J Ophthalmol*. 2013;97(11):1443–1446.
13. Papadopoulos N, Martin J, Ruan Q, et al. Binding and neutralization of vascular endothelial growth factor (VEGF) and related ligands by VEGF Trap, ranibizumab and bevacizumab. *Angiogenesis*. 2012;15(2):171–185.
14. Rakic JM, Lambert V, Devy L, et al. Placental growth factor, a member of the VEGF family, contributes to the development of choroidal neovascularization. *Invest Ophthalmol Vis Sci*. 2003;44(7):3186–3193.
15. Brown DM, Michels M, Kaiser PK, et al. Ranibizumab versus verteporfin photodynamic therapy for neovascular age-related macular degeneration: two-year results of the ANCHOR study. *Ophthalmology*. 2009;116(1):57–65.
16. Heier JS, Brown DM, Chong V, et al. Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration. *Ophthalmology*. 2012;119(12):2537–2548.
17. Schmidt-Erfurth U, Kaiser PK, Korobelnik JF, et al. Intravitreal aflibercept injection for neovascular age-related macular degeneration: ninety-six-week results of the VIEW studies. *Ophthalmology*. 2014;121(1):193–201.
18. Waldstein SM, Simader C, Staurengi G, et al. Morphology and visual acuity in aflibercept and ranibizumab therapy for neovascular age-related macular degeneration in the VIEW trials. *Ophthalmology*. 2016;123(7):1521–1529.
19. Hiraoka T, Fujinami K, Watanabe K, Sasaki M, Noda T, Akiyama K. One-year outcome of intravitreal aflibercept injection for age-related macular degeneration resistant to ranibizumab: rapid morphologic recovery and subsequent visual improvement. *Clin Ophthalmol*. 2016;10:969–977.
20. Ricci F, Parravano M, Regine F, et al. Aflibercept in persistent neovascular AMD: comparison of different treatment strategies in switching therapy. *Eye*. 2016;30(8):1077–1083.
21. Sarao V, Parravano M, Veritti D, Arias L, Varano M, Lanzetta P. Intravitreal aflibercept for choroidal neovascularization due to age-related macular degeneration unresponsive to ranibizumab therapy. *Retina*. 2016;36(4):770–777.
22. Yamamoto A, Okada AA, Nakayama M, Yoshida Y, Kobayashi H. One-year outcomes of a treat-and-extend regimen of aflibercept for exudative age-related macular degeneration. *Ophthalmologica*. 2017;237(3):139–144.
23. Essex RW, Nguyen V, Walton R, et al. Treatment patterns and visual outcomes during the maintenance phase of treat-and-extend therapy for age-related macular degeneration. *Ophthalmology*. 2016;123(11):2393–2400.
24. Seguin-Greenstein S, Lightman S, Tomkins-Netzer O. A meta-analysis of studies evaluating visual and anatomical outcomes in patients with treatment resistant neovascular age-related macular degeneration following switching to treatment with aflibercept. *J Ophthalmol*. 2016;2016:4095852.
25. Chatziralli I, Nicholson L, Vrızidou E, et al. Predictors of outcome in patients with neovascular age-related macular degeneration switched from ranibizumab to 8-weekly aflibercept. *Ophthalmology*. 2016;123(8):1762–1770.

26. Pinheiro-Costa J, Costa JM, Beato JN, et al. Switch to aflibercept in the treatment of neovascular AMD: one-year results in clinical practice. *Ophthalmologica*. 2015;233(3–4):155–161.
27. Hata M, Tsujikawa A, Miyake M, et al. Two-year visual outcome of ranibizumab in typical neovascular age-related macular degeneration and polypoidal choroidal vasculopathy. *Graefes Arch Clin Exp Ophthalmol*. 2015;253(2):221–227.
28. Kawashima Y, Oishi A, Tsujikawa A, et al. Effects of aflibercept for ranibizumab-resistant neovascular age-related macular degeneration and polypoidal choroidal vasculopathy. *Graefes Arch Clin Exp Ophthalmol*. 2015;253(9):1471–1477.
29. Miura M, Iwasaki T, Goto H. Intravitreal aflibercept for polypoidal choroidal vasculopathy after developing ranibizumab tachyphylaxis. *Clin Ophthalmol*. 2013;7:1591–1595.
30. Cho HJ, Kim KM, Kim HS, et al. Intravitreal aflibercept and ranibizumab injections for polypoidal choroidal vasculopathy. *Am J Ophthalmol*. 2016;165:1–6.
31. Stangos AN, Gandhi JS, Nair-Sahni J, Heimann H, Pournaras CJ, Harding SP. Polypoidal choroidal vasculopathy masquerading as neovascular age-related macular degeneration refractory to ranibizumab. *Am J Ophthalmol*. 2010;150(5):666–673.
32. Jorstad ØK, Faber RT, Moe MC. Two-year functional and anatomical results after converting treatment resistant eyes with exudative age-related macular degeneration to aflibercept in accordance with a treat and extend protocol. *Acta Ophthalmol*. 2017;95(5):460–463.
33. Azuma K, Obata R, Nomura Y, Tan X, Takahashi H, Yanagi Y. Angiographic findings of ranibizumab-resistant polypoidal choroidal vasculopathy after switching to a treat-and-extend regimen with intravitreal aflibercept. *Retina*. 2016;36(11):2158–2165.
34. Cho HJ, Kim HS, Jang YS, et al. Effects of choroidal vascular hyperpermeability on anti-vascular endothelial growth factor treatment for polypoidal choroidal vasculopathy. *Am J Ophthalmol*. 2013;156(6):1192–1200.
35. Jirattanasopa P, Ooto S, Nakata I, et al. Choroidal thickness, vascular hyperpermeability, and complement factor H in age-related macular degeneration and polypoidal choroidal vasculopathy. *Invest Ophthalmol Vis Sci*. 2012;53(7):3663–3672.
36. Koizumi H, Kano M, Yamamoto A, et al. Subfoveal choroidal thickness during aflibercept therapy for neovascular age-related macular degeneration: twelve-month results. *Ophthalmology*. 2016;123(3):617–624.
37. Miyake M, Tsujikawa A, Yamashiro K, et al. Choroidal neovascularization in eyes with choroidal vascular hyperpermeability. *Invest Ophthalmol Vis Sci*. 2014;55(5):3223–3230.
38. Koh A, Lee WK, Chen LJ, et al. EVEREST study: efficacy and safety of verteporfin photodynamic therapy in combination with ranibizumab or alone versus ranibizumab monotherapy in patients with symptomatic macular polypoidal choroidal vasculopathy. *Retina*. 2012;32(8):1453–1464.
39. Saito M, Kano M, Itagaki K, Ise S, Imaizumi K, Sekiryu T. Subfoveal choroidal thickness in polypoidal choroidal vasculopathy after switching to intravitreal aflibercept injection. *Jpn J Ophthalmol*. 2016;60(1):35–41.
40. Burnham KP, Anderson DR, Inference M. Multimodel inference understanding AIC and BIC in model selection. *Sociol Methods Res*. 2004;33(2):261–304.
41. Mallows CL. Some comments on C_p . *Technometrics*. 1973;15(4):661–675.
42. Tibshirani RJ, Taylor J. Degrees of freedom in lasso problems. *Ann Stat*. 2012;40(2):1198–1232.
43. Arcinue CA, Ma F, Barteselli G, Sharpsten L, Gomez ML, Freeman WR. One-year outcomes of aflibercept in recurrent or persistent neovascular age-related macular degeneration. *Am J Ophthalmol*. 2015;159(3):426–436.
44. Singh RP, Srivastava SK, Ehlers JP, et al. A single-arm, investigator-initiated study of the efficacy, safety, and tolerability of intravitreal aflibercept injection in subjects with exudative age-related macular degeneration previously treated with ranibizumab or bevacizumab (ASSESS study): 12-month analysis. *Clin Ophthalmol*. 2015;9:1759–1766.
45. Berg K, Hadzalic E, Gjertsen I, et al. Ranibizumab or bevacizumab for neovascular age-related macular degeneration according to the lucentis compared to avastin study treat-and-extend protocol: two-year results. *Ophthalmology*. 2016;123(1):51–59.
46. Kvannli L, Krohn J. Switching from pro re nata to treat-and-extend regimen improves visual acuity in patients with neovascular age-related macular degeneration. *Acta Ophthalmol*. 2017;95(7):678–682.
47. Almutaseb H, Johnston RL, Talks JS, Lotery AJ. Second-year visual acuity outcomes of nAMD patients treated with aflibercept: data analysis from the UK Aflibercept Users Group. *Eye*. 2017;31(11):1582–1588.
48. Morimoto M, Matsumoto H, Mimura K, Akiyama H. Two-year results of a treat-and-extend regimen with aflibercept for polypoidal choroidal vasculopathy. *Graefes Arch Clin Exp Ophthalmol*. 2017;255(10):1891–1897.
49. Cho M, Barbazetto IA, Freund KB. Refractory neovascular age-related macular degeneration secondary to polypoidal choroidal vasculopathy. *Am J Ophthalmol*. 2009;14878(1):70.
50. Hikichi T, Higuchi M, Matsushita T, et al. Results of 2 years of treatment with as-needed ranibizumab reinjection for polypoidal choroidal vasculopathy. *Br J Ophthalmol*. 2013;97(5):617–621.
51. Oishi A, Kojima H, Mandai M, et al. Comparison of the effect of ranibizumab and verteporfin for polypoidal choroidal vasculopathy: 12-month LAPTOS study results. *Am J Ophthalmol*. 2013;156(4):644–651.
52. Oishi A, Miyamoto N, Mandai M, et al. LAPTOS study: a 24-month trial of verteporfin versus ranibizumab for polypoidal choroidal vasculopathy. *Ophthalmology*. 2014;121(5):1151–1152.
53. Oishi A, Tsujikawa A, Yamashiro K, et al. One-year result of aflibercept treatment on age-related macular degeneration and predictive factors for visual outcome. *Am J Ophthalmol*. 2015;159(5):853–860.
54. Hikichi T, Kitamei H, Shioya S. Prognostic factors of 2-year outcomes of ranibizumab therapy for polypoidal choroidal vasculopathy. *Br J Ophthalmol*. 2015;99(6):817–822.
55. Waldstein SM, Wright J, Warburton J, Margaron P, Simader C, Schmidt-Erfurth U. Predictive value of retinal morphology for visual acuity outcomes of different ranibizumab treatment regimens for neovascular AMD. *Ophthalmology*. 2016;123(1):60–69.
56. Freund KB, Zweifel SA, Engelbert M. Do we need a new classification for choroidal neovascularization in age-related macular degeneration? *Retina*. 2010;30(9):1333–1349.
57. Sharma S, Toth CA, Daniel E, et al. Macular morphology and visual acuity in the second year of the comparison of age-related macular degeneration treatments trials. *Ophthalmology*. 2016;123(4):865–875.
58. Koizumi H, Kano M, Yamamoto A, et al. Short-term changes in choroidal thickness after aflibercept therapy for neovascular age-related macular degeneration. *Am J Ophthalmol*. 2015;159(4):627–633.
59. Nishide T, Hayakawa N, Shibuya E, Yagi Y, Mizuki N. Choroidal thickness is affected by many factors which may change the effect of ranibizumab: author's response. *Graefes Arch Clin Exp Ophthalmol*. 2014;252(5):849–850.
60. Saito M, Kano M, Itagaki K, Oguchi Y, Sekiryu T. Switching to intravitreal aflibercept injection for polypoidal choroidal vasculopathy refractory to ranibizumab. *Retina*. 2014;34(11):2192–2201.
61. Stewart MW, Rosenfeld PJ. Predicted biological activity of intravitreal VEGF Trap. *Br J Ophthalmol*. 2008;92(5):667–668.
62. Ferrara N, Damico L, Shams N, Lowman H, Kim R. Development of ranibizumab, an anti-vascular endothelial growth factor antigen binding fragment, as therapy for neovascular age-related macular degeneration. *Retina*. 2006;26(8):859–870.
63. Lowe J, Araujo J, Yang J, et al. Ranibizumab inhibits multiple forms of biologically active vascular endothelial growth factor in vitro and in vivo. *Exp Eye Res*. 2007;85(4):425–430.
64. Hood JD, Meininger CJ, Ziche M, Granger HJ. VEGF upregulates eNOS message, protein, and NO production in human endothelial cells. *Am J Physiol*. 1998;274(3 Pt 2):H1054–H1058.

Clinical Ophthalmology

Dovepress

Publish your work in this journal

Clinical Ophthalmology is an international, peer-reviewed journal covering all subspecialties within ophthalmology. Key topics include: Optometry; Visual science; Pharmacology and drug therapy in eye diseases; Basic Sciences; Primary and Secondary eye care; Patient Safety and Quality of Care Improvements. This journal is indexed on

Submit your manuscript here: <http://www.dovepress.com/clinical-ophthalmology-journal>

PubMed Central and CAS, and is the official journal of The Society of Clinical Ophthalmology (SCO). The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.