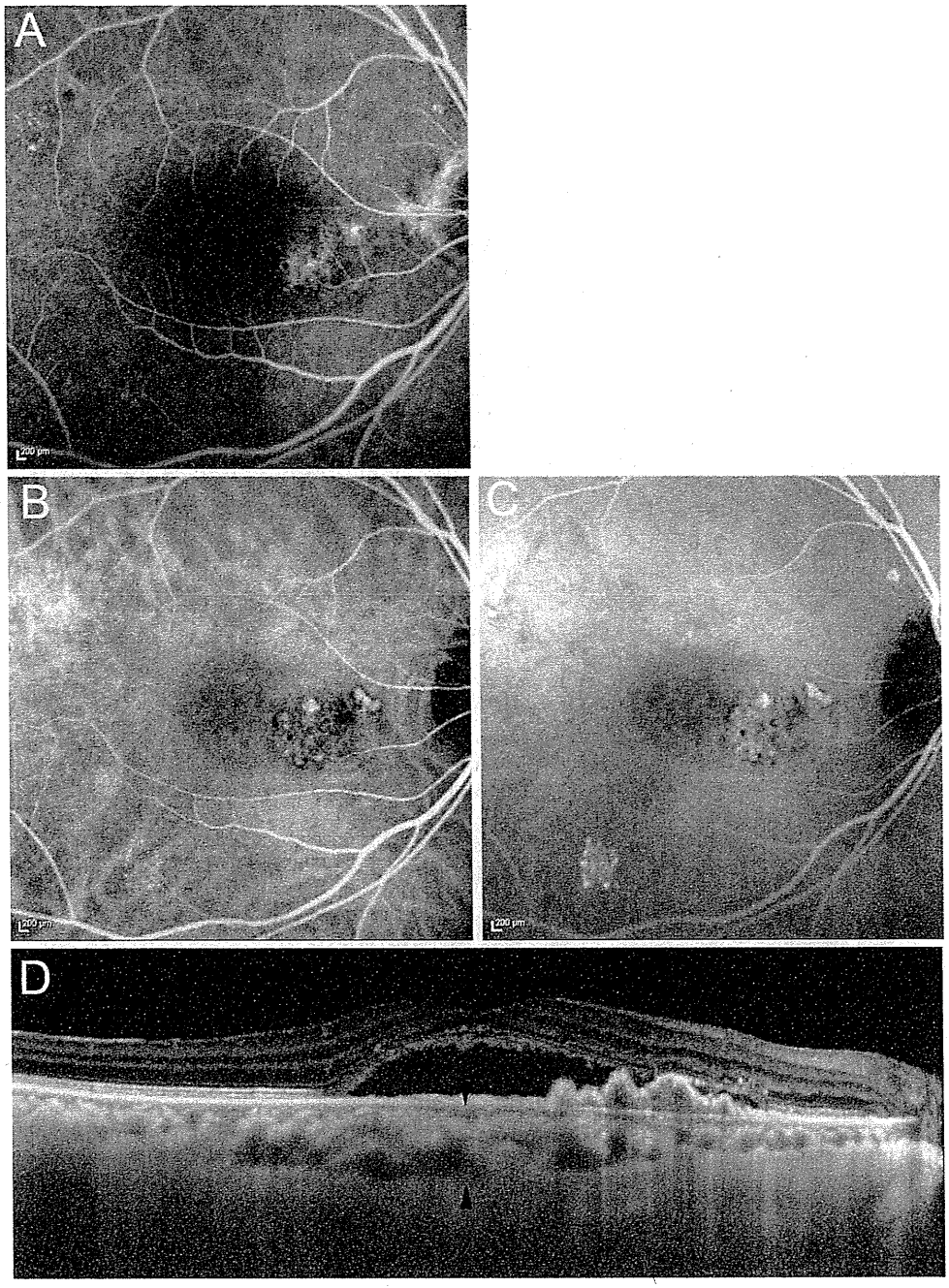

FIGURE 4. PCV with choroidal hyperpermeability. (**A**) FA shows late leakage. (**B**) Middle-phase IA shows a branching vascular network that terminates in polypoid lesions. (**C**) Late-phase IA shows choroidal vascular hyperpermeability. (**D**) EDI-OCT shows SRD, protrusions of the RPE suggesting polypoidal lesions, and thick choroid. Subfoveal choroidal thickness was 310 μm (*between arrowheads*).

subfoveal choroidal thickness was significantly greater in eyes with PCV than that in eyes with typical AMD ($P = 0.001$, *t*-test) (Figs. 3 and 5, Table 2).

Choroidal Thickness in Unilateral Disease Eyes and Fellow Eyes

In the present study, EDI-OCT had been performed in both eyes in 101 patients with unilateral diseases; thus, subfoveal choroidal thickness in unilateral disease eyes and fellow eyes was compared in these patients. In patients with unilateral typical AMD and PCV, no significant difference was observed between the mean subfoveal choroidal thickness in disease eyes and fellow eyes ($P = 0.938$ in typical AMD and $P = 0.996$ in PCV, *t*-test) (Table 3). Mean subfoveal choroidal thickness was significantly thinner in eyes with typical AMD than that in eyes with PCV both in disease eyes ($P = 0.023$, *t*-test) and in fellow eyes ($P = 0.026$, *t*-test) (Table 3). In the fellow eyes of patients with typical AMD, the mean subfoveal choroidal thickness was significantly greater in eyes with choroidal vascular hyperpermeability on IA than that in eyes without it ($P < 0.001$, *t*-test) (Table 4). Similarly, in the fellow eyes of patients with PCV, the mean subfoveal choroidal thickness was significantly greater in eyes with choroidal vascular hyperpermeability on IA than that in eyes without it ($P = 0.027$, *t*-test) (Table 4).

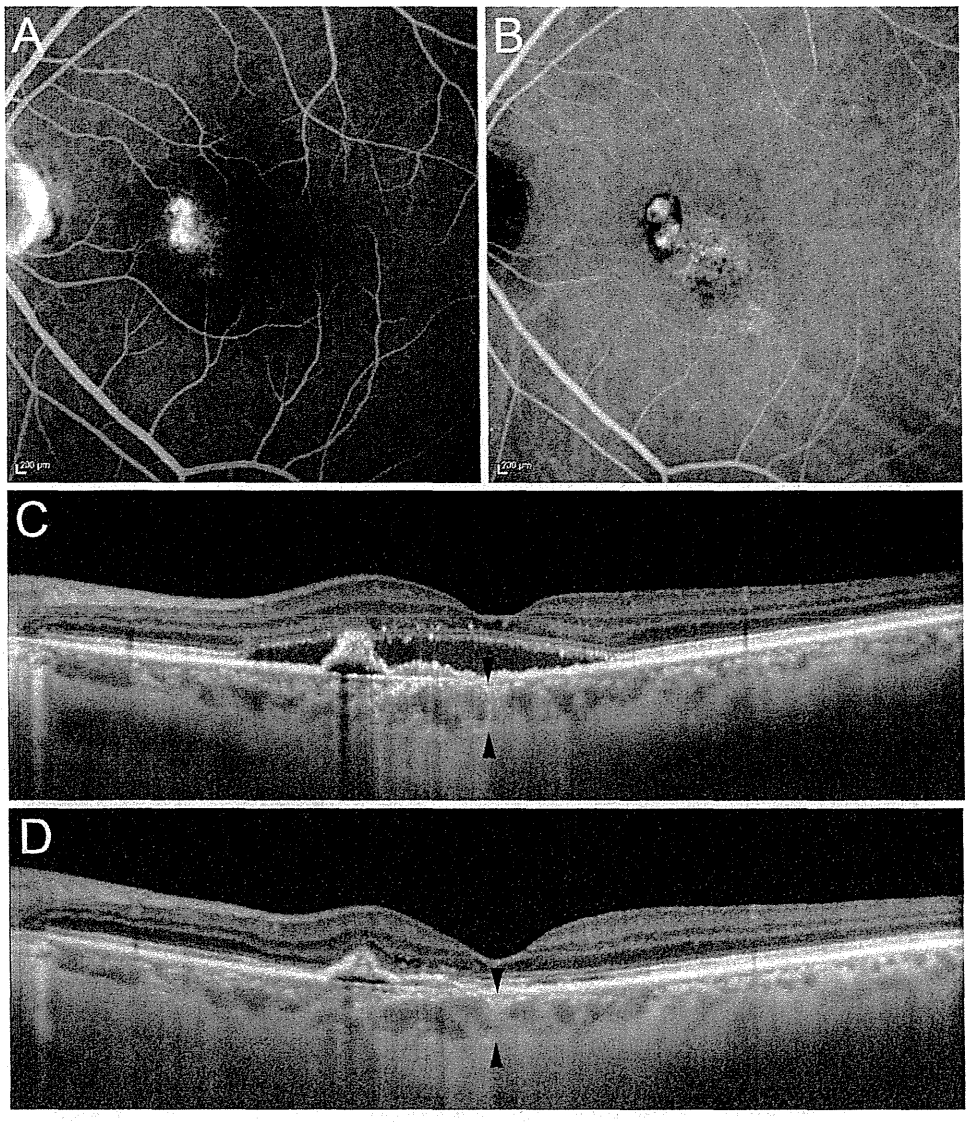

FIGURE 5. PCV without choroidal hyperpermeability. (**A**) FA shows late leakage. (**B**) Late-phase IA shows a branching vascular network that terminates in polypoid lesions, but shows no choroidal hyperpermeability. (**C**) EDI-OCT shows SRD, protrusions of the RPE, and thinner choroid compared with Figure 4. Subfoveal choroidal thickness was 230 μm (*between arrowheads*). (**D**) After 3 monthly injections of intravitreal ranibizumab, EDI-OCT shows resolution of SRD and almost stable choroidal thickness. Subfoveal choroidal thickness was 222 μm (*between arrowheads*).

In eyes with choroidal hyperpermeability, mean subfoveal choroidal thickness was not different between the fellow eyes of patients with typical AMD and PCV ($P = 0.401$, *t*-test) (Table 4). In contrast, in eyes without choroidal vascular hyperpermeability, the mean subfoveal choroidal thickness was significantly greater in the fellow eyes of patients with PCV than that in the fellow eyes of patients with typical AMD ($P = 0.004$, *t*-test) (Table 4).

TABLE 3. Subfoveal Choroidal Thickness in Unilateral Disease Eyes and Fellow Eyes

	Disease Eyes	Fellow Eyes	P Value (t-test)
Typical AMD ($n = 47$)	202.1 6 88.4 (μm)	203.5 6 83.6 (μm)	0.938
PCV ($n = 54$)	242.3 6 86.6 (μm)	242.4 6 88.5 (μm)	0.996
P value (*t*-test)	0.023	0.026	

With bilateral choroidal hyperpermeability, mean subfoveal choroidal thickness was similar in eyes with typical AMD/PCV and fellow eyes (Table 5).

Choroidal Thickness Changes after Treatment

After combination therapy (PDT and intravitreous ranibizumab), the mean subfoveal choroidal thickness was decreased in typical AMD and PCV ($P = 0.054$ in eyes with choroidal hyperpermeability and $P = 0.010$ in eyes without choroidal hyperpermeability, paired *t*-test) (Table 6). In eyes with typical AMD, subfoveal choroidal thickness decreased from 234.7 6 114.2 to 191.4 6 111.2 μm 3 months after PDT combined with intravitreal ranibizumab ($P = 0.016$, paired *t*-test) (Fig. 2). In eyes with PCV, subfoveal choroidal thickness decreased from 201.0 6 101.1 to 172.9 6 91.0 μm 3 months after PDT combined with intravitreal ranibizumab ($P = 0.036$, paired *t*-test). In contrast, three injections of intravitreous ranibizumab did not decrease subfoveal choroidal thickness in typical AMD

TABLE 4. Subfoveal Choroidal Thickness and Choroidal Hyperpermeability in Fellow Eyes

		With Choroidal Hyperpermeability	Without Choroidal Hyperpermeability	P Value (t-test)
Fellow eyes of typical AMD (n = 47)	n	19	28	
	Subfoveal CT (μm)	258.6 6 69.8 (μm)	166.1 6 71.1 (μm)	<0.001
Fellow eyes of PCV (n = 54)	n	17	37	
	Subfoveal CT (μm)	280.4 6 83.8 (μm)	224.8 6 83.5 (μm)	0.027
P value (t-test)		0.401	0.004	

CT, choroidal thickness.

and PCV ($P = 0.415$ in eyes with choroidal hyperpermeability and $P = 0.173$ in eyes without choroidal hyperpermeability, paired t-test) (Table 6, Figs. 3 and 5).

Visual acuity improved after monthly injections of intravitreal ranibizumab regardless of choroidal hyperpermeability (Table 7). In contrast, visual acuity was stable after PDT combined with intravitreal ranibizumab regardless of choroidal hyperpermeability (Table 7).

Genomic Association

The I62V polymorphism in the *CFH* gene seemed to contribute to choroidal thickness. Mean subfoveal choroidal thickness was 247.5 6 97.7 μm in genotype AA, 248.2 6 97.6 μm in genotype GA, and 221.9 6 102.7 μm in genotype GG (P = 0.117, Jonckheere-Terpstra test) (Fig. 6). Specifically in eyes with PCV, mean subfoveal choroidal thickness was 274.9 6 79.0 μm in genotype AA, 273.9 6 99.2 μm in genotype GA, and 219.5 6 90.0 μm in genotype GG ($P = 0.043$, Jonckheere-Terpstra test) (Fig. 6). In contrast, the Y402H polymorphism in the *CFH* gene and the A69S polymorphism in the *ARMS2* gene did not contribute to subfoveal choroidal thickness ($P = 0.461$ and 0.248, respectively, Jonckheere-Terpstra test).

The frequency of the minor allele in *CFH* I62V polymorphism was 34% in patients with choroidal hyperpermeability and 24% in patients without choroidal hyperpermeability (Table 8). Upon analyzing the genotypes using the 2 × 2 table from the allelic χ^2 test, the G allele did not contribute to choroidal hyperpermeability (P = 0.169). The T allele and C allele in *CFH* Y402H and *ARMS2* A69S, respectively, also did not contribute to choroidal hyperpermeability ($P = 0.575$ and 0.244, respectively).

DISCUSSION

Several researchers have reported on the subfoveal choroidal thickness in eyes with PCV and typical AMD.[21–24] However, little is known about the relationship between choroidal thickness and angiographic changes or genotypes in these eyes. In the present study, we investigated a consecutive series of treatment-naïve patients with typical AMD and PCV and found a relationship between choroidal thickness and subtypes of AMD, choroidal vascular hyperpermeability, and polymorphisms in the *CFH* gene in these diseases.

TABLE 5. Subfoveal Choroidal Thickness in Disease Eyes and Fellow Eyes with Bilateral Choroidal Hyperpermeability

	Disease Eyes	Fellow Eyes	P Value (t-test)
Typical AMD (n = 7)	251.6 6 87.9	258.3 6 80.7	0.885
PCV (n = 11)	274.8 6 96.2	255.2 6 77.5	0.606
P value (t-test)	0.615	0.937	

Subfoveal choroidal thickness was reported to be greater in eyes with PCV than that in eyes with typical AMD,[22–24] which is consistent with the present study. In addition, in the present study, subfoveal choroidal thickness of the fellow eyes was greater in eyes with PCV than that in eyes with typical AMD. These differences in choroidal thickness may indicate a significant structural difference in the choroid between typical AMD and PCV.

In eyes without choroidal vascular hyperpermeability, the mean subfoveal choroidal thickness was significantly greater in eyes with PCV than that in eyes with typical AMD. The same was true in the fellow eyes of patients with typical AMD and PCV. Thus, in eyes without choroidal hyperpermeability, the difference in choroidal thickness may reflect the different pathologic mechanisms of the two diseases. The decreased ability of the choroid to deliver oxygen and other metabolites to the retina, which is due mainly to choroidal blood volume rather than velocity of flow, has been postulated to lead to CNV in typical AMD.[27] Our results showing thinner choroidal thickness in eyes with typical AMD may be explained by this postulation. In addition, dilation of choroidal vessels and a collection of dilated thin-walled vessels derived from choroidal vessels beneath the retinal pigment epithelium (RPE) have been noted in histopathologic studies of PCV.[28–31] The present results regarding choroidal thickness of PCV may reflect those of histologic studies.

Choroidal thickness has a relationship not only with subtypes of AMD but also with choroidal vascular hyperpermeability. Maruko et al.[21] reported that choroid in PCV eyes with choroidal hyperpermeability was thicker than that in eyes without choroidal hyperpermeability, consistent with the present study. We first showed that, in typical AMD, the mean subfoveal choroidal thickness in eyes with choroidal vascular hyperpermeability on IA was significantly greater than that in eyes without it. In addition, in the fellow eyes of patients with typical AMD and PCV, the mean subfoveal choroidal thickness in eyes with choroidal vascular hyperpermeability on IA was significantly greater than that in eyes without it. These findings suggest that choroidal thickening is closely associated with choroidal hyperpermeability both in typical AMD and PCV, and both in disease eyes and fellow eyes. Thus, typical AMD and PCV may share, at least in part, a common pathology with choroidal vascular abnormalities with regard to choroidal hyperpermeability. In fact, in eyes with choroidal hyperpermeability, the mean choroidal thickness was similar between eyes with typical AMD and PCV. Hydrostatic pressure within the choroid may increase in areas with choroidal vascular hyperpermeability, resulting in increased extravascular volume within the choroid and increased choroidal thickness in typical AMD and PCV with choroidal hyperpermeability.

Recently, Maruko et al.[21] reported that subfoveal choroidal thickness was decreased by PDT monotherapy and PDT combined with intravitreous ranibizumab in eyes with PCV. In the present study, after PDT combined with intravitreous

TABLE 6. Mean Subfoveal Choroidal Thickness Change before and after Treatment in Eyes with and without Choroidal Vascular Hyperpermeability

	Treatment (n)	Baseline	3-Month Follow-up	P Value (t-test)
With choroidal hyperpermeability	PDT + IVR (6)	292.8 6 89.2	240.1 6 103.4	0.054
	Mono-IVR (20)	286.1 6 105.5	288.1 6 106.2	0.415
Without choroidal hyperpermeability	PDT + IVR (10)	170.3 6 97.4	133.1 6 82.4	0.010
	Mono-IVR (43)	200.8 6 106.4	198.0 6 109.0	0.173

Treatment consisted of intravitreal ranibizumab monotherapy or PDT combined with intravitreal ranibizumab. IVR, intravitreal ranibizumab.

TABLE 7. Mean logMAR BCVA before and after treatment in Eyes with and without Choroidal Vascular Hyperpermeability

	Treatment (n)	Baseline	3-Month Follow-up	P Value (t-test)
With choroidal hyperpermeability	PDT + IVR (6)	0.46 6 0.28	0.34 6 0.39	0.314
	Mono-IVR (20)	0.41 6 0.36	0.33 6 0.33	0.040
Without choroidal hyperpermeability	PDT + IVR (10)	0.76 6 0.55	0.64 6 0.59	0.226
	Mono-IVR (43)	0.49 6 0.43	0.42 6 0.41	0.014

Treatment consisted of intravitreal ranibizumab monotherapy or PDT combined with intravitreal ranibizumab. IVR, intravitreal ranibizumab.

ranibizumab, the mean subfoveal choroidal thickness was decreased in both typical AMD and PCV. Taken together, PDT leads to choroidal thinning not only in PCV but also in typical AMD eyes, whereas intravitreal ranibizumab has less effect on choroidal thickness in these diseases. These findings may be reflective of the different treatment effects of PDT on typical AMD and PCV.[3,7] Choroidal thickness is lower in typical AMD than that in PCV; thus, additional thinning of the choroid after PDT may have adverse effects and influence visual prognosis, especially in typical AMD.

Existing evidence suggests an association between AMD and polymorphisms in the *CFH* and *ARMS2* genes.[32–35] In a Japanese cohort, we have shown that three single nucleotide polymorphisms of *CFH* Y402H, I62V, and *ARMS2* A69S are associated with typical AMD and PCV.[36] However, possible associations between choroidal thickness and genetic background remained unknown. In the present study, the I62V polymorphism in the *CFH* gene seemed to contribute to choroidal thickness in patients with PCV. *CFH* expression has been shown to occur primarily in the RPE, drusen, and choroidal capillaries.[32] *CFH* is a critical negative regulator of

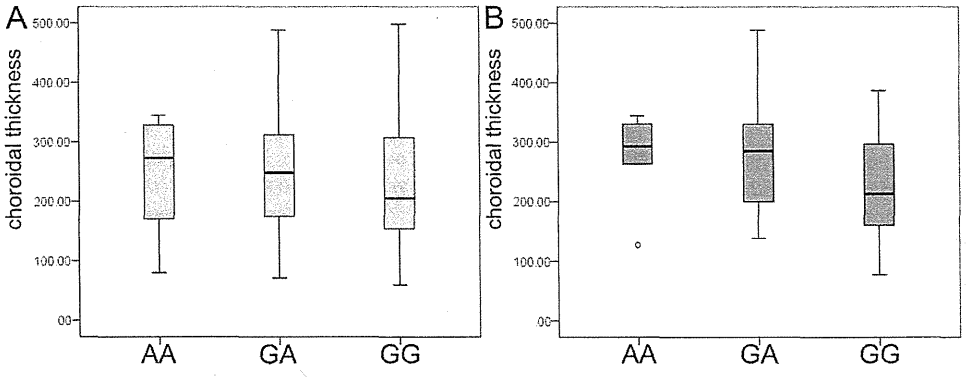

FIGURE 6. Subfoveal choroidal thickness and I62V polymorphism in the complement factor H gene. (**A**) Eyes with typical AMD and PCV. Mean choroidal thickness was 247.5 6 97.7 μm in genotype AA, 248.2 6 97.6 μm in genotype GA, and 221.9 6 102.7 μm in genotype GG. (**B**) Eyes with PCV. Mean choroidal thickness was 274.9 6 79.0 μm in genotype AA, 273.9 6 99.2 μm in genotype GA, and 219.5 6 90.0 μm in genotype GG.

TABLE 8. Distribution of *ARMS2* A69S, *CFH* I62V, and *CFH* Y402 Genotypes in Patients with and without Choroidal Hyperpermeability

	Hyperpermeability (+)					Hyperpermeability (-)					
	Genotype, No. (%)			Allele, No. (%)		Genotype, No. (%)			Allele, No. (%)		P *
ARMS2 A69S	GG	GT	TT	G	T	GG	GT	TT	G	T	
	6 (19)	15 (47)	11 (34)	27 (42)	37 (58)	7 (13)	22 (41)	25 (46)	36 (33)	72 (67)	0.244
CFH I62V	AA	GA	GG	A	G	AA	GA	GG	A	G	
	5 (16)	11 (35)	15 (48)	21 (34)	41 (66)	4 (7)	18 (33)	32 (59)	26 (24)	82 (76)	0.169
CFH Y402	CC	CT	TT	C	T	CC	CT	TT	C	T	
	1 (3)	5 (16)	26 (81)	7 (11)	57 (89)	1 (2)	13 (24)	40 (74)	15 (14)	93 (86)	0.575

*P value from allelic χ^2 test 2 × 2 table for its exact counterpart. *ARMS2*, age-related maculopathy susceptibility 2; *CFH*, complement factor H.

the alternative pathway of the complement system.[32] The association between *CFH* and choroidal thickness in PCV leads to the hypothesis that inflammation may be involved in the choroidal thickness changes in PCV. A histopathologic study demonstrated infiltration of T and B lymphocytes present throughout the choroid in an eye with PCV and infiltration of macrophages among PCV lesions,[37] suggesting that inflammation is implicated in the pathogenesis of PCV. Further genetic study in a large cohort should deepen our understanding of the clinical significance of choroidal thickness and choroidal hyperpermeability, which may be involved in the pathology of typical AMD and PCV.

This study has some limitations. In addition to the retrospective nature of the study and lack of controls, the choroidal thickness in all images was evaluated manually because no automated computer software is available to calculate choroidal thickness. Although EDI-OCT increases the sensitivity of the choroid, light scattering by the RPE and choroid still occurs; this hampers visualization of the chorioscleral interface in some patients, especially in eyes with a very thick choroid. In such eyes, 5-10 points at which the chorioscleral interface could be identified were chosen and connected to form a segmentation line, and the subfoveal choroidal thickness was measured. Despite these limitations, we found that choroidal thickness was associated with subtypes of AMD, choroidal hyperpermeability, and polymorphisms in the *CFH* gene. Choroidal thickness was greater in PCV than that in typical AMD. Choroidal thickness was greater in eyes with choroidal hyperpermeability, both in typical AMD and PCV, and both in disease eyes and fellow eyes. In eyes without choroidal hyperpermeability, EDI-OCT is useful as an auxiliary measure for differentiating typical AMD and PCV. PDT combined with intravitreal ranibizumab decreased the choroidal thickness both in typical AMD and PCV; thus, a lengthy follow-up study is needed for evaluating this combined therapy. Further research on the association of inflammation and choroidal structure will deepen our understanding of the pathology of these diseases.

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Graefes Arch Clin Exp Ophthalmol (2013) 251:1–7
DOI 10.1007/s00417-012-2022-8

RETINAL DISORDERS

Long-term effect of intravitreal injection of anti-VEGF agent for visual acuity and chorioretinal atrophy progression in myopic choroidal neovascularization

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Received: 25 January 2012 / Revised: 23 March 2012 / Accepted: 26 March 2012 / Published online: 19 April 2012

Abstract
Purpose To investigate the long-term visual prognosis and progression of chorioretinal atrophy in patients with myopic choroidal neovascularization (mCNV) treated with intravitreal injections of bevacizumab.
Methods Hospital-based, retrospective, cross-sectional study. In total, 22 patients (22 eyes) with treatment-naïve mCNV who underwent intravitreal injection of bevacizumab and were followed up for more than 48 months were investigated. Visual acuity and fundus photographs before and 1, 2, 3, and 4 years after initial treatment in the clinics were compared and judged if chorioretinal atrophy (CRA) developed/enlarged or remained unchanged. The influence of clinical characteristics including age, sex, axial length, baseline visual acuity, CNV area, CNV location, and number of injections were investigated with logistic regression analysis.
Results Mean logarithm of the minimum angle of resolution (logMAR) improved from 0.76 to 0.52 ($P<.01$), 0.48 ($P<.01$), and 0.54 ($P<.05$) after 1, 2, and 3 years, respectively. The effect slightly declined to marginally non-significant levels after 4 years (logMAR, 0.59; $P=.07$). CRA developed or enlarged in nine cases (41 %) in 1 year, reaching 16 cases (73 %) at the final visit. Those without CRA enlargement achieved better visual improvement. None of the aforementioned patient characteristics significantly affected CRA.
Conclusions Anti-VEGF therapy for mCNV is effective for vision improvement in the long term. On the other hand, development or enlargement of CRA frequently occurred, and affected visual improvement. Strategies to manage atrophy should be the next step in achieving better visual outcome upon mCNV treatment.

Keywords Choroidal neovascularization · High myopia · Bevacizumab · Anti-VEGF therapy · Chorioretinal atrophy

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Introduction

Pathologic myopia is one of the major causes of visual impairment worldwide. The disease, marked by elongation of axial length and changes in the fundus of the eye, may cause complications such as posterior staphyloma, chorioretinal atrophy (CRA), or choroidal neovascularization (CNV). Considering that myopia is more prevalent in younger populations [1, 2], the impact on social health will be more profound in the near future.

Myopic CNV (mCNV) is reported to occur in up to 10 % of myopic patients [3], with a prevalence of up to 40 % in highly myopic patients [4]. Since long-term visual prognosis is poor in the absence of treatment [5, 6], a wide range of therapeutic alternatives, including photocoagulation, macular translocation, surgical CNV removal, administration of triamcinolone acetonide, and photodynamic therapy (PDT) have been explored [7]. Although PDT can stabilize the disease activity, formation of subretinal fibrosis [8] or CRA, a cause of the poor natural course of mCNV [6, 9], frequently occurs after the treatment [10], and may affect visual function significantly in the long term. In fact, the most reliable trial (Verteporfin In Photodynamic Therapy: VIP study) failed to show significant improvement in vision 2 years after the treatment [11].

After the PDT era, anti-vascular endothelial growth factor (VEGF) therapy was developed and proved to be effective against mCNV [12–24]. Although the treatment regimens were not equivalent in these studies, intravitreal anti-VEGF therapy seems to promote the regression of CNV more effectively and decrease the frequency of CRA, compared to PDT [25–28]. However, even with anti-VEGF therapy, CRA still develops [17, 18, 24, 25] and may affect the long-term visual prognosis [24]. In fact, vision improvement became non-significant in some of these studies by the end of 2 years of follow-up [17, 29–31]. Although a recent report showed favorable effects after 3 years of follow-up [32], some of the studied subjects had previously been treated with PDT. Thus, long-term prognosis of anti-VEGF therapy, especially for treatment-naïve mCNV, is still unclear.

In the present study, we investigated long-term visual prognosis of treatment-naïve mCNV patients who underwent anti-VEGF therapy. We also investigated how often CRA progression occurs in these patients, and explored the difference between those with and without CRA enlargement.

Methods

All procedures conformed to the tenets of the Declaration of Helsinki, and were approved by the Institutional Review Board at Kyoto University Graduate School of Medicine. Written informed consent was obtained from each patient.

We retrospectively reviewed the clinical records of mCNV patients. Inclusion criteria were as follows: (1) presence of subfoveal or juxtafoveal CNV, (2) refractive error greater or equal to −6.0 diopters or axial length greater or equal to 26.5 mm, (3) undergoing intravitreal injection of 1.25 mg bevacizumab at Kyoto University Hospital, and (4) no previous ocular surgery other than phacoemulsification and aspiration for cataract. When both eyes of one patient met the inclusion criteria, only the right eye was included. Exclusion criteria were: (1) any treatment for mCNV other than anti-VEGF therapy prior to or during the observation period, (2) a follow-up period of less than 48 months, and (3) intraocular surgery or development of other ocular diseases during the follow-up.

Initial and follow-up fluorescein angiography (FA) was performed with a confocal scanning laser ophthalmoscope (HRA2; Heidelberg Engineering, Heidelberg, Germany), and 45-degree fundus photographs were taken with a fundus camera (TRC NW6S; TOPCON, Tokyo, Japan). Injections of 1.25 mg bevacizumab were performed under sterile conditions, and prophylactic topical antibiotics were applied from a few days before to 1 week after the injection. Follow-up intervals were 1, 3, 6, 12, 18, 24, 30, 36, and 48 months. Additional follow-up was planned for each patient at the clinician's discretion. Visual acuity, funduscopic examination, and optical coherence tomography (OCT) examination were performed at each visit. FA was performed when subjective symptoms worsened, but OCT did not show obvious exudative changes. After the initial treatment, additional treatment was applied as needed. The need for re-treatment was determined according to objective/subjective decline of vision, exudative changes in OCT images, and/or dye leakage in FA. The same dose of bevacizumab had been injected for re-treatment until December, 2008 when we encountered the outbreak of aseptic endophthalmitis [33]. Thereafter, 0.3 mg of pegaptanib had been used for 5 months. Then, after use of ranibizumab was officially approved in May 2009, 0.5 mg of ranibizumab was applied for the recurrences.

Development or enlargement of CRA was judged with photographs taken each year by two of the authors (AO and KY), who were blinded to the other characteristics of the patient. The judgment was based on changes in patchy atrophy; color changes in tessellation or diffuse atrophy without patchy atrophy were not considered as CRA progression (Fig. 1). CRAs, which were not adjacent to original CNV location, were not counted. When the two authors disagreed, a third author (AT) was asked to arbitrate. The CNV area was manually measured in early-phase FA images with measuring tools which were coupled to the HRA2. Location of CNV was judged from FA; those involving the center of the foveal avascular area on FA were judged as subfoveal. When it was difficult to judge only from FA images, OCT images were used to confirm whether CNV membranes lay beneath the fovea.

Statistical analyses were conducted using IBM SPSS Statistics Desktop (version 19.0; IBM Japan, Tokyo, Japan). Descriptive analyses were recorded as means ± standard deviation unless otherwise specified. The BCVA was measured based on a Landolt C chart, and then converted to logarithm of the minimal angle of resolution (logMAR) equivalents. Differences in VA from baseline were analyzed using repeated measures ANOVA with post-hoc Tukey's test. Logistic regression analysis of the clinical variables was performed with development/enlargement of CRA as the dependent variable. Independent variables were chosen based on forward stepwise regression. Correlations between the variables were also evaluated with Spearman rank correlation. Differences in age, axial length, BCVA, and number of injections between those with and without CRA progression were evaluated with the Mann–Whitney U test. Chi-square test was applied to assess the difference in sex or CNV location (subfovea/juxtafovea) between those with and without CRA progression.

Results

Forty eyes of 40 patients met the inclusion criteria. Two patients had bilateral involvement, but only their right eyes

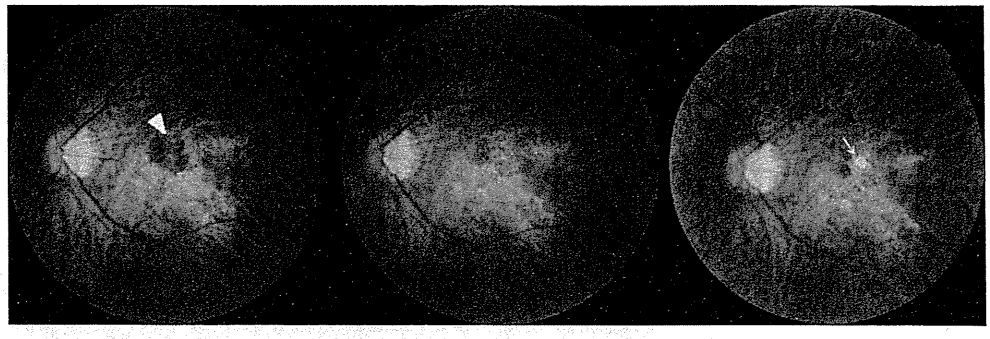

Fig. 1 Color fundus photographs of a representative case with subfoveal choroidal neovascularization (CNV) (*left*, pretreatment; *triangle*, CNV). Patchy atrophy was not evident after 1 year (*middle*) but developed thereafter (*right*, 48 months after the treatment; *arrow*, CRA)

were included. We excluded one patient who developed aseptic endophthalmitis, one who developed central retinal vein occlusion, two who underwent vitrectomy for retinoschisis, and four who underwent additional PDT. Ten patients dropped out before the end of the 48 months of follow-up. Finally, 22 eyes of 22 patients were eligible for the study. Among them, seven were men and 15 were women. The mean age of the participants was 64.1± 9.6 years (range, 47 to 81 years), and axial length was 28.9±1.6 mm (range, 26.28 to 32.63 mm). The refractive error of phakic patients was −11.9±3.7 diopter (range, −7 to −21). Mean number of injections was 2.1±1.9 (range, 1 to 7) including 41 times of bevacizumab and six times of ranibizumab injections.

Development or enlargement of CRA was noted in nine eyes (40.9 %) in 1st year, 14 eyes (63.6 %) in 2nd year, and 16 eyes (72.7 %) in 3rd and 4th years; those without CRA progression after 3 years did not show remarkable change in the 4th year. Logistic regression analysis showed non-significant effect of age (P=.08) and location of CNV for CRA progression at 1 year (P=.07). After 2 years, none of the parameters showed significant effect. Table 1 shows characteristics of those with and without CRA progression at 4 years after the treatment. Visual improvement was better in those without CRA progression than those with CRA progression. Those without CRA progression tended to include juxtafoveal CNV more frequently, but the difference was not significant (P=.21). Representative cases are shown in Figs. 1, 2, 3, 4 and 5. Some patients developed CRA early after the treatment (Fig. 1), whereas others developed CRA after 1 or 2 years (Fig. 2). The minority of patients was free of CRA progression during the course of the 48-month follow-up (Fig. 3).

Visual acuity improved from baseline, but slightly declined thereafter. The difference from baseline was significant until 3 years, and was marginally insignificant at 4 years after the treatment (Fig. 4). Among the baseline CNV characteristics, CNV size measured with FA image was associated with visual improvement (r=.434, P=.04); larger CNV resulted in poor visual improvement.

Discussion

We investigated long-term visual outcome and progression of CRA in treatment-naïve mCNV patients who underwent anti-VEGF therapy. The study showed significant improvement of vision over the 3 years of follow-up, despite that the P value was barely non-significant in the 4th year, and confirmed the beneficial effect of anti-VEGF therapy for mCNV. At the same time, the study showed that most patients finally experience the progression of CRA irrespective of baseline characteristics, and that CRA compromises the vision-improving effect.

Anti-VEGF therapy is becoming a standard treatment for mCNV, although its application is not yet officially approved in many countries. The present study confirmed the long-term effect of the therapy. Considering that the effect of PDT is limited to maintain vision, [10, 34], anti-VEGF therapy should be the first choice until a novel method is proven to be more effective.

On the other hand, the present study raised some concerns regarding longer-term prognosis: the progression of CRA. Anti-VEGF therapy is considered to be superior to

Table 1 Characteristics of patients with and without chorioretinal atrophy progression 4 years after intravitreal injection of bevacizumab

	CRA	Non-CRA	P value
Age (years)	63.5⊠0.7	65.7⊠6.3	n.s.
Sex (male/female)	5/11	2/4	n.s.
Axial length (mm)	29.06⊠1.52	28.32⊠1.96	n.s.
Baseline logMAR (unit)	0.76⊠0.38	0.76⊠0.22	n.s.
Final logMAR (unit)	0.67⊠0.51	0.38⊠0.39	n.s.
Visual improvement	0.10⊠0.34	□0.37⊠0.33	P=.049
Area of CNV (mm^2)	1.55⊠1.21	1.03⊠0.79	n.s.
Location of CNV (subfovea/juxtafovea)	10/6*	2/4	n.s.
Number of injections	2.1⊠1.7	2.2⊠2.4	n.s.

CRA: chorioretinal atrophy progression; logMAR: logarithm of the minimum angle of resolution; CNV: chorioretinal atrophy; n.s.: not significant

*One eye with juxtafoveal CNV showed recurrence involving the subfovea

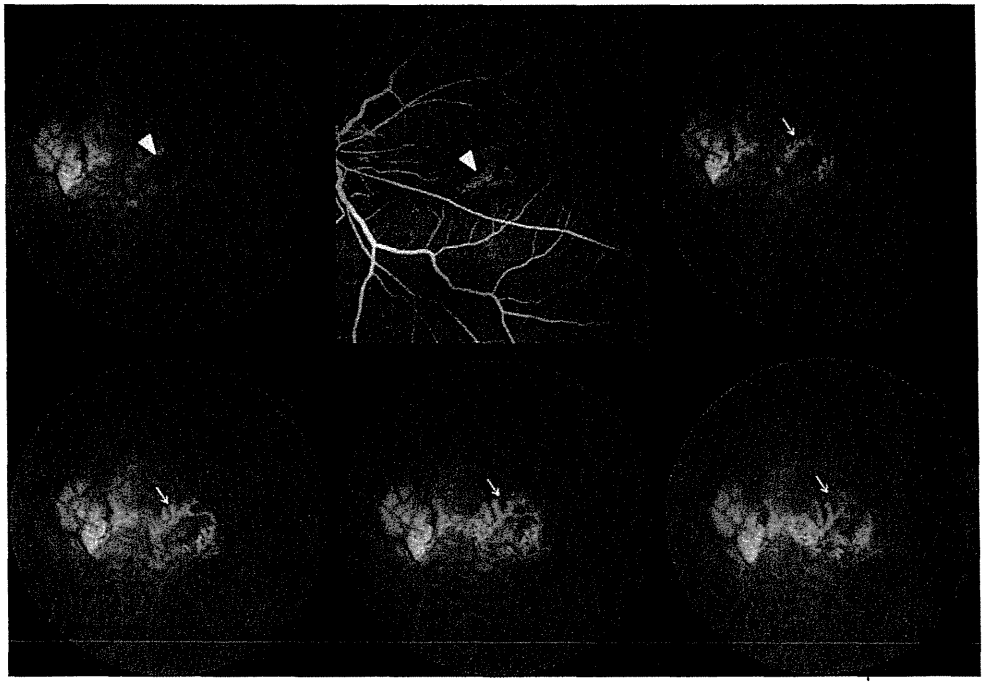

Fig. 2 Color fundus photographs and fluorescein angiography image of a 62-year-old woman. She had subfoveal CNV (*upper left and middle* panels; *triangle*, CNV) and was administered two bevacizumab injections. Chorioretinal atrophy (*arrows*) developed as early as 1 year after treatment (*upper right*) and progressed further thereafter (*lower left, middle, and right* panels: 2, 3, and 4 years, respectively). Her visual acuity, calculated as logMAR, improved from 0.15 to 0.4 in 1 year but declined to 0.2 in the subsequent year, ultimately reaching 0.08

PDT partly because it induces CRA less frequently. However, the present result showed that the assumption is not necessarily applicable in the long term. In fact, CRA developed or enlarged in as many as 80 % of the patients. Even considering that only 3/10 dropout patients showed CRA progression at their final visit, the percentage of patients with CRA progression should be at least $[(16+3)/(22+10)] \times 100=59.4$ %. This figure is comparable to the 70 % in PDT-treated eyes after 4 years [10], or the 77.8 % (35/45 eyes) in eyes after the natural course of 5 years [35] but not to the 95.1 % reported for the 80-months result [36]. Hence, CRA progression is often an inevitable consequence in the long-term follow-up of mCNV cases, probably due to natural history but to anti-VEGF therapy. Considering that those with CRA progression showed less visual improvement, the control of CRA should be the next step to be investigated.

Older age has been associated with development of CRA [36] or poor visual outcome [37, 38]. However, the present study did not show significant contribution of age for the development of CRA. One explanation could be the existence

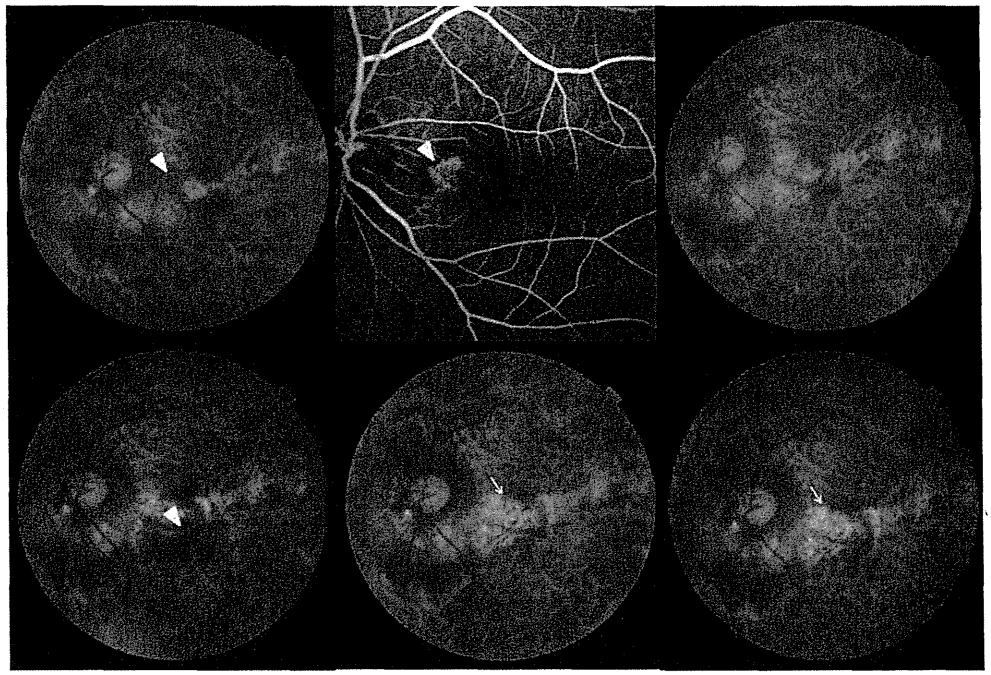

Fig. 3 Color fundus photographs and fluorescein angiography image of a 77-year-old woman. She had juxtafoveal mCNV (*upper left and middle* panels; *triangle*) and her left visual acuity, calculated as logMAR, was 0.1. mCNV diminished with an intravitreal injection of bevacizumab, and chorioretinal atrophy was not evident initially (*upper right*,1 year after treatment). However, CNV recurred in 20 months (*lower left*; *triangle*) and after six additional injections, chorioretinal atrophy (*arrows*) developed and enlarged (*lower middle and right* panels: 3 and 4 years, respectively). Finally, her visual acuity was 0.05

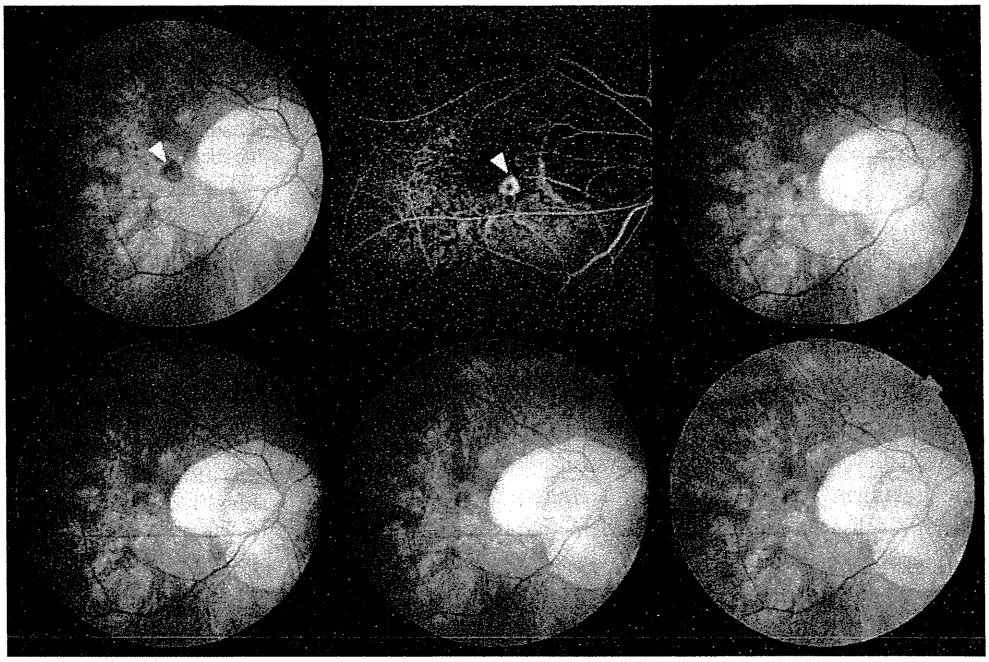

Fig. 4 Color fundus photographs and fluorescein angiography image of a 74-year-old man with juxtafoveal mCNV and visual acuity of 0.3 (*upper left and middle* panels; *triangle*). With a single injection of bevacizumab, mCNV efficiently regressed (*upper right*, 1 year after the treatment). Although the peripapillary atrophy enlarged within this period, mCNV-related chorioretinal atrophy was not noted (*lower left, middle, and right* panels: 2, 3, and 4 years after treatment respectively), and favorable improvement in vision was achieved (final visual acuity was 0.9)

of a critical age. Most of the previous studies investigated age-dependent differences by comparing aged and younger patients of 40 to 60 years of age. The population in the present study consisted of relatively older subjects; the average and median age of the participants in the present study was 64.1 and 64 years respectively. A small percentage of young patients could explain the non-significant effect of age.

The location of CNV is of clinical interest. Several groups, including ours, showed that patients with juxtafoveal CNV have better prognosis than subfoveal CNV during the natural course of the disease [35] or after anti-VEGF therapy [18, 39]. Moreover, subfoveal CNV induces larger CRA after PDT than do juxtafoveal or extrafoveal CNV [10], or induces CRA more frequently after intravitreal injection of bevacizumab [24]. In the present study, subfoveal CNV tended to cause CRA progression more frequently at 1 year after the initial treatment, although this was not statistically significant. Furthermore, four out of six patients who were free of CRA for 4 years had juxtafoveal CNV. The statistical non-significance may be partly due to the small sample size and the difficulty in treating recurrent cases: one case with juxtafoveal CNV recurred with subfoveal CNV and developed CRA thereafter. Although the underlying mechanism is not clear (e.g., could subfoveal CNV be a mere result of larger CNV size?), whether the location of CNV can be a practical prognostic parameter of CRA progression should be further investigated.

There still is a debate about which protocol is the most effective. Some authors used three monthly injections at the loading phase, whereas others adopted a single injection followed by additional as-needed injections. The dose of the drug also varies among reports, with 1, 1.25, and 2.5 mg of bevacizumab having been reported to be effective. Although we cannot draw any conclusion from the non-comparative study, we prefer the single injection and as-needed regimen due to lower risk and smaller cost, considering the relatively young age, healthier RPE, and slower progression of mCNV [40] compared to age-related macular degeneration. Randomized or meta-analysis study should be conducted to address the issue.

There are several limitations to the present study, including its retrospective design, uncontrolled examination

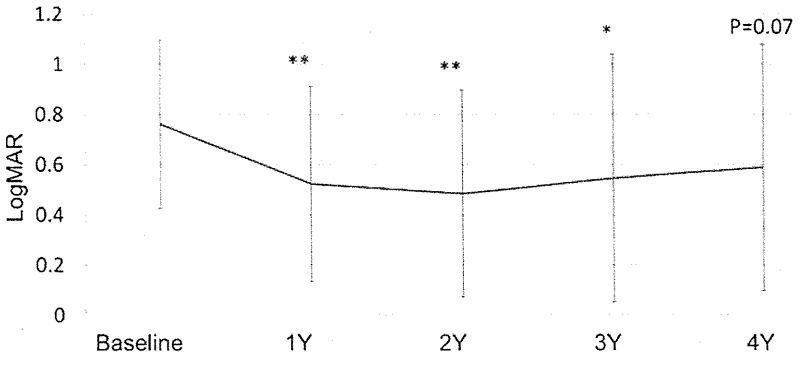

Fig. 5 Changes in visual acuity as a function of time. *Dot plots* represent mean values, and *whiskers* represent 95 % confidence intervals. Visual acuity improvement was roughly maintained during the 4-year period, despite the *P* value being barely non-significant in the fourth year. * $P<.05$ and ** $P<.01$ compared to baseline

interval, small sample size, and lack of a control group. In addition, a selection bias has existed, e.g., patients with persistent or recurrent CNV would more likely present to the hospital for a longer period or, conversely, patients with severe phenotypes might have undergone additional PDT and be excluded from the study. In addition, we did not investigate OCT images in detail, because the resolution of the devices used when the patients underwent initial treatment was limited. Further evaluation of pretreatment OCT image including retinal layer thickness or choroidal thickness would be interesting. These points should be noted when interpreting the results.

In conclusion, we showed that anti-VEGF therapy had satisfactory vision-improving effect for a 4-year period, but the treatment was not free of inducing CRA. To achieve better results, the causes and management of CRA should be further investigated.

Acknowledgment

Funding/support None.

Financial disclosures The authors have no proprietary interest in any aspect of this study.

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Factors Associated With the Response of Age-Related Macular Degeneration to Intravitreal Ranibizumab Treatment

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• PURPOSE: To investigate factors affecting patient response to intravitreal ranibizumab treatment for age-related macular degeneration (AMD).

• DESIGN: Retrospective chart review.

• METHODS: We reviewed medical records of 105 consecutive eyes with AMD treated with intravitreal ranibizumab injections and followed for more than 1 year after treatment. Response to ranibizumab treatment was compared between typical neovascular AMD and polypoidal choroidal vasculopathy (PCV). Furthermore, we investigated associations of age, lesion size, and single nucleotide polymorphisms (SNPs) in *CFH* and *ARMS2* genes with treatment response.

• RESULTS: Forty-nine eyes were diagnosed with typical neovascular AMD and 56 eyes with PCV. Serous retinal detachment and retinal edema resolved similarly in both typical neovascular AMD and PCV after treatment. However, visual acuity (VA) significantly improved in eyes with PCV, whereas VA was maintained in typical neovascular AMD. At the third and twelfth months after injection, VA was better in PCV than in typical neovascular AMD ($P = .027$ and $P = .044$, respectively), although there were no differences in baseline VA between the 2 groups. Age and size of greatest linear dimension were significantly associated with visual prognosis in typical neovascular AMD but not in PCV. There was no clear association between 3 SNPs and responsiveness to ranibizumab treatment.

• CONCLUSIONS: Although exudative changes were equivalent following ranibizumab treatment in both typical neovascular AMD and PCV, there was a significant increase in VA in PCV compared to typical neovascular AMD. Age and greatest linear dimension correlated with visual prognosis only in typical neovascular AMD and not in PCV. (Am J Ophthalmol 2012;154:125–136.

Accepted for publication Jan 5, 2012.

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AGE-RELATED MACULAR DEGENERATION (AMD) IS the leading cause of severe visual impairment in industrialized countries in people over 50 years of age. However, anti–vascular endothelial growth factor (VEGF) treatment, such as bevacizumab or ranibizumab, has dramatically improved visual prognosis in patients suffering from neovascular AMD. After numerous reports of favorable results following anti-VEGF treatment for neovascular AMD, anti-VEGF treatment has been extended to treat eyes with polypoidal choroidal vasculopathy (PCV), a subtype of neovascular AMD. Although some reports show that PCV is refractory to anti-VEGF treatment,[1,2] recent studies have demonstrated improvements in visual acuity (VA) after anti-VEGF treatment for PCV.[3–8]

Recently, increasing numbers of studies have compared the characteristics of PCV and typical AMD.[9–14] Maruko and associates demonstrated that Japanese patients with neovascular AMD could be further characterized into subtypes including PCV (54.7%), typical neovascular AMD (35.3%), retinal angiomatous proliferation (4.5%), and PCV + typical neovascular AMD (5.5%).[9] They included predominantly classic choroidal neovascularization (CNV), minimally classic CNV, and occult with no classic CNV into typical neovascular AMD. It has been reported that there is greater VA improvement in PCV compared to typical neovascular AMD after photodynamic therapy (PDT).[10] Furthermore, we have previously shown that there are significant differences in the genetic associations involved in the development of typical neovascular AMD and PCV.[11] For instance, the *ARMS2* gene is more strongly related to typical neovascular AMD development than PCV, whereas there is no significant difference in the association of the *CFH* gene with typical neovascular AMD or PCV.

In addition to disease development, recent studies have examined genetic associations with various treatments for AMD and PCV; several studies have shown a significant association between *ARMS2/HTRA1* and visual outcome in eyes with AMD and PCV after PDT, whereas a definitive association with *CFH* could not be found.[14–16] The association of the aforementioned genes with response to ranibizumab treatment is still controversial. In addition

0002-9394/$36.00
doi:10.1016/j.ajo.2012.01.010

TABLE 1. Demographics, Retinal Exudative Change, and Visual Acuity of the Neovascular Age-Related Macular Degeneration Patients Treated With Intravitreal Ranibizumab

	Typical Neovascular AMD	PCV	*P*
Number of eyes	49	56	
Age (years)	75.9 ± 8.8	74.2 ± 8.6	NS
Sex (male/female)	34/15	41/15	NS
Baseline retinal exudative change			
GLD (μm)	4490.4 ± 273.9	3988.1 ± 322.6	NS
Retinal edema	71.2%	50.0%	.025
SRD	69.3%	73.2%	NS
Disappearance of retinal exudative change			
3 months	65.3%	62.5%	NS
12 months	69.4%	55.3%	NS
Visual acuity (logMAR)			
Baseline	0.56 ± 0.42	0.48 ± 0.41	NS
3 months	0.57 ± 0.48	0.38 ± 0.37[a]	.027
12 months	0.60 ± 0.53	0.40 ± 0.47[b]	.044

AMD = age-related macular degeneration; GLD = greatest linear dimension; NS = not significant; PCV = polypoidal choroidal vasculopathy; SRD = serous retinal detachment.
[a] $P < .01$ compared with baseline.
[b] $P < .05$ compared with baseline.

to genetic associations, baseline VA, CNV lesion size, and age are important predictors of VA outcomes after ranibizumab treatment for AMD.[17,18] However, it is not clear if these factors are associated with VA outcomes after ranibizumab treatment for PCV.

In the present study, we aimed to elucidate predictive factors of response to ranibizumab in neovascular AMD. At first, we compared response to ranibizumab treatment between typical neovascular AMD and PCV. Furthermore, we evaluated the correlation of baseline VA, age, and lesion size to VA outcome after ranibizumab treatment in typical neovascular AMD and PCV patients. In addition, we investigated the association of 3 major AMD-susceptibility single nucleotide polymorphisms (SNPs) in the *CFH* (Y402H, I62V) and *ARMS2* (A69S) genes and attempted to correlate their presence with response to ranibizumab treatment.

METHODS

WE RETROSPECTIVELY REVIEWED THE MEDICAL RECORDS OF 105 eyes from 105 consecutive patients with subfoveal neovascular AMD. All patients were treated with 3 loading intravitreal injections of 0.5 mg ranibizumab (Lucentis; Novartis, Bülach, Switzerland) at 1-month intervals and were followed up for more than 12 months after the initial treatment at Kyoto University Hospital. Before treatment, all patients underwent a complete ophthalmologic examination, including measurement of best-corrected visual acuity (VA), intraocular pressure testing, indirect ophthalmoscopy, slit-lamp biomicroscopy with a contact lens, spectral-domain optical coherence tomography (OCT) (Spectralis HRA+OCT; Heidelberg Engineering, Heidelberg, Germany), and fluorescein and indocyanine green angiography (HRA-2; Heidelberg Engineering). Best-corrected VA was measured using a Landolt chart and converted to a logarithm of the minimal angle of resolution (logMAR) for statistical analysis. The diagnosis of PCV was based on indocyanine green angiography, which revealed a branching vascular network terminating in polypoidal swellings. Typical AMD involved classic CNV, occult CNV, or a combination of both. Greatest linear dimension was also determined by indocyanine green angiography.

Ranibizumab injections were administered in a sterile manner, and prophylactic topical antibiotics were applied regularly for 1 week after the injection. After the 3 loading injections, patients were followed up every month, and retreatments were performed as required when VA declined more than 0.2 logMAR along with signs of exudation on OCT or angiography, when retinal thickness increased greater than 100 μm, or if subretinal fluid, subretinal hemorrhage, or active CNV persisted or developed. Photodynamic therapy (PDT) was administered to some eyes whose retinal edema or subretinal fluid did not decrease after initial ranibizumab treatment; we judged that those eyes were resistant to ranibizumab.

Genotyping was performed in 78 patients. Genomic DNA was prepared from patients' peripheral blood using a DNA extraction kit (QuickGene-610L; Fujifilm, Minato, Tokyo, Japan). *CFH* Y402H rs1061170, I62V rs800292, and *ARMS2* A69S rs10490924 were genotyped using the

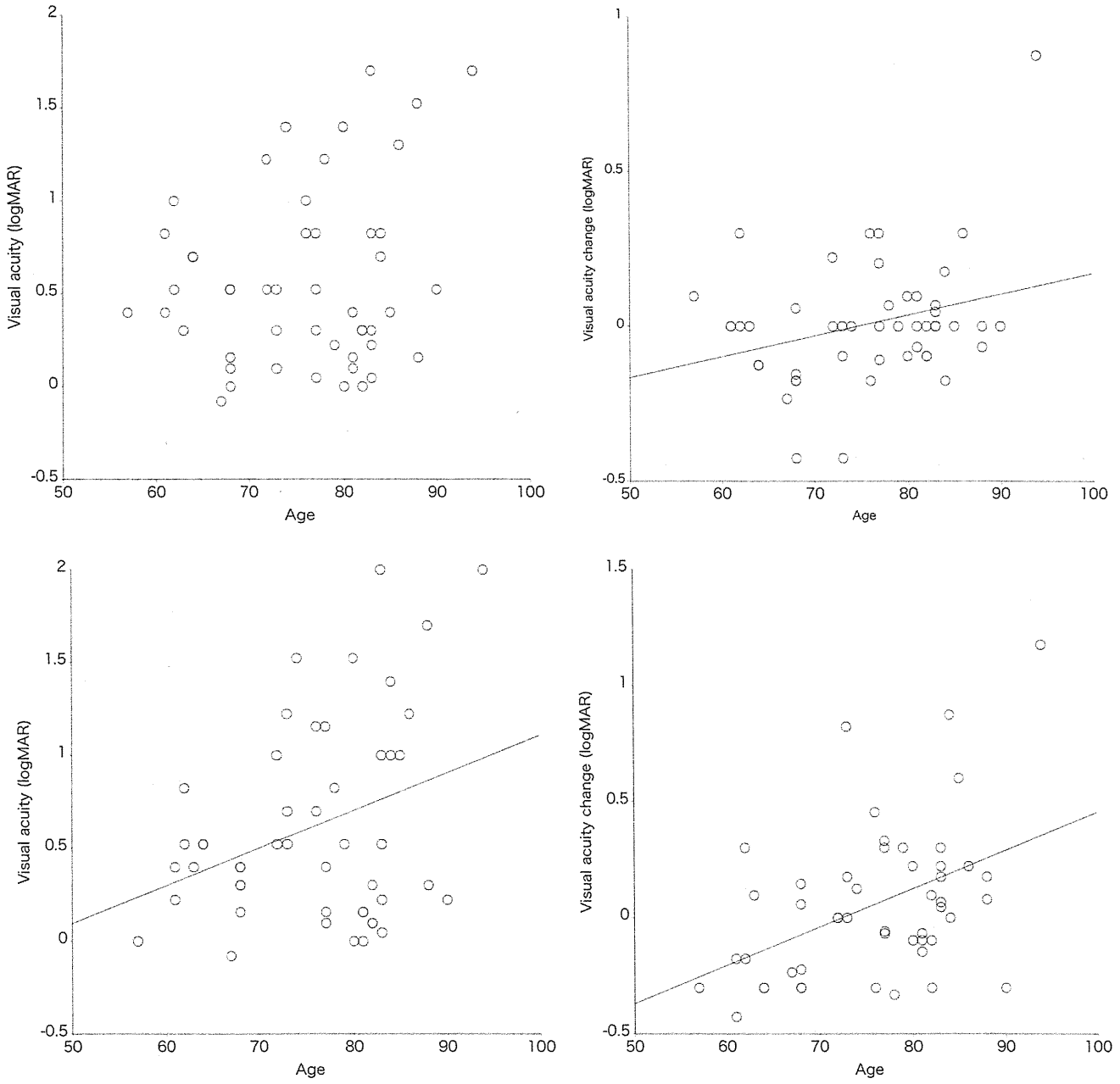

FIGURE 1. Relationship between visual prognosis after ranibizumab treatment and the age of patients with typical neovascular age-related macular degeneration. Visual acuity is expressed as a logarithm of the minimal angle of resolution (logMAR). Although there is no statistically significant correlation between visual acuity (VA) at 3 months and patient age (P = .18, Top left), age was significantly correlated with VA change at 3 months (P = .040, Top right), VA at 12 months (P = .020, Bottom left), and VA change at 12 months (P = .0014, Bottom right).

Taqman SNP assay with the ABI PRISM 7700 system (Applied Biosystems, Foster City, California, USA).

All values are presented as mean ± standard deviation. Patient age, baseline greatest linear dimension, and visual acuity at baseline, 3 months, and 12 months were compared using unpaired *t* test between typical neovascular AMD and PCV. Sex ratio, baseline existence rate of retinal edema and serous retinal detachment, and disappearance rate of retinal exudative change during follow-up were compared using χ^2 test between typical neovascular AMD and PCV. Visual acuity change during follow-up was evaluated using a paired *t* test. Associations of baseline visual acuity, patient age, and greatest linear dimension to visual acuity at 3 months and 12 months and visual acuity change during follow-up were evaluated with the Pearson correlation test. Associations of genotypes to visual acuity at 3 months and 12 months and visual acuity change during follow-up were evaluated with analysis of variance

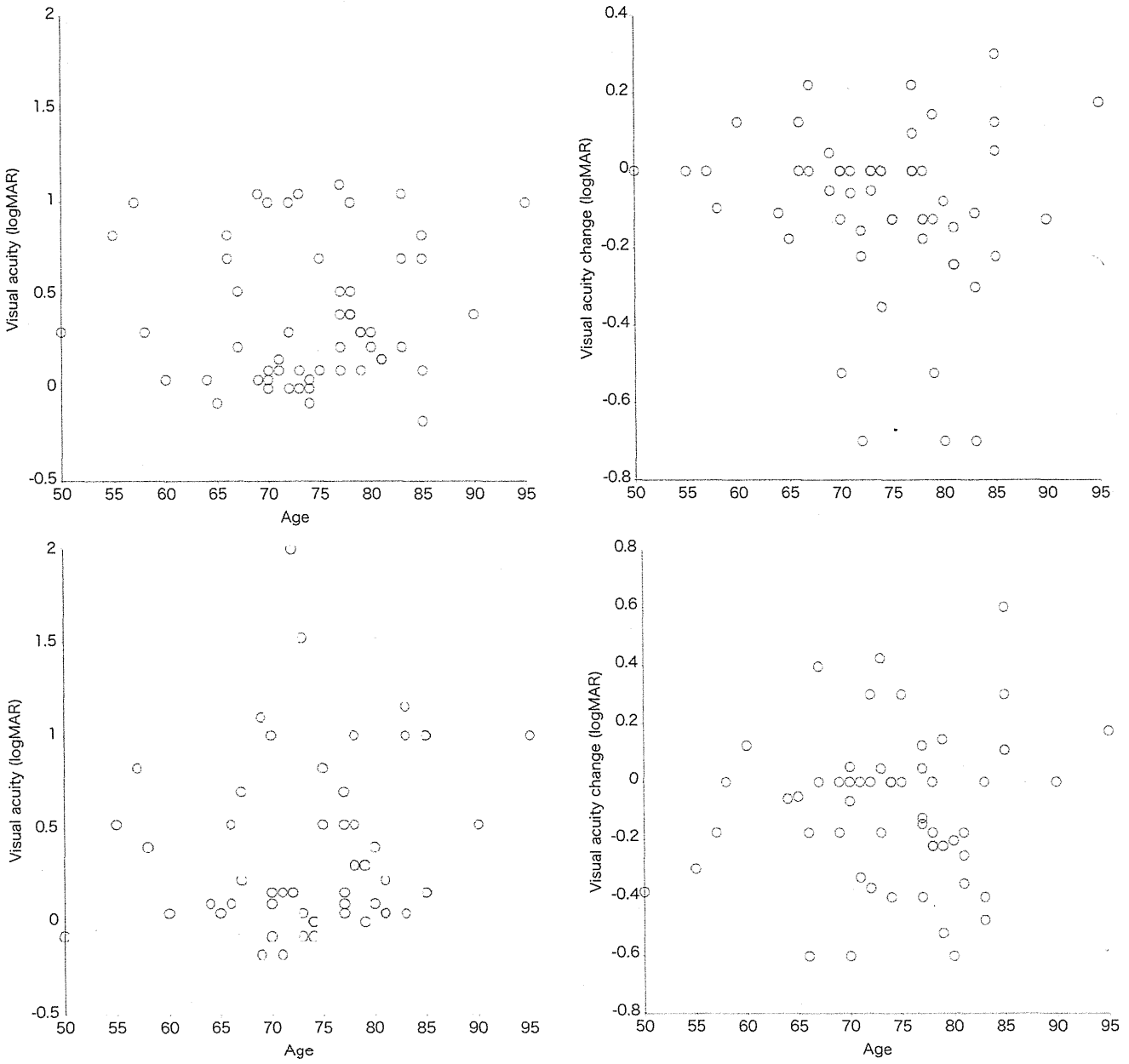

FIGURE 2. Relationship between visual prognosis after ranibizumab treatment and the age of patients with polypoidal choroidal vasculopathy. Patient age did not significantly correlate with VA at 3 months (P = .76, Top left), VA change at 3 months (P = .37, Top right), VA at 12 months (P = .22, Bottom left), or VA change at 12 months (P = .32, Bottom right).

and post hoc comparisons of Scheffe's procedure, and associations to disappearance of retinal exudative change at 3 months and 12 months were evaluated with χ^2 test for trend. *P* values of less than .05 were considered statistically significant.

RESULTS

DEMOGRAPHICS OF THE STUDY POPULATION ARE SHOWN in Table 1. Of the 105 eyes evaluated, 49 had typical neovascular AMD and 56 had PCV. Mean age was not significantly different between the 2 groups. All eyes presented with an exudative change attributable to AMD: retinal edema was seen in 35 of 49 eyes (71.4%) with typical neovascular AMD and in 28 of 56 eyes (50%) with PCV and serous retinal detachment was seen in 34 of 49 eyes (69.4%) with typical neovascular AMD and 41 of 56 eyes (73.2%) with PCV. All exudative features revealed by OCT resolved in 32 of 49 eyes (65.3%) with typical neovascular AMD and 35 of 56 eyes (62.5%) with PCV at the third month, and in 34 of 49 eyes (69.4%) with typical neovascular AMD and 31 of 56 eyes (55.4%) with PCV at the twelfth month. There were no significant differences

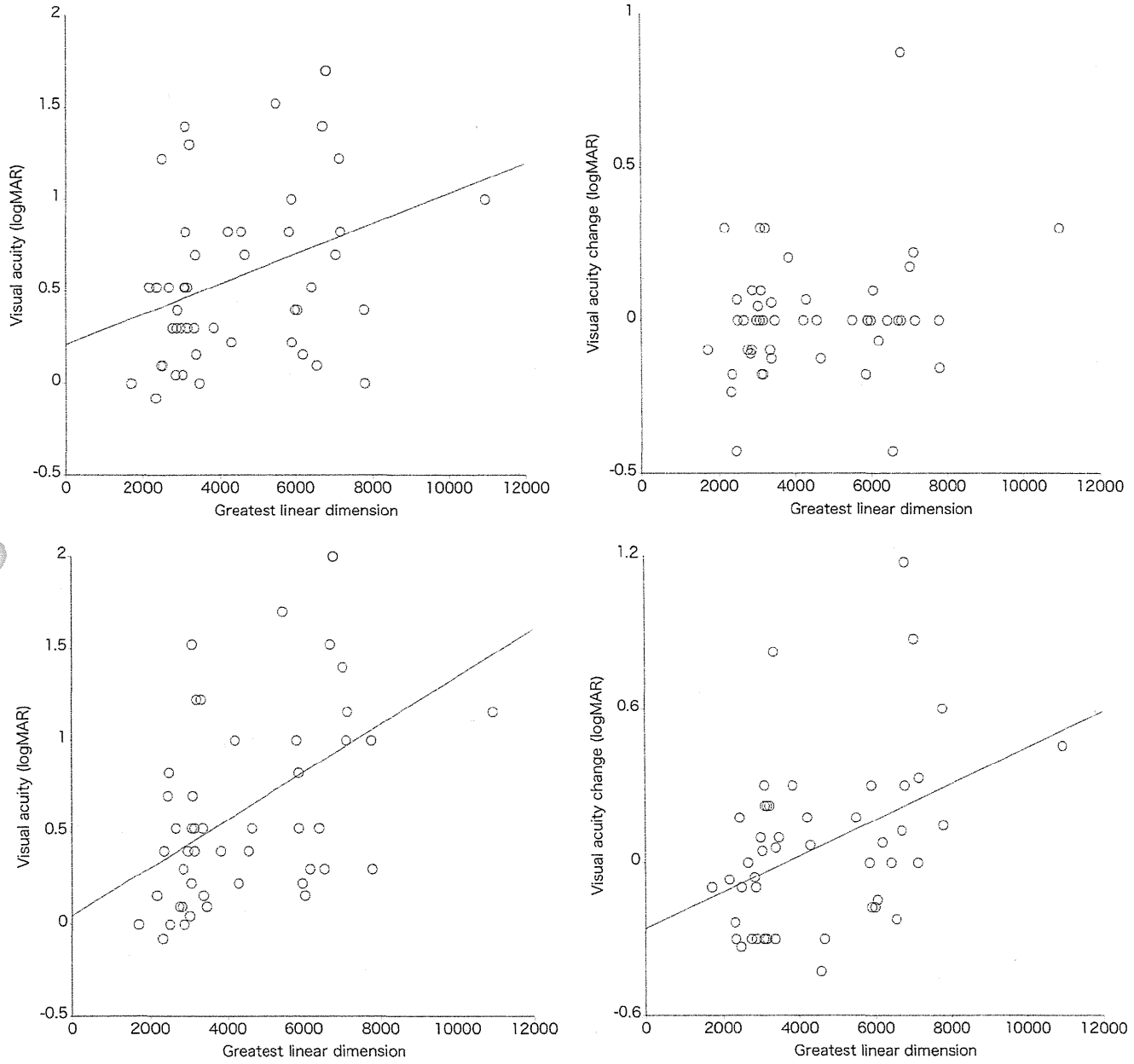

FIGURE 3. Relationship between visual prognosis after ranibizumab treatment and the greatest linear dimension size in typical neovascular age-related macular degeneration. Although there is no statistically significant correlation between VA change at 3 months and the greatest linear dimension size (P = .12, Top right), age significantly correlated with VA at 3 months (P = .015, Top left), VA at 12 months (P = .0004, Bottom left), or VA change at 12 months (P = .0021, Bottom right).

between typical neovascular AMD and PCV with respect to the effectiveness of ranibizumab to resolve retinal exudative change ($P = .77$ and $P = .14$, respectively).

Although there were no differences in baseline VA between typical neovascular AMD and PCV ($P = .29$), VAs were better in PCV than in AMD at the third and twelfth months ($P = .027$ and $P = .044$, respectively). So we compared VA change between typical neovascular AMD and PCV. In eyes with PCV, after the first treatment, VA significantly improved at the third month ($P = .002$) and at the twelfth month ($P = .028$), whereas in typical neovascular AMD, VA was stable at the third month ($P = .79$) and at the twelfth month ($P = .23$).

Twelve eyes with typical neovascular AMD and 15 eyes with PCV had been previously treated with anti-VEGF therapy, and 2 eyes with typical neovascular AMD and 7 eyes with PCV had been previously treated with PDT. After the 3 loading injections, an average of 1.37 ± 1.52 and 1.70 ± 1.88 injections were added to the treatment of patients with typical neovascular AMD and PCV, respectively, during the 1-year follow-up period. There was no significant difference in the frequency of additional treat-

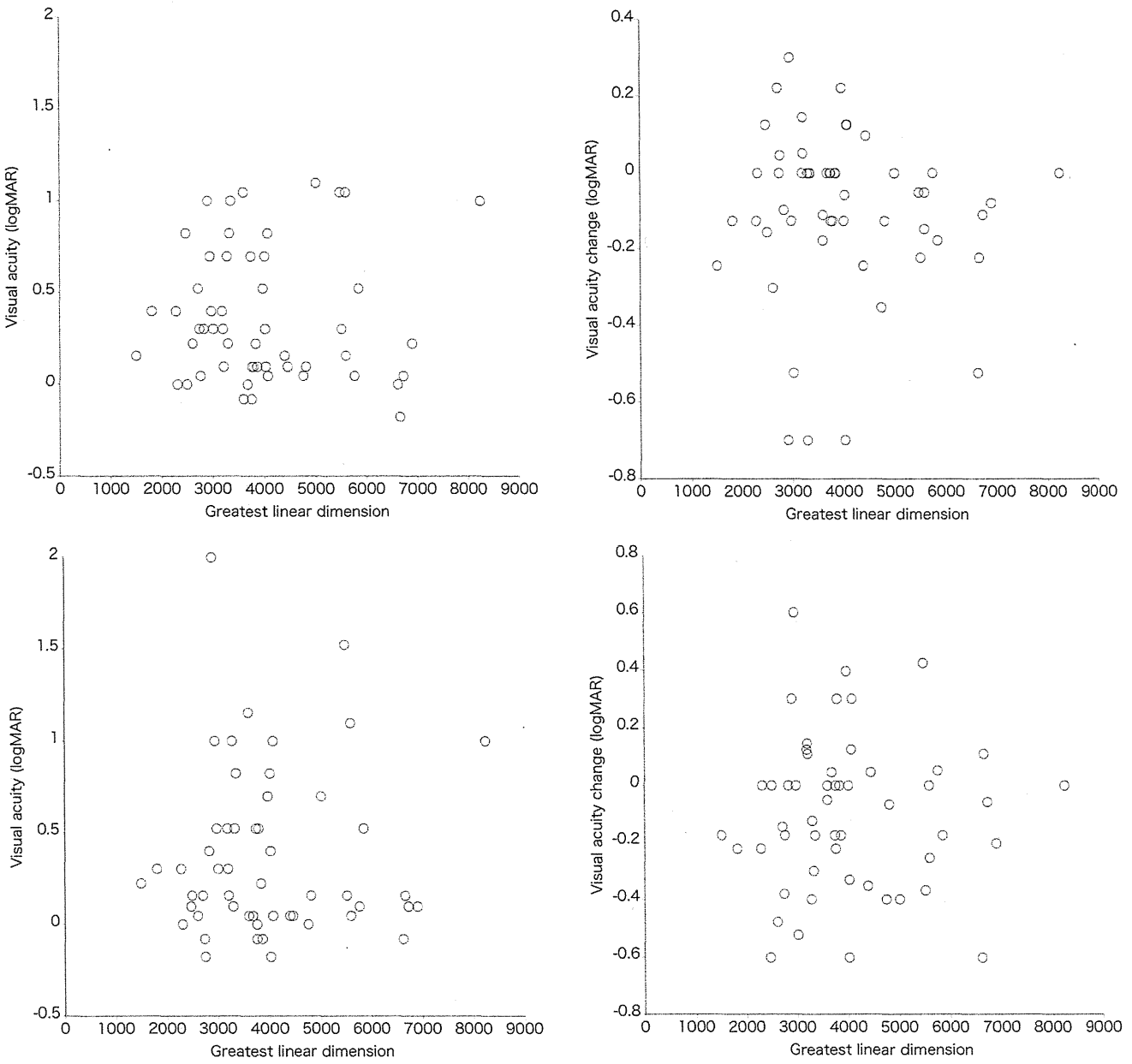

FIGURE 4. Relationship between visual prognosis after ranibizumab treatment and the greatest linear dimension size of polypoidal choroidal vasculopathy. The greatest linear dimension size did not significantly correlate with VA at 3 months ($P = .90$, Top left), VA change at 3 months ($P = .63$, Top right), VA at 12 months ($P = .70$, Bottom left), or VA change at 12 months ($P = .93$, Bottom right).

ments between the 2 groups ($P = .33$). Seven of 49 eyes (14.3%) with typical neovascular AMD and 8 of 56 eyes (14.3%) with PCV were treated with PDT after the initial treatment because ranibizumab treatment did not decrease the retinal edema or subretinal fluid. The number of eyes resistant to ranibizumab treatment was not significantly different between patients with typical neovascular AMD or PCV ($P > .99$). In the 7 typical neovascular AMD eyes and the 8 PCV eyes treated with PDT, the average VA did not significantly change at the third month ($P = .96$ and $P = .27$, respectively) and the twelfth month ($P = .55$ and $P = .60$, respectively). VA declined more than 0.2 logMAR in 1 or 2 eyes with typical neovascular AMD and PCV at the third month and twelfth month, while VA remained unchanged in most eyes.

Since the MARINA[17] and ANCHOR studies[18] have shown that important predictors of VA outcomes in AMD after ranibizumab treatment are baseline VA, CNV lesion size, and patient age, we evaluated the correlations of baseline VA, CNV lesion size, and patient age to the visual prognosis. The Pearson correlation test revealed significant correlation between baseline VA and the VA at the third

TABLE 2. Association of Single Nucleotide Polymorphisms With Visual Acuity and Visual Acuity Change After Intravitreal Ranibizumab Treatment for Neovascular Age-Related Macular Degeneration

	VA			VA Change	
	Baseline	3 Months	12 Months	3 Months	12 Months
Y402H-CC (n = 3, 4.0%)	0.52 ± 0.40	0.47 ± 0.42	0.51 ± 0.50	−0.04 ± 0.24	−0.01 ± 0.33
Y402H-CT (n = 19, 25.3%)	0.50 ± 0.39	0.49 ± 0.42	0.52 ± 0.46	−0.02 ± 0.12	0.03 ± 0.28
Y402H-TT(n = 53, 70.7%)	0.89 ± 0.77	0.93 ± 0.80	0.94 ± 1.09	0.04 ± 0.12	0.03 ± 0.33
P	NS	NS	NS	NS	NS
I62V-GG (n = 47, 65.3%)	0.49 ± 0.39	0.51 ± 0.46	0.52 ± 0.54	0.23 ± 0.19	0.05 ± 0.34
I62V-GA (n = 21, 29.1%)	0.58 ± 0.42	0.40 ± 0.37	0.49 ± 0.40	−0.18 ± 0.24	−0.09 ± 0.28
I62V-AA (n = 4, 5.6%)	0.53 ± 0.27	0.48 ± 0.17	0.43 ± 0.34	−0.05 ± 0.12	−0.10 ± 0.18
P	NS	NS	NS	.0009	NS
A69S-TT (n = 33, 44.0%)	0.58 ± 0.45	0.56 ± 0.50	0.61 ± 0.57	−0.01 ± 0.25	0.03 ± 0.33
A69S-TG (n = 26, 34.7%)	0.41 ± 0.34	0.38 ± 0.35	0.39 ± 0.41	−0.03 ± 0.19	−0.01 ± 0.27
A69S-GG (n = 16, 21.3%)	0.62 ± 0.40	0.55 ± 0.42	0.58 ± 0.53	−0.07 ± 0.20	−0.03 ± 0.36
P	NS	NS	NS	NS	NS

NS = not significant; VA = visual acuity.

TABLE 3. Association of Single Nucleotide Polymorphisms With Disappearance of Retinal Exudative Change After Intravitreal Ranibizumab Treatment for Neovascular Age-Related Macular Degeneration

	Retinal Exudative Change			
	3 Months		12 Months	
	Resolved	Remained	Resolved	Remained
Y402H-CC (n = 3, 4.0%)	2	1	3	0
Y402H-CT (n = 19, 25.3%)	14	5	10	9
Y402H-TT (n = 53, 70.7%)	35	18	34	18
P	NS	NS	NS	NS
I62V-GG (n = 47, 65.3%)	30	17	30	16
I62V-GA (n = 21, 29.1%)	16	5	12	9
I62V-AA (n = 4, 5.6%)	3	1	2	2
P	NS	NS	NS	NS
A69S-TT (n = 33, 44.0%)	23	10	18	14
A69S-TG (n = 26, 34.7%)	21	5	20	9
A69S-GG (n = 16, 21.3%)	7	9	9	7
P	NS	NS	NS	NS

NS = not significant.

month in both the typical neovascular AMD and PCV groups ($P < .0001$). Better baseline VA resulted in better VA outcome after ranibizumab treatment. Similarly, VA at twelfth month was significantly correlated with baseline VA ($P < .0001$).

In patients with typical neovascular AMD, patient age was significantly associated with VA change at the third month, VA at the twelfth month, and VA change at the twelfth month (Figure 1, $P = .040$, $P = .020$, and $P = .0014$, respectively). In contrast, the age of patients with PCV was not associated with VA or VA change at the third and twelfth months (Figure 2, $P > .22$).

The association of greatest linear dimension with VA or VA change showed a trend similar to that of the aforementioned age association. In patients with typical neovascular AMD, the greatest linear dimension showed a significant association with VA at the third month and twelfth month, and VA change at the twelfth month (Figure 3; $P = .015$, $P = .0004$, and $P = .0021$, respectively). In contrast, greatest linear dimension in patients with PCV was not associated with VA or VA change at either the third or twelfth month (Figure 4, $P > .63$).

Finally, we evaluated the association of genetic polymorphisms with the treatment response in AMD. For