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;xx:xxx. © 2012 by Elsevier Inc. All rights reserved.)

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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

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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

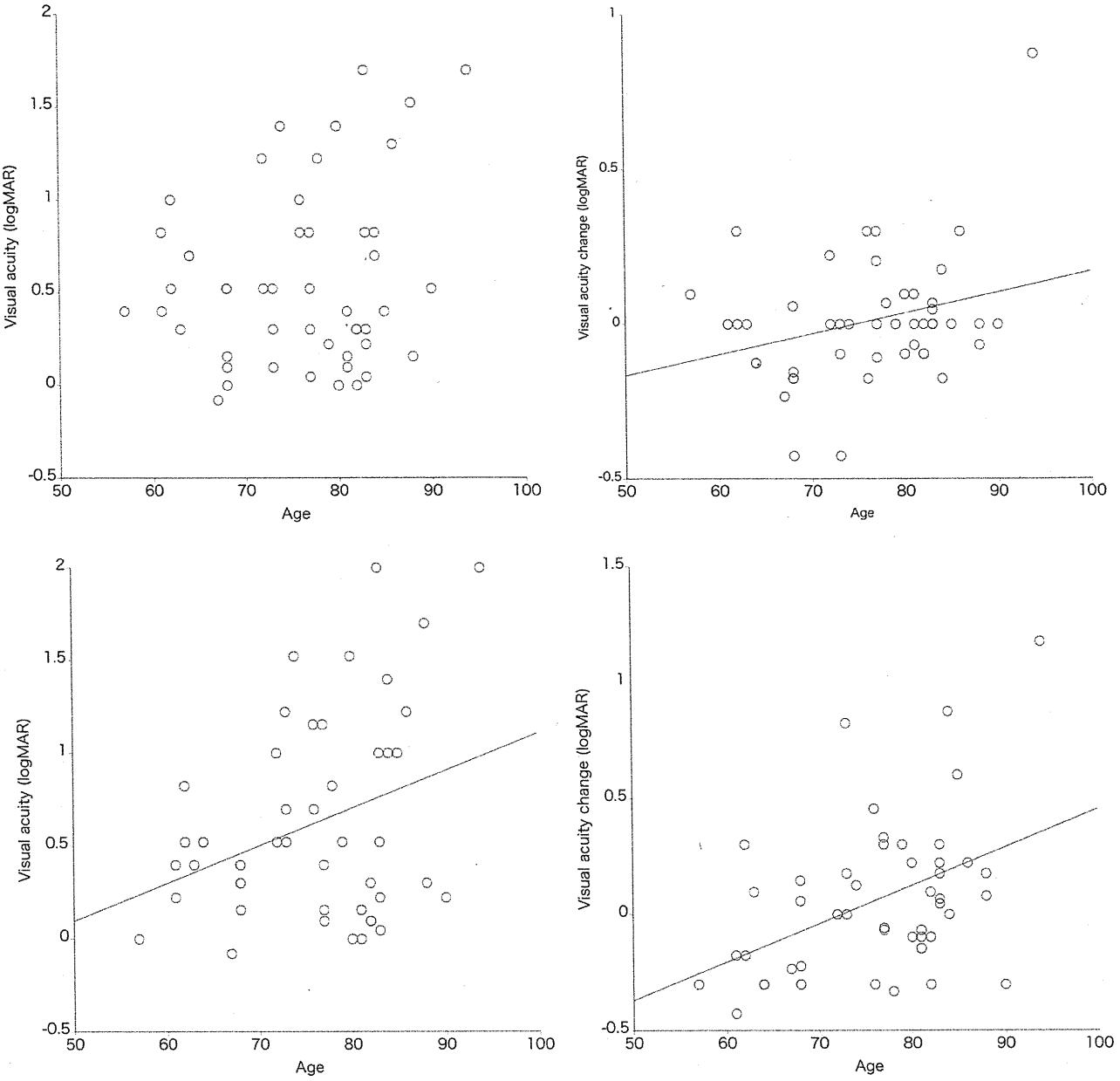

FIGURE 1. Relationship between visual prognosis after ranibizumab treatment and the age of patients with typical neovascular age-related macular degeneration. Visual acuity is expressed as a logarithm of the minimal angle of resolution (logMAR). Although there is no statistically significant correlation 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

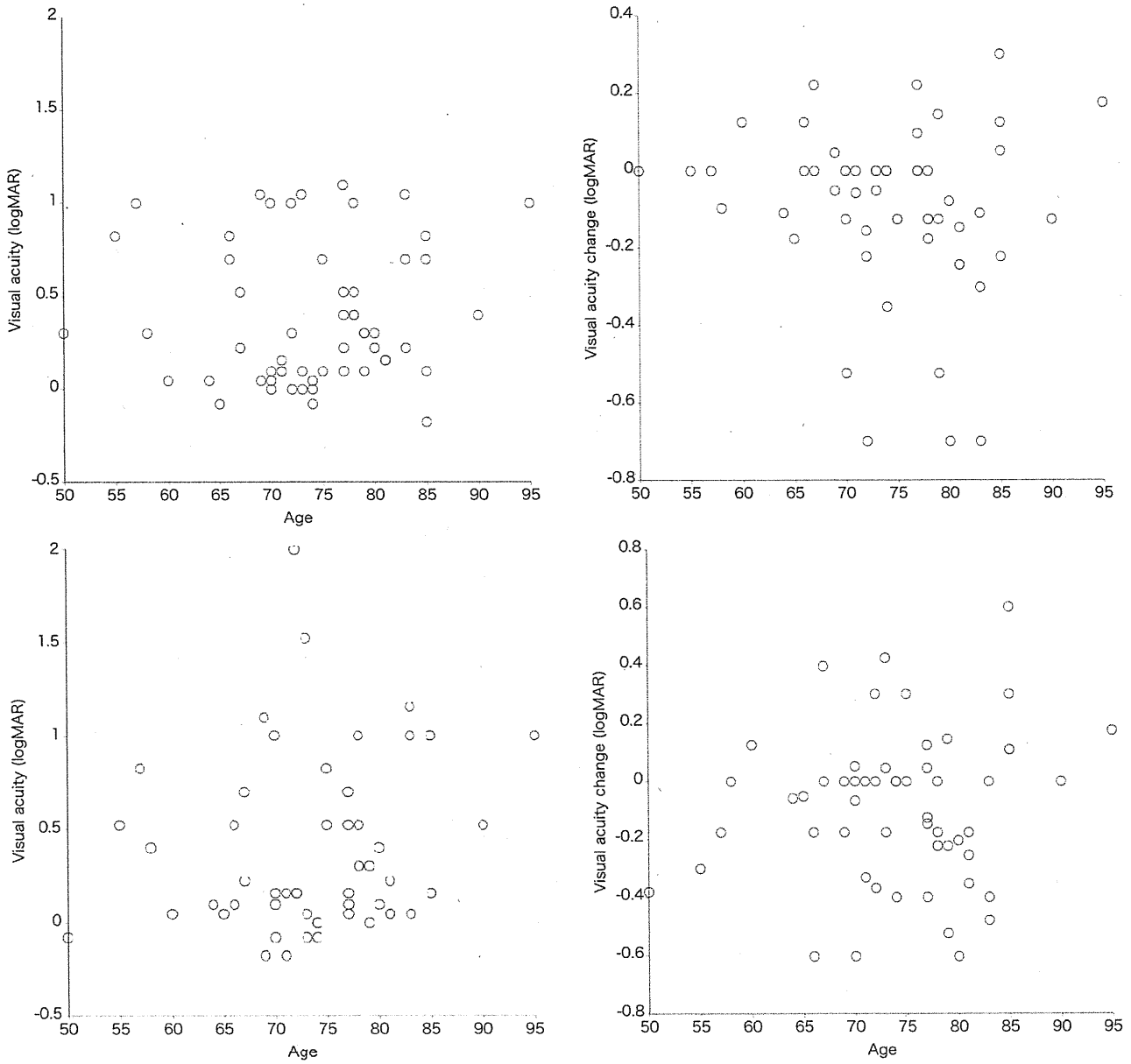

FIGURE 2. Relationship between visual prognosis after ranibizumab treatment and the age of patients with polypoidal choroidal vasculopathy. Patient age did not significantly correlate with VA at 3 months (P = .76, Top left), VA change at 3 months (P = .37, Top right), VA at 12 months (P = .22, Bottom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

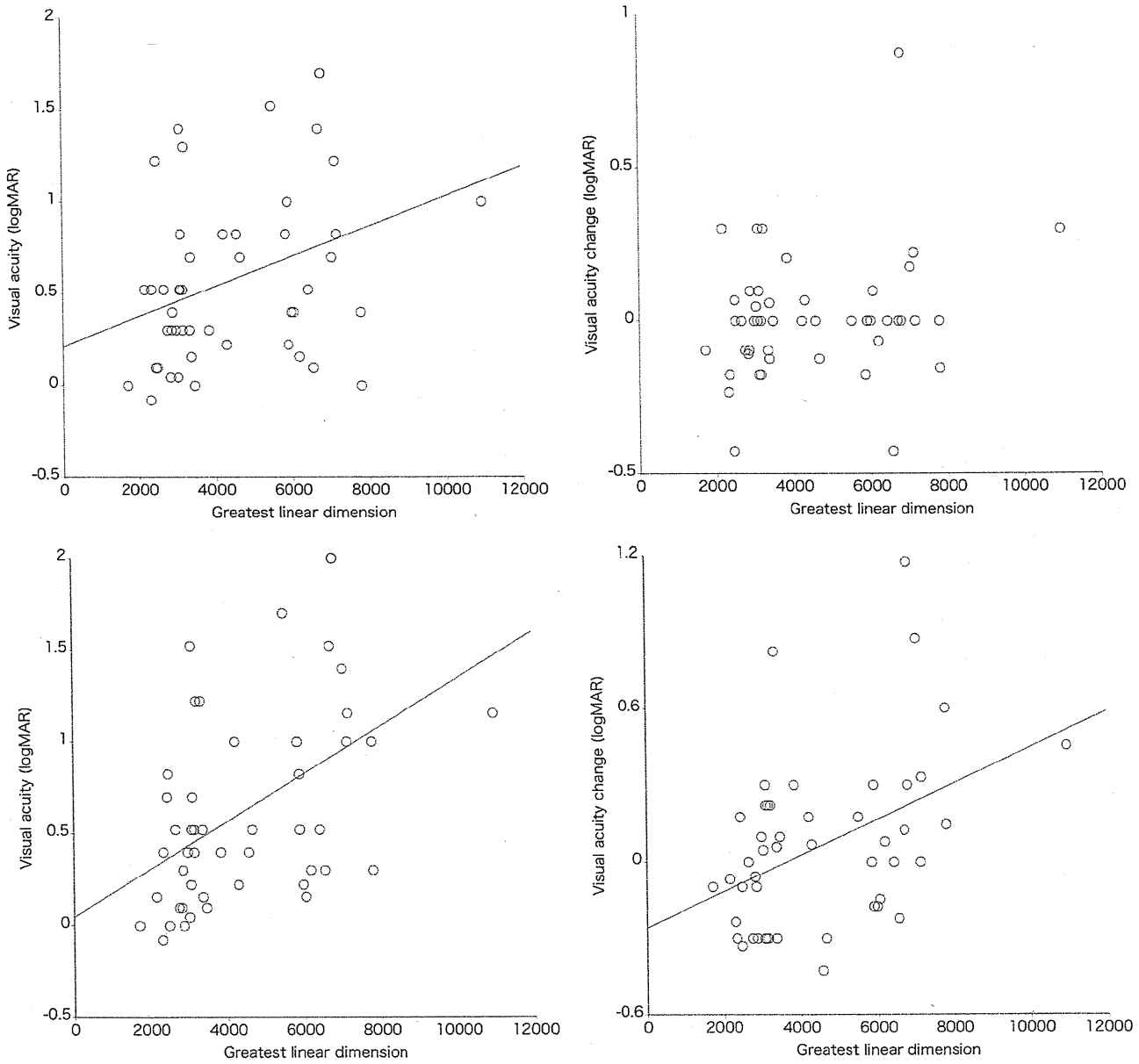

FIGURE 3. Relationship between visual prognosis after ranibizumab treatment and the greatest linear dimension size in typical neovascular age-related macular degeneration. Although there is no statistically significant correlation between VA change at 3 months and the greatest linear dimension size ($P = .12$, 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-

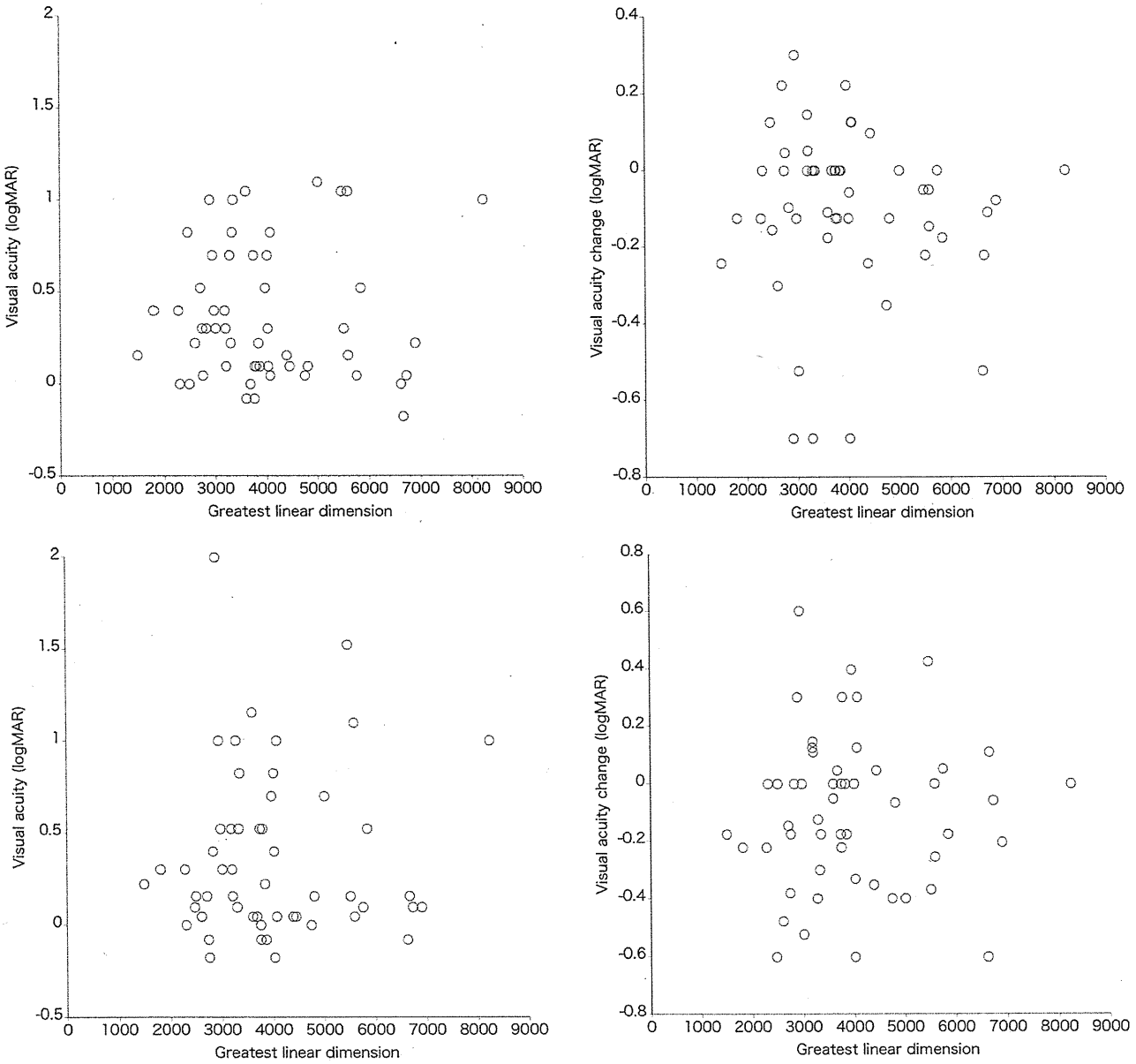

FIGURE 4. Relationship between visual prognosis after ranibizumab treatment and the greatest linear dimension size of polypoidal choroidal vasculopathy. The greatest linear dimension size did not significantly correlate with VA at 3 months (P = .90, Top left), VA change at 3 months (P = .63, Top right),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

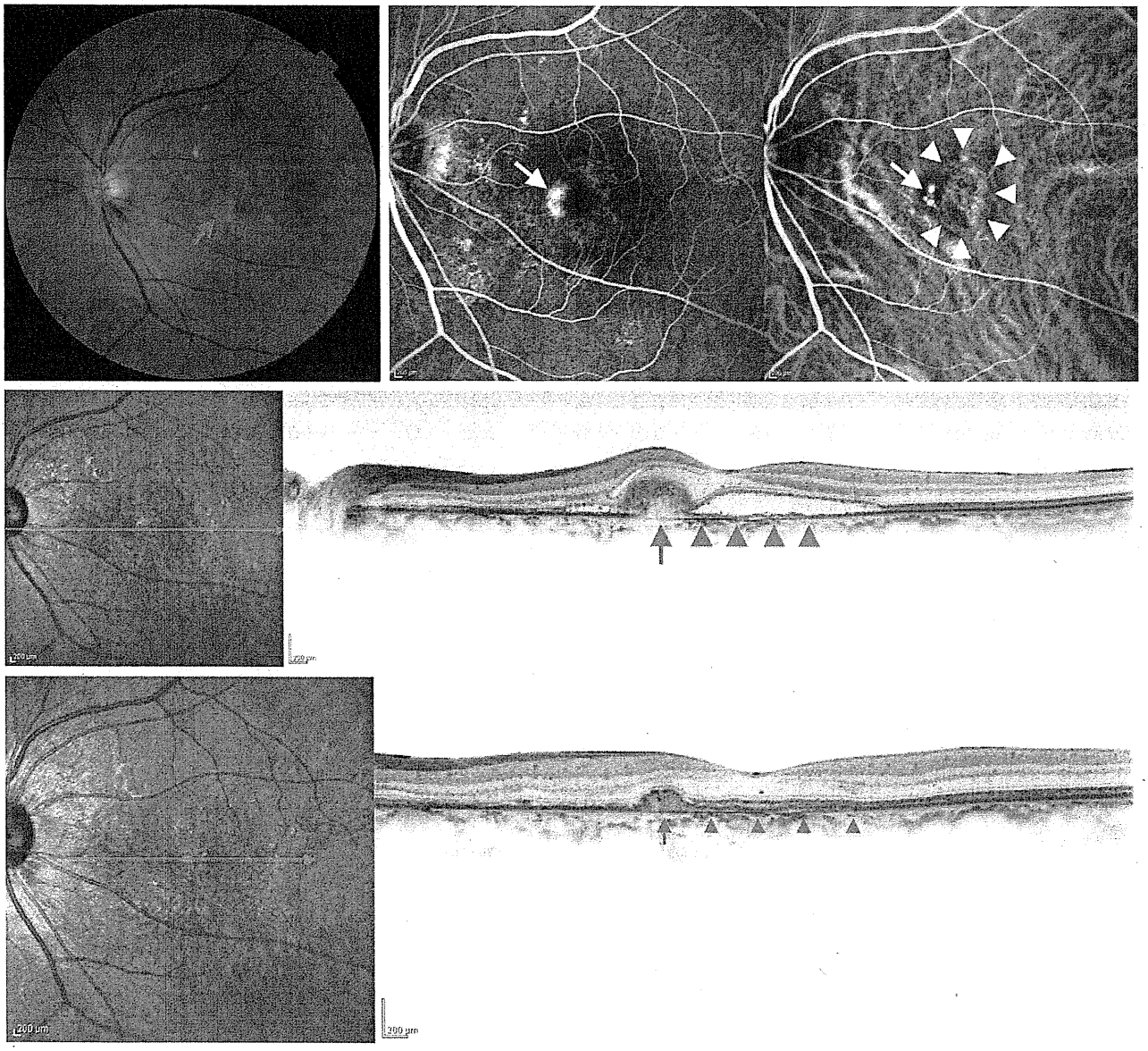

FIGURE 5. An eye with PCV at baseline and 3 months after the first ranibizumab injection. At baseline, (Top left) color photograph shows fibrin exudate (arrow) over the polypoidal lesion, (Top middle) fluorescein angiograph shows fluorescein leakage (arrow) from the polypoidal lesion, and (Top right) indocyanine green angiography shows polypoidal lesion (arrow) and network vessels (arrowheads) beneath the fovea. (Middle) Optical coherence tomography shows fibrin and retinal edema over the polypoidal lesion (arrow) and retinal detachment over the network vessels (arrowheads). The visual acuity was 18/20. (Bottom) At 3 months after the first ranibizumab injection, optical coherence tomography shows polypoidal lesion (arrow) and network vessels (arrowheads) without retinal detachment or retinal edema and the visual acuity improved to 24/20.

this analysis, typical neovascular AMD and PCV were first combined for evaluation and then separated for further evaluation. The associations of SNPs (CFH Y402H, I62V, and ARMS2 A69S) with VA and/or VA change are shown in Table 2. There was no significant association between these SNPs and baseline VA, VA or VA change at the third month, and VA or VA change at the twelfth month, except for the association between CFH I62V and VA change at the third month; eyes with a GA genotype had better VA change than those with a GG genotype ($P = .0009$). After Bonferroni's correction, the association of I62V with VA change at the third months became weaker ($P = .027$). Furthermore, there was not an association trend such as GG > GA > AA or GG < GA < AA. In the OCT findings, the 3 SNPs were not significantly associated with the resolution of retinal exudative change at either the third or twelfth month (Table 3). When patients with typical neovascular AMD and PCV were evaluated separately, the 3 SNPs did not show any association

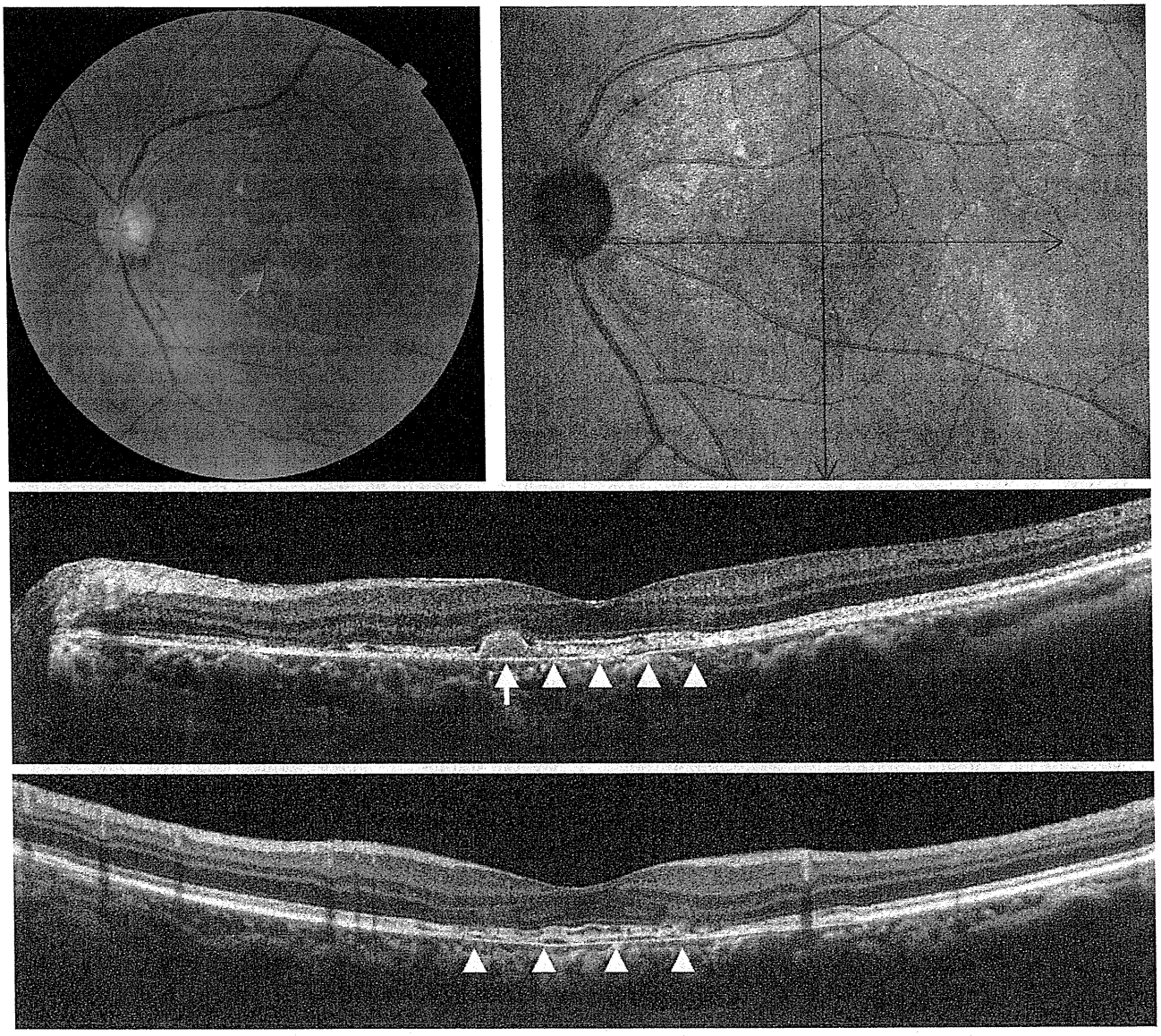

FIGURE 6. Twelve months after the first intravitreal injection of ranibizumab. (Top left and right) Color photograph shows disappearance of fibrin exudate, and (Middle) horizontal optical coherence tomography shows inactivated polypoidal lesion (arrow) without retinal detachment or retinal edema over the network vessels (arrowheads). (Bottom) Vertical optical coherence tomography shows no retinal detachment or retinal edema over the network vessels (arrowheads). The visual acuity was maintained at 24/20.

with VA, VA change, or the resolution rate of retinal exudation.

DISCUSSION

IN THE PRESENT STUDY, WE HAVE SHOWN THAT RANIBIzumab treatment equivalently reduced retinal exudative changes in patients with typical neovascular AMD or PCV. However, visual prognosis after treatment was better in patients with PCV compared to those with typical neovascular AMD. Furthermore, age and greatest linear dimension size were significantly associated with visual prognosis only in patients with typical neovascular AMD, not in those with PCV. SNPs in *CFH* and *ARMS2* genes were not associated with VA prognosis or resolution of retinal exudation in patients with either typical neovascular AMD or PCV after ranibizumab treatment.

Recently, it has been shown that ranibizumab can only maintain VA when used in AMD patients with relatively good VA.[19] Most studies that have shown VA improvements in AMD after ranibizumab treatment have only included patients with VA of 20/40 to 20/400.[20–23] Therefore, it is surprising that in our study, VA significantly

improved in patients with PCV, because we included patients with relatively good baseline VA. The baseline VA was better than 20/20 in 8 eyes (7.62%), better than 20/25 in 17 eyes (16.2%), and better than 20/40 in 45 eyes (42.9%). Including patients with good VA makes it more difficult to detect VA improvement after treatment. Indeed, the VA in eyes with typical neovascular AMD in the present study was only maintained and did not improve. However, patients with PCV showed significant VA improvement after ranibizumab treatment. Thus, a diagnosis of PCV is a favorable factor for VA outcome after ranibizumab treatment. Considering that retinal edema was observed more often in typical neovascular AMD than PCV, less retinal edema in PCV might lead to better VA outcome after treatment.

Seven eyes with typical neovascular AMD (14.3%) and 8 eyes with PCV (14.3%) received additional treatment with PDT, as these eyes were resistant to ranibizumab injections. Since the average VA in these eyes did not significantly change during follow-up, the aforementioned favorable visual prognosis in patients with PCV can be attributed to the effects of ranibizumab. Although early reports have suggested relatively poor results when ranibizumab is used to treat PCV, recent studies have shown that the VA in eyes afflicted with PCV improves after ranibizumab treatment.[3–8] Some of these studies have included patients with relatively good baseline VA.[5,8] Thus, the VA in eyes with PCV might improve after ranibizumab treatment, even if the eyes have a relatively good baseline VA. The rate of eyes resistant to ranibizumab (14.3%) seems to be higher than previously reported resistance rates (less than 5%). Previous treatment might increase the rate of eyes resistant to ranibizumab. In the present study, furthermore, additional PDT was performed when their retinal edema or subretinal fluid did not decrease after initial 3-loading-injection ranibizumab treatment. If we continue ranibizumab treatment after the 3 loading injections, the retinal edema or subretinal fluid might disappear.

The visual prognosis in eyes with PCV has been generally thought to be better than in those with typical neovascular AMD.[24,25] Visual outcomes after PDT were also reported to be better in PCV than in typical neovascular AMD.[10] Therefore, it should not be surprising that the VA prognosis after ranibizumab treatment was better in PCV than in typical neovascular AMD, because accumulating evidence has revealed substantial effects of anti-VEGF treatment on resolving retinal exudative changes in PCV.[3,4,6–8,26,27] Also in the present study, ranibizumab significantly reduced retinal exudative change in eyes with PCV (Figures 5 and 6). However, the polypoidal lesions of PCV are barely resolved following anti-VEGF treatment.[7,27–29] Although residual polypoidal lesions might easily cause a relapse in retinal exudative changes, the number of additional treatments was not significantly different between the typical neovascular AMD and PCV groups in the present study. Studies with follow-up periods of more than 1 year might reveal differences in the number of additional treatments required between patients with typical neovascular AMD and those with PCV.

Both the MARINA[17] and ANCHOR studies[18] have shown that important predictors of VA outcomes in AMD are baseline VA, CNV lesion size, and age at the time of ranibizumab treatment. The present study also confirmed that baseline VA is significantly correlated with VA outcomes in both typical neovascular AMD and PCV. However, the size of greatest linear dimension and age only correlated with VA outcome in patients with typical neovascular AMD and not in those with PCV. This inconsistency has also been reported in similar studies that used PDT; the size of greatest linear dimension was significantly correlated with VA outcome in typical neovascular AMD, while the same could not be said for PCV.[30] It has been suggested that VA outcome in eyes with PCV cannot be predicted on the basis of lesion size after any type of treatment.

Recently, the association between the response to treatments and polymorphisms in AMD/PCV susceptibility genes has been intensively explored. With respect to VA outcome after PDT, several studies have shown significant associations of *ARMS2/HTRA1* with AMD and PCV,[14–16] while *CFH* does not have a definite association. However, the association of *ARMS2/HTRA1* or *CFH* with visual outcome after ranibizumab treatment is still controversial. Several studies[31–33] have shown that eyes with a CC genotype in *CFH* Y402H have worse visual prognosis after anti-VEGF treatment, while a recent study[34] has shown that eyes with a TT genotype have worse visual prognosis. Lee and associates[35] have shown no association between Y402H and visual outcome after ranibizumab treatment in AMD. In general, genetic variations in *ARMS2/HTRA1* do not seem to be associated with response to anti-VEGF treatment;[31,32,34] however, 1 study[36] has reported that eyes with the TT genotype in *ARMS2* A69S have worse VA outcome. The present study did not reveal any associations of SNPs in *CFH* and *ARMS2* with VA outcome. Our negative findings are consistent with previous reports from Europe and the United States.[31,32,34] Also in East Asian populations, *ARMS2/HTRA1* could not be associated with response to ranibizumab treatment.

Regarding *CFH* Y402H, Imai and associates evaluated VA change in 83 Japanese patients with AMD for 3 months after bevacizumab treatment. In their study, they showed that eyes with the CT genotype have worse VA outcomes than eyes with the TT genotype, although there was no CC genotype in their cohort.[37] The frequency of the Y402H C allele is very low in East Asian populations; this often leads to false-negative results in association studies.[11,38] Although our findings suggest no association between *CFH* gene polymorphisms and response to ranibizumab treatment in both typical neovascular AMD and PCV, a potential association should be further evaluated using a larger cohort.

Limitations of this study include its retrospective nature and small sample size. In the present study, previous treatments had been performed in 25.7% of patients. It has been demonstrated that VA prognosis after PDT combined with anti-VEGF treatment is worse in eyes with PCV that recurred after PDT.[39,40] Although previous treatment did not affect the visual outcome in the present study (data not shown), increasing the cohort size might reveal a significant effect of previous treatments on the response to ranibizumab. Increasing the cohort size might also reveal associations between SNP variations and response to ranibizumab. Furthermore, our findings would have to be investigated with prospective studies since this study is retrospective. Recently, Yamaoka and associates have shown that hypertension is associated with the occurrence of PCV.[41] Although other study reported no association between hypertension and PCV[42] and the prevalence of hypertension was not significantly different between typical neovascular AMD and PCV in the present study (69% vs 66%, $P = .83$), examinations of the association between hypertension and treatment response might lead to further understanding of the pathophysiology of PCV.

In conclusion, we have shown that AMD subtype can be a predictive factor for response to ranibizumab treatment. VA outcome is better in patients with PCV compared to those with typical neovascular AMD, whereas the resolution of retinal exudative changes is similar in both groups. Lesion size and age can be used to predict the VA prognosis after ranibizumab treatment in typical neovascular AMD; however, these parameters cannot be used to predict the VA prognosis in PCV. Our study suggests that there is no association between SNPs in the *CFH* and *ARMS2* genes and responsiveness of typical neovascular AMD or PCV to ranibizumab treatment.

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RETINAL DISORDERS

Relationship between retinal morphological findings and visual function in age-related macular degeneration

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Abstract
Background We aimed to study the retinal morphological findings associated with exudative age-related macular degeneration (AMD) and their association with visual prognosis.
Methods We retrospectively reviewed the medical records of 96 consecutive patients (96 eyes) with exudative AMD. Retinal structural changes were examined using optical coherence tomography (OCT).
Results Initial OCT examination showed cystoid macular edema in 18 eyes (18.8%), fibrin exudate in 56 eyes (58.3%), and hyperreflective foci within the neurosensory retina in 78 eyes (81.3%). Upon initial examination, an external limiting membrane (ELM) line was detected under the fovea in 64 eyes (66.7%). Using Pearson's correlation analyses, final visual acuity (VA) was correlated with initial VA (r=0.61, p<0.001), age (r=0.34, p<0.001), initial total foveal thickness (r=0.41, p<0.001), presence of hyperreflective foci (r=0.40, p<0.001), and detection of a foveal ELM line (r=0.55, p<0.001). After multiple regression analysis, final VA correlated with initial VA (r=0.48, p< 0.001), initial presence of hyperreflective foci (r=0.23, p= 0.054), and detection of a foveal ELM line (r=0.36, p= 0.008).
Conclusions In eyes with exudative AMD, final VA was most correlated with initial VA. In addition, the initial integrity of the foveal outer retina was partially correlated with the visual prognosis. The initial ELM condition was associated with good final VA, while the initial presence of hyperreflective foci in the foveal neurosensory retina was associated with poor final VA.

Keywords Age-related macular degeneration · External limiting membrane · Hyperreflective foci · Optical coherence tomography · Polypoidal choroidal vasculopathy

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Introduction

Age-related macular degeneration (AMD) is a leading cause of blindness worldwide in individuals aged more than 50 years [1]. Although treatment for the disease has progressed dramatically since the development of anti-vascular endothelial growth factor (VEGF) therapy, not all patients achieve good vision [2–4]. A combination of photodynamic therapy (PDT) and anti-VEGF therapy is a promising option [5], but it might not markedly alter the prognosis of AMD [6]. Considering both the physical and financial costs of treatment [7], prediction of the visual prognosis at the patients' initial visits would be very useful to both patients and clinicians.

A more detailed evaluation of retinal structure and function is needed to predict visual prognosis [8]. For this purpose, we have been trying to make the best use of optical coherence tomography (OCT). Current models of commercially available spectral-domain OCT instruments provide fine images (up to 5-μm resolution) of the retinal structure [9, 10]. Using spectral-domain OCT, Hayashi et al. showed a correlation between retinal structure and function in eyes with AMD that had undergone PDT [11]. In short, the status of the junction between the inner and outer segments of the photoreceptors (IS/OS) [12, 13], which is considered to

reflect photoreceptor integrity, is associated with visual acuity (VA) [14]. Other authors have confirmed the association of IS/OS status with VA [15] and with retinal sensitivity as measured using microperimetry [16]. In addition to IS/OS, the status of the external limiting membrane (ELM) has also been reported to be a good indicator of visual function in eyes with AMD [17]. Evaluation of alterations in these retinal layer patterns at the time of the initial examination provides more detailed information about the retinal status [8, 18, 19].

In addition to the retinal layer pattern, the presence of hyperreflective foci represents another possible predictive factor of VA [18]. Hyperreflective foci are reported to be present in diabetic macular edema [20], retinal vein occlusion [21], and AMD [18], and have been suggested to be subclinical features of lipoprotein extravasation, which implies blood–retinal barrier impairment. Results consistent with this finding have been reported by other authors; the presence of hyperreflective foci is associated with hard exudate deposition [22]. The breakdown of the blood–retinal barrier, and the accumulation of hard exudates, would both be detrimental to eyes with AMD [18].

Based on this structure–function relationship, we hypothesized that there might be a correlation between the pretreatment structure of eyes with AMD and the visual prognosis. However, to date, limited information is available about predictive factors of visual prognosis among the features obtained from initial OCT sections in exudative AMD [23–25]. In the study reported herein, we longitudinally investigated OCT images of eyes with AMD throughout the course of anti-VEGF therapy, and examined the relationship between pretreatment features seen on OCT images and the visual prognosis.

Material and methods

For this observational study, we retrospectively reviewed the medical records of 96 consecutive patients (96 eyes) with exudative AMD who were seen by the Macula Service in the Department of Ophthalmology at Kyoto University Hospital between January 2008 and October 2009. Inclusion criteria included: (1) symptomatic subfoveal AMD, (2) the presence of choroidal neovascularization (CNV) beneath the foveal center, (3) the presence of macula-related exudative or hemorrhagic features, and (4) a minimum follow-up of 12 months after the initial visit. The current study included eyes with typical AMD and those with polypoidal choroidal vasculopathy (PCV). The diagnosis of PCV was based on indocyanine green angiography, which reveals a branching vascular network that terminates in polypoidal swelling. When both eyes met the inclusion criteria, only the eye with the more active lesion was included in the current study. Eyes with other macular abnormalities (i.e., pathologic myopia, retinal angiomatous proliferation, idiopathic CNV, presumed ocular histoplasmosis, angioid streaks, or other secondary CNV) and those with senile cataracts that resulted in poor-quality OCT images were excluded from the current study. This study was approved by the Institutional Review Board at the Kyoto University Graduate School of Medicine, and adhered to the tenets of the Declaration of Helsinki.

At the initial visit, each patient underwent a comprehensive ophthalmologic examination, including measurement of best-corrected VA (using the Landolt C test), determination of intraocular pressure, indirect ophthalmoscopy, slit-lamp biomicroscopy with a contact lens, spectral-domain OCT (Spectralis HRA+OCT; Heidelberg Engineering, Heidelberg, Germany), and fluorescein and indocyanine green angiography (HRA2; Heidelberg Engineering). At each scheduled follow-up visit, each patient underwent a complete ophthalmologic examination, including VA measurement, slit-lamp biomicroscopy, indirect fundus ophthalmoscopy, and OCT examination. Fluorescein and indocyanine green angiography were performed as deemed necessary.

After the initial visit, each eye was treated based on disease activity and VA. Eyes with exudative AMD were treated either with PDT combined with intravitreal injection of an anti-VEGF agent, or with intravitreal injections of anti-VEGF agents alone. After the initial combined therapy, each eye was considered for retreatment with the combined therapy every 3 months if the eye exhibited residual or recurrent polypoidal lesions upon indocyanine green angiography. In eyes treated with intravitreal injections of anti-VEGF agents alone, additional injections were administered on an as-needed basis.

In the current study, we evaluated the OCT images obtained from all eligible patients both quantitatively and qualitatively. In both the initial and final OCT images, we measured total foveal thickness, defined as the distance between the vitreoretinal interface and the retinal pigment epithelium (Fig. 1a). Furthermore, we examined the IS/OS line and the ELM to assess outer foveal photoreceptor layer integrity. The status of the IS/OS line and the ELM line under the fovea was defined as either complete or incomplete. OCT images in eyes with exudative AMD often exhibited subretinal fluid and hemorrhages beneath the neurosensory retina. In addition, most OCT images revealed morphological changes in the neurosensory retina. Cystoid spaces and hyperreflective foci were seen in many cases within the neurosensory retina. Fibrin derived from active CNV or polypoidal lesions was observed as amorphous hyperreflective material, not only in the subretinal space but also within the neurosensory retina. Using horizontal and longitudinal OCT sections, we evaluated whether cystoid macular edema, hyperreflective foci, and fibrin exudates were seen within the 1×1 mm area around the fovea (Fig. 1b).

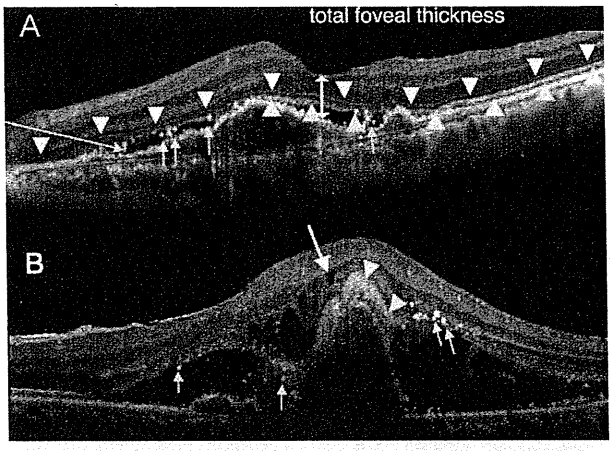

Fig. 1 **a** Horizontal image of the fovea obtained using optical coherence tomography (OCT) of an eye with active exudative age-related macular degeneration. Using an initial OCT image, three measurements were made in the fovea, including total foveal thickness, continuity of the external limiting membrane (ELM; *white arrowheads*), and continuity of the junction between the inner and outer photoreceptor segments (IS/OS; *yellow arrowheads*). **b** Cross-sectional image of the foveal region obtained using OCT. Using these OCT sections, we determined whether cystoid macular edema (*white arrow*), hyperreflective foci (*yellow arrows*), or fibrin exudate (*yellow arrowheads*) were seen within the 1×1 mm square area around the fovea

Statistical analysis was performed using software designed for this purpose (IBM SPSS Statistics Desktop, version 19.0.0; IBM Japan, Tokyo, Japan). All values are presented in terms of means and standard deviation. Best-corrected VA was converted to a logarithm of the minimum angle of resolution (logMAR) equivalent for statistical analysis. Values in typical AMD and PCV were compared using the Student's *t*-test. Bivariate relationships were analyzed using the Pearson's correlation coefficient or the Spearman rank correlation coefficient. Stepwise forward multivariate linear regression analyses were also performed to evaluate the contribution of each initially identifiable factor to final VA. A value of $p<0.05$ was considered statistically significant.

Results

In the current study, 96 eyes from 96 patients (72 men and 24 women) with exudative AMD who were 57–90 years of age (mean, 73.2±8.5 years) were examined (Table 1). Of these 96 eyes, 61 had PCV and 35 had typical AMD. The mean initial VA (logMAR) and foveal thickness were 0.58±0.49 and 422.5±255.9 μm respectively; there were no significant differences in these parameters between eyes with typical AMD or PCV ($p=0.889$, $p=0.787$). Active CNV lesions were treated with intravitreal injections of anti-VEGF agents in 38 eyes, and with PDT combined with anti-VEGF agents in 37 eyes. No treatments were performed in 21 eyes. The mean number of injections was 4.7±3.2 and mean number of PDT

Table 1 Characteristics of the study population

Number of eyes	96
Age (years; mean [SD[a]])	73.2 (8.5)
Gender (women/men)	24/72
Initial examination	
Visual acuity (logMAR[b]; mean [SD])	0.58 (0.49)
Total foveal thickness (μm; mean [SD])	422.5 (255.9)
Detection of IS/OS[c] under the fovea (complete/incomplete)	22/74
Detection of ELM[d] under the fovea (complete/incomplete)	64/32
Cystoid macular edema, number of eyes (%)	18 (18.8)
Hyperreflective foci, number of eyes (%)	78 (81.3)
Fibrin, number of eyes (%)	56 (58.3)
Follow-up (months; mean [SD])	24.6 (5.7)
Treatment	
Photodynamic therapy (%)	37 (38.5)
Anti-vascular endothelial growth factor therapy (%)	38 (39.6)
Final examination	
Visual acuity (logMAR; mean [SD])	0.65 (0.61)
Total foveal thickness (μm; mean [SD])	305.4 (224.9)
Detection of IS/OS under the fovea (complete/incomplete)	28/68
Detection of ELM under the fovea (complete/incomplete)	52/44
Cystoid macular edema, number of eyes (%)	11 (11.5)
Hyperreflective foci, number of eyes (%)	39 (40.6)
Fibrin, number of eyes (%)	22 (22.9)

[a] SD, standard deviation; [b] logMAR, logarithm of the minimum angle of resolution; [c] IS/OS, junction between the inner and outer photoreceptor segments; [d] ELM, external limiting membrane

treatments was 1.7±1.0. The mean duration from the final treatment to the final examination was 13.4±9.4 months. The mean follow-up period was 24.6±5.7 months.

At the initial visit, all eyes exhibited exudative changes beneath the neurosensory retina derived from active CNV (subretinal fluid and hemorrhage). In addition, most OCT images revealed morphological changes within the neurosensory retina. Cystoid macular edema was observed in 18.8% of eyes. Cystoid spaces were usually observed within neurosensory retinas that were in direct contact with the underlying type 2 CNV, whereas detached retinas were rarely seen in any of the cystoid spaces. In 58.3% of eyes, OCT revealed that the fibrin exudate was an amorphous hyperreflective material within the subretinal space. Fibrin, which was often seen just over the underlying active type 2 CNV or polypoidal lesions, often appeared to infiltrate the overlying neurosensory retina, especially in the outer aspect, resulting in a lack of IS/OS or ELM lines. In these eyes, the ELM seemed to work in some instances as a blocking agent against the exudates (Fig. 2). In 81.3% of eyes, intraretinal hyperreflective foci were seen within the neurosensory

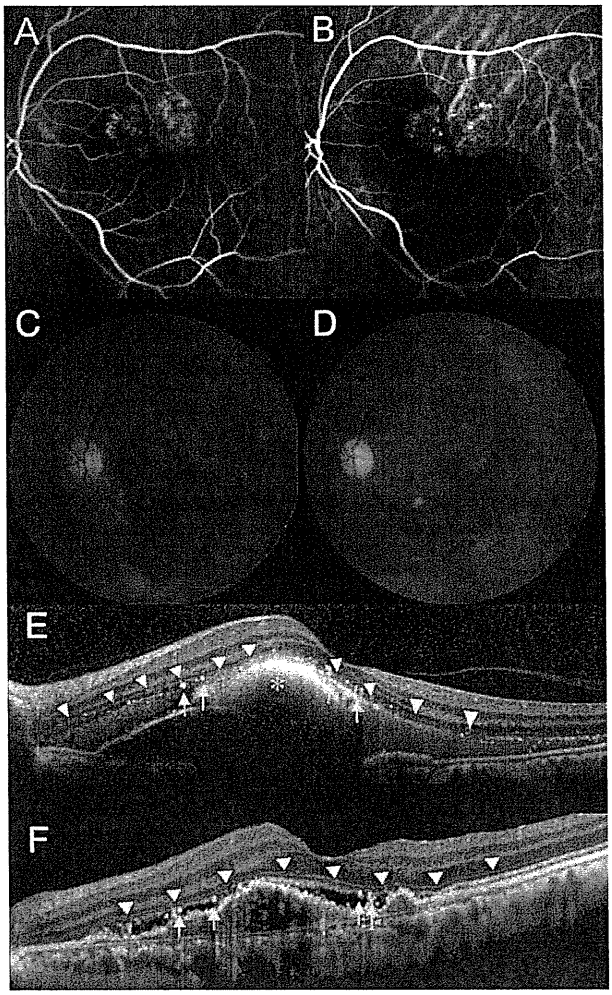

Fig. 2 Changes in retinal structure seen in polypoidal choroidal vasculopathy. **a** Initial fluorescein angiography. **b** Initial indocyanine green angiography shows numerous polypoidal lesions. **c** Initial fundus photograph exhibiting reddish-orange nodules and an adjacent detachment of the pigment epithelium. **d** Fundus photograph at final visit. **e** Sectional image obtained using optical coherence tomography (OCT) at the initial visit. Numerous hyperreflective foci (*yellow arrows*), as well as subretinal fluid/fibrin (*yellow asterisk*) are seen. The fibrin appears to have infiltrated the outer retina but appears to be blocked at the external limiting membrane (*white arrowheads*). The structure of the neurosensory retina seems to be relatively well-preserved. The line of the external limiting membrane is detectable under the fovea. The visual acuity was 0.3 by the Landolt chart. **f** Sectional image obtained using OCT at the final visit. The visual acuity was 0.9 by the Landolt chart

retina. Intraretinal hyperreflective foci were frequently seen throughout the entire outer retina, not only outside but also beyond the ELM (Figs. 1 and 2). In our patients, the integrity of the inner and outer segments of the foveal photoreceptor cells appeared to be compromised due to exudative change from the CNV. At the initial examination, foveal ELM was seen in 66.7% of the eyes examined, whereas foveal IS/OS was seen in only 22.9% of the eyes examined. Figure 3.

Table 2 shows the correlations of initial VA with other measurements obtained at the initial examination. Both the total foveal thickness and the presence of cystoid macular edema were correlated with initial VA (r=0.39, p<0.001; r=0.39, p< 0.001). In addition, foveal IS/OS and ELM were also correlated with initial VA (r=0.35, p<0.001; r=0.48, p<0.001).

At the final examination, the mean total thickness was significantly reduced to 305.4±224.9 μm (p<0.001), while

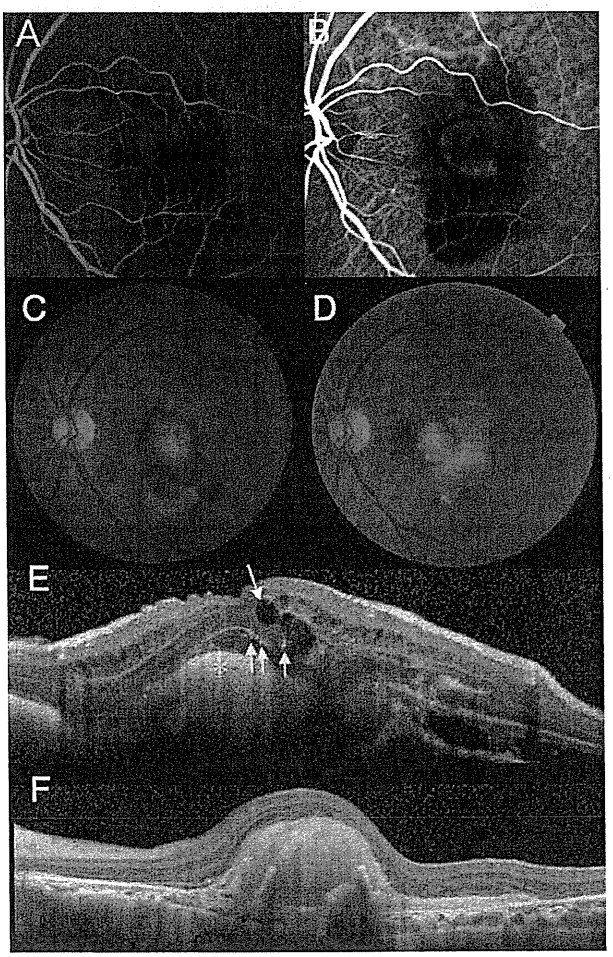

Fig. 3 Changes in retinal structure seen in typical age-related macular degeneration. **a** Initial fluorescein angiography shows minimally classic choroidal neovascularization (CNV). **b** Initial indocyanine green angiography. **c** Fundus photograph at initial visit shows subfoveal exudate with surrounding subretinal hemorrhage. **d** Fundus photograph at final visit shows subfoveal fibrous tissue. **e** Sectional image obtained using optical coherence tomography (OCT) at the initial visit. Hyperreflective foci (*yellow arrows*) and cystoid macular edema (*white arrow*) are seen within the neurosensory retina. Subretinal fluid/fibrin (*yellow asterisk*) is seen subfoveally. The line of the external limiting membrane is not detectable under the fovea. Visual acuity was 0.2 by the Landolt chart. **f** Sectional image obtained using OCT at the final visit. Sectional OCT image at 20 months shows thick subfoveal deposit. The visual acuity was 0.1 by the Landolt chart

Table 2 Association between initial visual acuity and other measurements obtained at initial examination

	R	*P* value
Age	0.20	0.048
Gender	0.03	0.782
Diabetes mellitus	0.04	0.720
Hypertension	0.08	0.413
Smoking	0.09	0.370
Type of disease	0.03	0.787
Total foveal thickness	0.39	<0.001
Cystoid macular edema	0.39	<0.001
Hyperreflective foci	0.11	0.261
Fibrin	0.05	0.603
Detection of IS/OS[a] under the fovea	0.35	<0.001
Detection of ELM[b] under the fovea	0.48	<0.001

[a] IS/OS, junction between the inner and outer photoreceptor segments; [b] ELM, external limiting membrane

cystoid macular edema was still seen in 11.5% of the eyes. Despite treatment, restoration of the integrity of the outer photoreceptor layer was limited. Complete detection of the IS/OS and ELM lines was achieved in only 29.1% and 54.2% of eyes respectively. Table 3 shows the correlations between final VA and other measurements obtained at the final examination. The total foveal thickness and presence of cystoid macular edema were correlated with poor final VA (r=0.27, p<0.001; r=0.33, p<0.001), whereas detection of foveal IS/OS and ELM lines was correlated with good final VA (r=0.57, p<0.001; r=0.58, p<0.001). There were no differences in final VA between eyes with typical AMD and PCV (p=0.149).

Table 4 shows the correlations of final VA with measurements obtained at the initial examination (Pearson's correlation analyses); of these, initial VA showed the closest correlation with final VA (r=0.61, p<0.001). Age (r=0.34, p<0.001), total foveal thickness (r=0.40, p<0.001), and the presence of hyperreflective foci or cystoid macular edema (r=0.26, p=0.012) at the initial visit also correlated with final VA. In addition, the initial detection of the foveal IS/OS and ELM lines was correlated with final VA (r=0.42, p<0.001 and r=0.55, p<0.001 respectively). However, there were no differences in final VA between treatment types (p=0.637). Table 5 shows the correlations between VA and the measurements obtained at the initial examination in each group, stratified by treatment. In each group, while the correlations had similar tendencies, some were not statistically significant, perhaps due to the small number of eyes.

Table 6 shows the correlations between final VA and the measurements obtained at the initial examination after multiple regression analysis. By multiple regression analysis, final VA was correlated with initial VA (r=0.48, p<0.001) and the detection of a foveal ELM line (r=0.33, p=0.008). The initial presence of cystoid macular edema was associated with initial poor VA (r=0.39, p<0.001), but had no significant correlation with final visual function. On the other hand, the initial presence of hyperreflective foci had no significant correlation with initial VA (r=0.11, p=0.261), but showed a marginal correlation with final VA (r=0.23, p=0.054).

Table 3 Association between final visual acuity and other measurements obtained at final examination

	R	*P* value
Age	0.34	<0.001
Gender	0.03	0.770
Follow-up period	0.03	0.787
Diabetes mellitus	0.06	0.589
Hypertension	0.02	0.827
Smoking	0.01	0.908
Total foveal thickness	0.27	<0.001
Cystoid macular edema	0.33	<0.001
Hyperreflective foci	0.16	0.120
Fibrin	0.12	0.258
Detection of IS/OS[a] under the fovea	0.57	<0.001
Detection of ELM[b] under the fovea	0.58	<0.001

[a] IS/OS, junction between the inner and outer photoreceptor segments; [b] ELM, external limiting membrane

*Fisher's least significant difference test

Table 4 Associations between final visual acuity and measurements obtained at initial examination and during treatment

	R	*P* value
Age	0.34	<0.001
Gender	0.03	0.770
Diabetes mellitus	0.06	0.589
Hypertension	0.02	0.827
Smoking	0.01	0.908
Type of disease	0.15	0.149
Visual acuity (logMAR[a])	0.61	<0.001
Total foveal thickness	0.40	<0.001
Cystoid macular edema	0.34	<0.001
Hyperreflective foci	0.26	0.012
Fibrin	0.06	0.513
Detection of IS/OS[b] under the fovea	0.42	<0.001
Detection of ELM[c] under the fovea	0.55	<0.001
Treatment	–	0.637*

[a] logMAR, logarithm of the minimum angle of resolution; [b] IS/OS, junction between inner and outer segments of the photoreceptors; [c] ELM, external limiting membrane

*Fisher's least significant difference test

Table 5 Association between final visual acuity and other measurements obtained at initial examination in each group, stratified by treatment

	No treatment (n=21)		Photodynamic therapy with anti-VEGF agents (n=37)		Anti-VEGF[a] agents (n=38)	
	R	P value	R	P value	R	P value
Age	0.50	0.022	0.32	0.058	0.27	0.106
Gender	0.40	0.073	0.23	0.177	0.03	0.869
Diabetes mellitus	0.09	0.712	0.27	0.101	0.22	0.175
Hypertension	0.13	0.576	0.15	0.367	0.04	0.793
Smoking	0.02	0.926	0.12	0.481	0.14	0.397
Visual acuity (logMAR[b])	0.76	<0.001	0.48	0.003	0.62	<0.001
Total foveal thickness	0.45	0.042	0.36	0.029	0.40	0.013
Cystoid macular edema	NA	NA	0.26	0.117	0.49	0.002
Hyperreflective foci	0.38	0.090	0.01	0.968	0.28	0.093
Fibrin	0.01	0.957	0.07	0.666	0.12	0.469
Detection of IS/OS[c] under the fovea	0.47	0.034	0.32	0.055	0.46	0.004
Detection of ELM[d] under the fovea	0.71	<0.001	0.26	0.117	0.65	<0.001

[a] VEGF, vascular endothelial growth factor; [b] logMAR, logarithm of the minimum angle of resolution; [c] IS/OS, junction between inner and outer photoreceptor segments; [d] ELM, external limiting membrane

No eyes exhibited cystoid macular edema at the initial visit in the no-treatment group

Discussion

In this study, we evaluated the morphological findings of the retina associated with exudative AMD, and found that initial ELM status and the presence of hyperreflective foci are associated with the visual prognosis. Although the predictive power was inferior to that of initial VA, these parameters at the time of the initial examination can be of help in predicting the visual prognosis.

Table 6 Association between final visual acuity and measurements obtained at initial examination, evaluated by multiple regression analysis

	Partial regression coefficient	P value
Age	0.01	0.036
Gender	NA[a]	–
Diabetes mellitus	NA	–
Hypertension	NA	–
Smoking	NA	–
Type of disease	NA	–
Visual acuity (logMAR[b])	0.48	<0.001
Total foveal thickness	<0.01	0.292
Cystoid macular edema	0.02	0.856
Hyperreflective foci	0.23	0.054
Fibrin	NA	–
Detection of IS/OS[c] under the fovea	0.13	0.279
Detection of ELM[d] under the fovea	0.33	0.008

[a] NA, not applicable; [b] logMAR, logarithm of the minimum angle of resolution; [c] IS/OS, junction between inner and outer photoreceptor segments; [d] ELM, external limiting membrane

Although both ELM and IS/OS status were correlated with visual prognosis in bivariate relationship analysis, the multiple regression model showed that only ELM, and not IS/OS status, contributes to visual prognosis. This finding can be explained, at least in part, by the previously held notion that the IS/OS change is too sensitive for use in the evaluation of diseases that cause severe retinal damage, such as exudative AMD [17]. In the current study, of the 96 eyes, IS/OS and ELM lines just beneath the fovea were confirmed in 22 eyes (22.9%) and 64 eyes (66.7%) respectively, suggesting that the IS/OS is impaired relatively early in the course of AMD. In fact, the ELM line was always confirmed when an IS/OS line was detectable. This finding is consistent with the findings of previous studies that examined other macular diseases (e.g., macular hole [26], retinal detachment [27]). Taken together, these facts indicate that the IS/OS is more susceptible and is disrupted in earlier stages than is the ELM. Photoreceptor damage appears as disruption of the IS/OS at first and subsequently of the ELM in these conditions, so the evaluation of the ELM and of the IS/OS depends on the severity of the disease.

An intact ELM might indicate the preservation of the anatomic barrier as well as photoreceptor integrity. The ELM consists of the zonula adherens between the Müller cells and the photoreceptors at the base of the outer segments; this junction is not as tight as that of the zonula occludens, but it does limit the movement of large molecules [28]. As shown in Fig. 2, some eyes demonstrated

termination of subretinal fibrin at the ELM border, suggesting that the ELM actually acts as a barrier to subretinal proteins or lipids. The prevention of molecular invasion and the subsequent retinal fluid accumulation would have beneficial effects on visual prognosis, providing another reason to study ELM status and its relationship with visual prognosis.

The present study also showed that hyperreflective foci could possibly predict vision, as the presence of hyperreflective foci was negatively associated with the visual prognosis. Although hyperreflective foci are not a functional retinal component, and subfoveal hard exudate accumulation was not a cause of poor visual prognosis, we believe that the presence of hyperreflective foci are a hallmark of blood–retinal barrier function, and thus reflect visual outcome. Hyperreflective foci were visible before treatment in many eyes (81.3%) but tended to disappear as the exudative changes improved (40.6% at final examination). An earlier report also suggested that the presence of hyperreflective foci reflects blood–retinal barrier impairment [20]. It is possible that eyes with hyperreflective foci at the initial examination had more active CNV and more severe blood–retinal barrier damage. In other words, the small percentage of cases without hyperreflective foci had milder CNV and milder blood–retinal barrier damage; this difference in the degree of blood–retinal barrier damage might have affected visual prognosis.

There are many limitations to the present study, including the retrospective study design, the relatively small study population from a single institution, and the variety of treatment regimens used. While the heterogeneity in disease types might have affected the results, there were no differences in initial and final VA between eyes with typical AMD and PCV. In the current study, eyes with exudative AMD were treated with intravitreal injections of anti-VEGF agents with or without PDT. When stratified by treatment, the correlations showed similar tendencies, some of which were not statistically significant, perhaps due to the small number of eyes. Eyes treated with combination therapy showed the lowest association between the initial condition of the outer retina and final VA. While the phototoxic effect of PDT might be involved in this low correlation, the exact reason is unclear. It is possible that the treatment regimen used have some effect on the visual prognosis.

Another limitation is the very nature of OCT examinations. The device used depicts only a difference in light reflectance. Furthermore, we are not completely sure what the presence of an intact ELM or hyperreflective foci implies. Both of these are issues that need to be addressed in future studies. Although initial VA is most strongly associated with the visual prognosis, the initial condition of the outer retina may be of help in predicting the visual prognosis in eyes with AMD. This information will help clinicians provide appropriate information to their patients. A further prospective study is necessary to establish the factors that predict visual prognosis in eyes with exudative AMD.

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