TABLE 2. Preoperative VFQ-25 Composite Score and 12 Subscales in the Patients with Vitreoretinal Disorders and the Normal Control Subjects

VFQ-25 Scores	NC	PDR	DME	BRVO	CRVO	MH	ERM
General health	57.8 (19.0)	39.1 (19.6)*	44.1 (19.7)†	40.0 (12.9)†	47.9 (17.4)	51.2 (17.4)‡	55.3 (15.0)
General vision	71.6 (14.8)	44.2 (21.2)*	46.3 (18.1)*	44.0 (21.1)*	51.7 (21.7)†	56.2 (17.2)	53.9 (17.7)*
Ocular pain	80.6 (15.2)	75.1 (22.3)	73.4 (20.6)	73.1 (20.0)	78.1 (20.7)	82.1 (17.9)	76.1 (17.2)
Near activities	81.8 (14.1)	44.2 (22.6)*	46.5 (21.1)*	44.4 (14.8)*	54.9 (22.6)*	59.5 (19.6)*	57.1 (17.3)*
Distance activities	82.3 (13.5)	48.1 (22.8)*	51.5 (24.3)*	53.5 (18.5)*	56.3 (22.8)*	64.9 (21.3)*	60.7 (14.7)*
Social functioning	90.9 (11.1)	59.5 (24.2)*	55.6 (27.7)*	61.3 (19.4)*	66.7 (19.5)*	78.0 (19.3)*	71.6 (19.3)*
Mental health	87.0 (13.6)	43.6 (23.8)*	44.4 (25.8)*	50.9 (23.3)*	52.1 (29.0)*	69.3 (18.3)*	64.8 (16.6)*
Role difficulties	84.9 (15.9)	52.9 (26.0)*	53.3 (29.3)*	48.8 (25.9)*	58.3 (24.6)*	72.6 (23.0)†	67.0 (17.3)*
Dependency	95.5 (9.9)	53.3 (29.7)*	55.3 (31.7)*	62.5 (26.3)*	66.7 (23.3)*	83.1 (18.2)*	77.5 (17.7)*
Driving	83.5 (12.3)	41.7 (34.2)*	45.4 (34.5)*	42.7 (28.4)*	57.5 (23.7)*	75.0 (19.2)	61.5 (23.0)*
Color vision	94.0 (10.7)	69.5 (25.2)*	68.4 (23.7)*	70.0 (20.8)*	68.8 (24.1)*	86.6 (14.9)†	79.5 (14.6)*
Peripheral vision	82.5 (18.6)	46.6 (23.3)*	45.4 (26.5)*	46.3 (18.6)*	54.2 (20.9)*	67.9 (20.9)†	67.4 (17.1)*
Composite score	85.0 (9.1)	52.8 (19.0)*	53.0 (20.5)*	54.7 (15.5)*	60.4 (17.6)*	71.2 (14.3)*	66.9 (10.5)*

Data are expressed as the mean (SD). NC, normal control subjects. *P*, significantly different from the normal controls (Mann-Whitney's U test).
* $P < 0.0001$.
† $P < 0.01$.
‡ $P < 0.05$.

scores, composite scores, and age among vitreoretinal disorders. The relationship between the preoperative and postoperative VFQ-25 composite scores and between the preoperative scores and changes in the VFQ-25 composite scores were examined with the Pearson's correlation coefficient. Before and after surgery, multiple regression analysis was performed to investigate the relationship between various explanatory variables and VFQ-25 composite scores. Variables tested were better-seeing BCVA, worse-seeing BCVA, better-seeing CS, worse-seeing CS, and severity of metamorphopsia. The relationship between changes in the VFQ-25 composite score and changes in the explanatory variables was also evaluated. All tests of association were considered statistically significant at $P < 0.05$ (StatView, ver. 5.0; SAS Inc., Cary, NC).

RESULTS

Table 1 summarizes the background data of the normal control subjects and the patients with vitreoretinal disorders. The patients in the RD group were significantly younger than those in the other groups ($P < 0.05$, Fisher's PLSD). Among the 299 patients with vitreoretinal disorders, 24 were pseudophakic and 275 were phakic; 180 patients underwent combined cataract surgery and vitrectomy. Fifty-two eyes had vitreous hemorrhage (42 eyes with PDR, 7 eyes with BRVO, 2 eyes with RD, and 1 eye with RD).

Vitrectomy significantly improved VFQ-25 composite score in all vitreoretinal disorders except for RD in which preoperative VFQ-25 was not tested (Fig. 1). Change in the VFQ-25 composite score was significantly higher in eyes with vitreous hemorrhage (15.0 ± 11.4) than in eyes without vitreous hemorrhage (7.8 ± 10.7). The results of pre- and postoperative VFQ-25 composite scores and 12 subscales in the patients with each vitreoretinal disorder and the normal control subjects are shown in Tables 2 and 3, respectively. The preoperative VFQ-25 composite score was significantly lower in the patients with vitreoretinal disorders than in the normal control subjects. In addition, the postoperative VFQ-25 composite scores remained significantly lower in the patients with disease than in the normal control subjects.

The box-and-whisker plots of the VFQ-25 scores in each group are displayed in Figure 2. The preoperative VFQ-25 composite scores in the patients with MH and ERM were significantly higher than those in the patients with PDR, DME, and BRVO. The postoperative VFQ-25 composite scores in the patients with the MH, ERM, and RD were significantly higher than those in the patients with PDR, DME, BRVO, and CRVO. Changes in the VFQ-25 composite scores in the patients with ERM were significantly larger than those in the patients with DME.

TABLE 3. Postoperative VFQ-25 Composite Score and 12 Subscales in the Patients with Vitreoretinal Disorders and the Normal Control Subjects

VFQ-25 Scores	NC	PDR	DME	BRVO	CRVO	MH	ERM	RD
General health	57.8 (19.0)	39.0 (20.6)*	46.7 (16.6)†	43.8 (16.0)†	41.7 (16.3)†	53.6 (17.1)	55.3 (15.0)	54.2 (16.6)
General vision	71.6 (14.8)	61.6 (17.6)*	53.2 (18.2)*	56.0 (19.0)†	60.0 (19.1)†	69.0 (14.1)	69.1 (11.3)	70.7 (14.9)
Ocular pain	80.6 (15.2)	79.0 (19.6)	75.7 (20.3)	73.6 (19.0)	83.3 (13.4)	84.8 (16.0)	87.9 (11.9)‡	82.4 (14.7)
Near activities	81.8 (14.1)	55.6 (22.1)*	53.5 (21.0)*	63.3 (17.6)*	64.6 (19.2)†	70.2 (18.8)†	71.0 (18.2)†	75.3 (17.3)‡
Distance activities	82.3 (13.5)	58.8 (20.7)*	53.7 (23.6)*	63.8 (17.6)*	61.8 (17.2)†	72.2 (19.4)†	73.4 (16.0)†	75.6 (16.9)†
Social functioning	90.9 (11.1)	74.6 (72.7)*	62.2 (25.6)*	70.0 (18.3)*	67.7 (8.4)*	82.7 (15.6)†	83.0 (9.3)*	88.2 (14.9)
Mental health	87.0 (13.6)	59.1 (23.1)*	54.9 (26.2)*	57.5 (25.1)*	58.9 (25.2)*	76.6 (14.1)*	78.4 (13.1)†	77.5 (18.4)†
Role difficulties	84.9 (15.9)	62.6 (23.9)*	57.9 (29.3)*	60.6 (25.4)*	62.5 (27.2)†	78.6 (21.8)	76.5 (20.0)‡	78.5 (24.3)
Dependency	95.5 (9.9)	66.3 (25.7)*	63.6 (31.8)*	73.2 (18.3)*	70.1 (22.9)*	85.7 (19.2)*	88.9 (11.0)*	87.2 (17.3)†
Driving	83.5 (12.3)	54.5 (33.0)*	47.1 (35.3)*	50.0 (29.2)*	65.0 (16.5)†	78.6 (12.6)	76.0 (16.9)	75.5 (24.0)
Color vision	94.0 (10.7)	72.2 (23.5)*	71.1 (27.0)*	76.3 (20.6)*	72.9 (16.7)*	85.7 (19.2)†	89.4 (12.5)‡	94.0 (10.8)
Peripheral vision	82.5 (18.6)	58.4 (21.2)*	54.6 (23.1)*	60.0 (20.5)*	60.4 (22.5)†	75.8 (19.3)	72.7 (17.0)†	72.2 (21.0)†
Composite score	85.0 (9.1)	63.6 (17.5)*	59.0 (21.0)*	64.9 (15.0)*	66.4 (11.0)*	79.2 (13.0)‡	78.5 (8.4)†	79.6 (14.2)‡

Data are expressed as the mean ± SD. NC, normal control subjects. *P*, significantly different from the normal control (Mann-Whitney's U test).
* $P < 0.0001$.
† $P < 0.01$.
‡ $P < 0.05$.

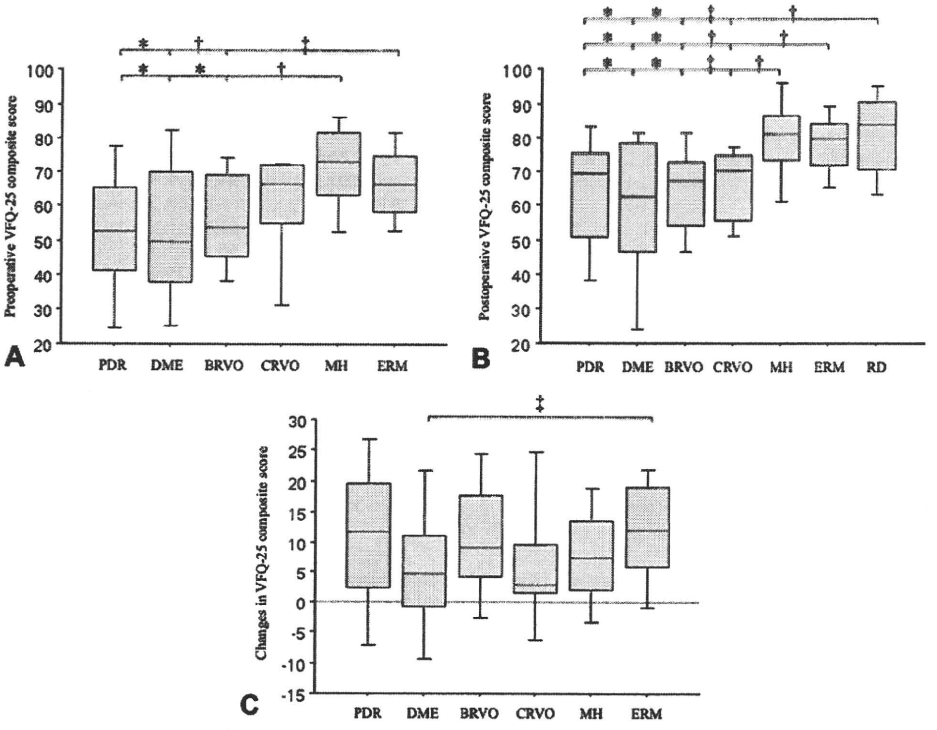

FIGURE 2. Box-and-whisker plots with the *top* and *bottom* boundaries of the boxes indicating the 75th and 25th percentiles, respectively. Whiskers above and below the box indicate the 90th and 10th percentiles, respectively. (**A**) Preoperative VFQ-25 composite score in the patients with vitreoretinal disorders. (**B**) Postoperative VFQ-25 composite score. (**C**) Changes in VFQ-25 composite score. $^*P < 0.0001$; $\dagger P < 0.01$; $\ddagger P < 0.05$.

When scores of all the patients with vitreoretinal disorders were analyzed, the preoperative VFQ-25 composite score correlated significantly with postoperative VFQ-25 composite score ($r = 0.799$, $P < 0.0001$, Fig. 3A) and changes in the VFQ-25 composite score ($r = 0.549$, $P < 0.0001$, Fig. 3B). The preoperative VFQ-25 composite score correlated significantly with the postoperative VFQ-25 composite score in each group (Table 4). In addition, the preoperative VFQ-25 composite score correlated significantly with changes in the VFQ-25 composite scores in the PDR, CRVO, MH, and ERM groups (Table 4).

Table 5 shows pre- and postoperative visual function in the patients with each disorder. Vitrectomy significantly improved BCVA and CS in all the disease groups except CRVO. The surgery significantly improved metamorphopsia in MH and ERM.

Tables 6, 7, and 8 summarize the results of multiple regression analysis on the relation between the VFQ-25 composite score and several explanatory variables, including visual function parameters. The preoperative better-seeing BCVA exhibited significant correlation with the preoperative VFQ-25 composite score in the patients with PDR and DME. In ERM, the preoperative severity of metamorphopsia showed significant correlation with the VFQ-25 composite score (Table 6). After surgery, the better- and worse-seeing BCVAs exhibited significant correlation with the postoperative VFQ-25 composite score in the patients with PDR. The postoperative severity of metamorphopsia showed significant correlation with the VFQ-25 composite score in MH and ERM. In the patients with RD, the postoperative VFQ-25 composite score correlated significantly with the postoperative worse-seeing CS (Table 7). In MH and ERM, changes in the severity of metamorphopsia were significantly relevant to changes in the VFQ-25 composite score, but changes in other variables were not, including BCVA and CS. In addition, changes in the VFQ-25 composite score exhibited significant correlation with CS, not with BCVA in the patients with PDR and DME (Table 8).

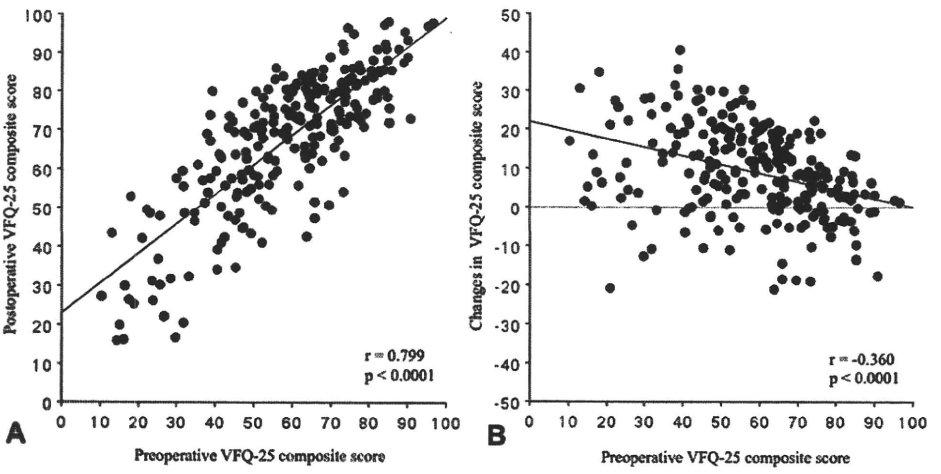

FIGURE 3. (**A**) The preoperative VFQ-25 score versus postoperative VFQ-25 composite score in all the patients. (**B**) Preoperative VFQ-25 composite score versus changes in VFQ-25 composite score in all patients.

TABLE 4. Relationship between Preoperative and Postoperative VFQ-25 Composite Scores and Changes in the Scores

	Preoperative and Postoperative VFQ-25 Composite Score		Preoperative and Changes in VFQ-25 Composite Score	
	r	*P*	*r*	*P*
PDR	0.757	<0.0001*	−0.374	<0.0001*
DME	0.753	<0.0001*	−0.251	0.130
BRVO	0.795	<0.0001*	−0.364	0.116
CRVO	0.687	<0.05*	−0.783	<0.005*
MH	0.833	<0.0001*	−0.418	<0.01*
ERM	0.611	<0.0001*	−0.624	<0.0001*

* Significantly different (Pearson's correlation coefficient).

DISCUSSION

In our present study, pre- and postoperative VR-QOL was assessed using VFQ-25 in the patients with various vitreoretinal disorders. The level of pre- and postoperative VR-QOL as well as changes in VR-QOL showed a wide variation depending on the type of disease. The VFQ-25 used in this study was a Japanese version, with modifications to suit the Japanese. One item was changed to make it more appropriate to the Japanese lifestyle and culture. The modified NEI VFQ-25 questionnaire has been assessed for reliability and validity, and it has been shown to accurately measure VR-QOL in Japanese individuals.[22] The VFQ-25 composite scores in our results were similar to those in the study using the original NEI VFQ-25 in patients with MH, ERM, DME, and CRVO.[9,13,15,23] When the preoperative VFQ-25 composite scores were compared among vitreoretinal diseases, we found that they were relatively high in MH and ERM, whereas those in PDR, DME, and CRVO tended to be lower. In addition, postoperative VR-QOL was relatively high in MH, ERM, and RD, but low in PDR, DME, BRVO, and CRVO. Such polarization can be attributed to the characteristics of individual vitreoretinal disorders. PDR and DME usually affect both eyes, and visual performance in these patients is often inferior to that in patients with other vitreoretinal diseases. VR-QOL in PDR and DME was found to be poorer because VR-QOL was also significantly influenced by the visual performance of the fellow eyes. Hariprasad et al.[23] demonstrated that the VFQ-25 composite score of patients with DME was similar to that of individuals with age-related macular degeneration, but lower than that of patients with type 1 diabetic retinopathy, glaucoma, and cataracts. On the other hand, MH, ERM, and RD are generally unilateral, and the visual performance of patients' fellow eyes remained unaffected. For this reason, preoperative VR-QOL in the patients with these unilateral diseases was rather high. As for patients with BRVO and CRVO who undergo vitrectomy, visual function, including visual acuity and visual field, is significantly decreased in many cases and thus it is not surprising that VR-QOL in these patients is also decreased compared with patients with MH and ERM.

As shown in the results, VR-QOL on each vitreoretinal disorder was significantly improved by vitrectomy. Previous studies have reported improvement in VR-QOL after ophthalmic surgery, such as cataract surgery, photorefractive excimer laser keratectomy, laser in situ keratomileusis and vitrectomy for PDR, ERM, MH, and age-related macular degeneration.[10,12,13,15,16,24–27] In this study, we compared the changes in the VFQ-25 composite scores among vitreoretinal disorders and found a statistically significant difference between ERM and DME. The preoperative VFQ-25 composite score in ERM was significantly lower than that in MH, but increased to a level similar to that of MH after surgery. Gupta et al.[28] used quality-adjusted-life-years (QALYs) methods to investigate VR-QOL in patients with ERM and reported that vitrectomy for ERM was a highly cost-effective procedure. The cost-effectiveness ratio of ERM surgery was higher than that of MH surgery. In MH, the preoperative VFQ-25 composite score was relatively high, and thus surgery-induced improvement in VR-QOL remained rather small. In PDR, the VFQ-25 composite score gained considerable increases by surgery, 10.8 points, but a wide variation was observed among patients. In DME and CRVO, we found that changes in the VFQ-25 composite score due to vitrectomy were 5 points or less. Thus, effectiveness of vitrectomy in these diseases may be relatively low.

Postoperative VR-QOL, even after successful vitrectomy in each vitreoretinal disorder, did not reach the level of that in the normal control subjects. This finding is consistent with the results of previous case-control studies on VR-QOL in retinal disorders such as rhegmatogenous retinal detachment and proliferative diabetic retinopathy.[10,11] These results indicate the importance and need for further improvement in surgical techniques and procedures, reviewing the timing of treatment, establishing means of early recognition and treatment, and considering effective prophylactic measures. When the scores were analyzed in the patients with vitreoretinal disorders altogether, preoperative VR-QOL was significantly associated with postoperative VR-QOL as well as changes in VR-QOL. It is suggested that surgical treatment should be considered as early as possible after a vitreoretinal disorder is recognized, so that vitrectomy can be performed to prevent further deterioration of the patient's VR-QOL.

Multiple regression analysis revealed that the preoperative better-seeing BCVA correlated significantly with the preoperative VFQ-25 composite score in the patients with PDR and DME, in agreement with previous reports.[10,29] Miskala et al.[29] investigated VR-QOL in patients with subfoveal choroidal neovascularization using VFQ-25, and demonstrated that changes

TABLE 5. Preoperative and Postoperative Visual Function in the Patients with Vitreoretinal Disorders

	BCVA		CS		Metamorphopsia	
	Preoperative	Postoperative	Preoperative	Postoperative	Preoperative	Postoperative
PDR	1.37 ± 0.75	0.53 ± 0.62*	5.4 ± 7.2	14.0 ± 7.9*		
DME	0.76 ± 0.49	0.55 ± 0.51†	9.2 ± 6.5	12.7 ± 7.1*		
BRVO	1.25 ± 0.63	0.38 ± 0.38†	6.5 ± 6.9	15.5 ± 6.9†		
CRVO	1.23 ± 0.59	1.14 ± 0.47	2.7 ± 6.1	3.9 ± 6.5		
MH	0.76 ± 0.38	0.49 ± 0.33*	14.3 ± 7.1	18.5 ± 4.3†	0.92 ± 0.52	0.42 ± 0.37*
ERM	0.47 ± 0.29	0.22 ± 0.28*	15.0 ± 5.2	19.0 ± 5.2*	0.83 ± 0.48	0.34 ± 0.42*
RD	0.55 ± 0.65	0.15 ± 0.24*	17.4 ± 3.4	19.7 ± 3.9†		

Data are expressed as the mean ± SD. *P*, significantly different from the preoperative values (Wilcoxon signed-ranks test).
* $P < 0.0001$.
† $P < 0.01$.

TABLE 6. Results of Multiple Regression Analyses of Preoperative Composite Score and Explanatory Variables

	BCVA		CS		
	Better-Seeing	Worse-Seeing	Better-Seeing	Worse-Seeing	Metamorphopsia
PDR	0.012*	0.215	0.969	0.672	—
DME	0.004*	0.594	0.187	0.943	—
BRVO	0.552	0.490	0.234	0.535	—
CRVO	0.244	0.729	0.664	0.702	—
MH	0.308	0.598	0.061	0.430	0.106
ERM	0.362	0.340	0.165	0.705	0.049*

Objective variable is the preoperative VFQ-25 composite score; explanatory variables are preoperative better-seeing BCVA, preoperative worse-seeing BCVA, preoperative better-seeing letter CS, preoperative worse-seeing CS, and preoperative metamorphopsia.

* Significant at $P < 0.05$.

in the overall and subscale scores were linearly related to changes in visual acuity of the better-seeing eye but are not associated with changes in the worse-seeing eye. In ERM, preoperative severity of metamorphopsia showed significant correlation with VFQ-25 composite score, whereas preoperative visual acuity and CS showed no relationship with VFQ-25 composite score. This observation is not consistent with the result of a previous study by Ghazi-Nouri et al.,[15] in which VFQ-25 responses significantly correlated with visual acuity, but not with CS and metamorphopsia in patients with ERM. Such discrepancy between our and prior studies may be attributable to the different methodology used to evaluate metamorphopsia. In previous studies, the severity of metamorphopsia was estimated using the Amsler charts, whereas we used the M-Charts to quantitatively record the severity of metamorphopsia in this study. With the Amsler chart, precise and reproducible assessment of metamorphopsia is difficult because patients have to self-describe the extent and degree of image distortion. On the other hand, the M-Charts can evaluate the degree of metamorphopsia quantitatively, since patients need simply to indicate whether the dotted line is distorted.

Multiple regression analysis revealed that the postoperative better- and worse-seeing BCVAs correlated significantly with the preoperative VFQ-25 composite score in the patients with PDR. These results are consistent with those in a previous report that assessed the relationship between postoperative BCVA and VFQ-25 score in the patients with PDR by simple regression analysis.[10] In PDR, the mean visual acuity in the better-seeing eye deteriorated considerably, and the difference between the better- and worse-seeing eyes was small. This slight difference seems to be the reason that VFQ-25 score correlated with the visual function not only in the better-seeing eye but also in the worse-seeing eye.

By multiple regression analysis, we found that change in the severity of metamorphopsia was the single factor relevant to VR-QOL in the patients with MH and ERM, while visual acuity and CS were not relevant factors. Until now, there has been no report that showed a significant relationship between increases in VR-QOL and improvement in visual function in patients with MH and ERM. Our results indicated that metamorphopsia plays a key role in the deterioration of visual functioning and VR-QOL in patients with MH and ERM.

As the results showed, changes in the VFQ-25 composite score exhibited significant correlation with CS, not with BCVA in the patients with PDR and DME. In several investigations of QOL outcomes after ocular surgery, only a weak or no correlation was observed between increases in QOL and improvement in visual acuity.[12,30] Visual acuity can be a poor predictor of many aspects of visual function.[31,32] CS has been shown to correlate with various aspects of activities requiring vision, including orientation, mobility, reading speed, and driving.[33,34] Carta et al.[35] reported that CS was strongly associated with VR-QOL, even with adjustment for visual acuity among ophthalmic patients with chronic eye conditions such as age-related macular degeneration. In the patients who underwent retinal detachment surgery, the postoperative VFQ-25 composite score correlated significantly with CS and low-contrast visual acuity, whereas there was no correlation between the VFQ-25 composite score and BCVA.[11] In other studies, VFQ-25 responses correlated with CS as well as visual acuity in patients with diabetes mellitus and age-related macular degeneration.[2,36] It is noteworthy that improvement in CS was significantly associated with increases in VR-QOL in the patients with PDR and DME in our study.

Our study had several limitations. First, the sample size was rather small, especially the number of patients with BRVO and

TABLE 7. Results of Multiple Regression Analysis on Postoperative VFQ-25 Composite Score and Explanatory Variables

	BCVA		CS		
	Better-Seeing	Worse-Seeing	Better-Seeing	Worse-Seeing	Metamorphopsia
PDR	0.033*	0.005*	0.824	0.311	—
DME	0.008*	0.337	0.067	0.871	—
BRVO	0.802	0.284	0.998	0.960	—
CRVO	0.752	0.992	0.742	0.917	—
MH	0.066	0.007*	0.903	0.437	0.005*
ERM	0.128	0.097	0.412	0.250	0.048*
RD	0.181	0.891	0.968	0.047*	—

Objective variable is the postoperative VFQ-25 composite score; explanatory variables are postoperative better-seeing BCVA, postoperative worse-seeing BCVA, postoperative better-seeing letter CS, postoperative worse-seeing CS, and postoperative metamorphopsia.

* Significant at $P < 0.05$.

TABLE 8. Results of Multiple Regression Analysis on Changes in VFQ-25 Composite Score and Explanatory Variables

	Changes in		
	BCVA	CS	Metamorphopsia
PDR	0.273	0.003*	—
DME	0.176	<0.0001*	—
BRVO	0.716	0.056	—
CRVO	0.609	0.288	—
MH	0.260	0.145	0.013*
ERM	0.993	0.328	0.009*

Objective variable, changes in VFQ-25 composite score; explanatory variables, changes in BCVA, changes in letter CS, and changes in metamorphopsia.

* Significant at $P < 0.05$.

CRVO, and that may have influenced the VFQ-25 measurements. Second, postoperative follow-up was short. We evaluated the patients at 3 months after surgery. It has been reported that the VFQ-25 score in the patients with ERM improved more at 1 year than at 3 months after surgery.[15] Thus, long-term investigations of patients after vitrectomy may yield different results regarding VR-QOL. Third, there may be some placebo effect in VFQ-25 measurements. The patients obviously recognized that they had surgery and may have answered postoperative VFQ-25 questions more positively with an expectation that they would benefit from the surgery. This effect cannot be avoided in designing the study, but it could account for some of the improvements in the VFQ-25 scores. Future studies with a larger sample size and longer follow-up period, with some attempt to avoid the placebo effect, will further facilitate our understanding of VR-QOL in patients undergoing surgery for vitreoretinal disorders.

References

1. Mangione CM, Lee PP, Gutierrez PR, Spitzer K, Berry S, Hays RD. National Eye Institute Visual Function Questionnaire Field Test Investigators. Development of the 25-item National Eye Institute Visual Function Questionnaire. *Arch Ophthalmol.* 2001;119:1050-1058.
2. Cusick M, SanGiovanni JP, Chew EY, et al. Central visual function and the NEI VFQ-25 near and distance activities subscale scores in people with type 1 and 2 diabetes. *Am J Ophthalmol.* 2005;139:1042-1050.
3. Berdeaux GH, Nordmann JP, Colin E, Arnould B. Vision-related quality of life in patients suffering from age-related macular degeneration. *Am J Ophthalmol.* 2005;139:271-279.
4. Cahill MT, Banks AD, Stinnett SS, Toth CA. Vision-related quality of life in patients with bilateral severe age-related macular degeneration. *Ophthalmology.* 2005;112:152-158.
5. Kymes SM, Walline JJ, Zadnik K, Gordon MO. Collaborative Longitudinal Evaluation of Keratoconus Study Group: quality of life in keratoconus. *Am J Ophthalmol.* 2004;138:527-535.
6. Hyman LG, Komaroff E, Heijl A, Bengtsson B, Leske MC. Early Manifest Trial Group: treatment and vision-related quality of life in the early manifest glaucoma trial. *Ophthalmology.* 2005;112:1505-1513.
7. Schiffman RM, Walt JG, Jacobsen G, Doyle JJ, Lebovics G, Sumner W. Utility assessment among patients with dry eye disease. *Ophthalmology.* 2003;110:1412-1419.
8. Bradley EA, Sloan JA, Novotny PJ, Garrity JA, Woog JJ, West SK. Evaluation of the National Eye Institute visual function questionnaire in Graves' ophthalmopathy. *Ophthalmology.* 2006;113:1450-1454.
9. Deramo VA, Cox TA, Syed AB, Lee PP, Fekrat S. Vision-related quality of life in people with central retinal vein occlusion using the 25-item National Eye Institute Visual Function Questionnaire. *Arch Ophthalmol.* 2003;121:1297-1302.
10. Okamoto F, Okamoto Y, Fukuda S, Hiraoka T, Oshika T. Vision-related quality of life and visual function following vitrectomy for proliferative diabetic retinopathy. *Am J Ophthalmol.* 2008;145:1031-1036.
11. Okamoto F, Okamoto Y, Hiraoka T, Oshika T. Vision-related quality of life and visual function after retinal detachment surgery. *Am J Ophthalmol.* 2008;146:85-90.
12. Hirneiss C, Neubauer AS, Gass CA, et al. Visual quality of life after macular hole surgery: outcome and predictive factors. *Br J Ophthalmol.* 2007;91:481-484.
13. Tranos PG, Ghazi-Nouri SM, Rubin GS, Adams ZC, Charteris DG. Visual function and subjective perception of visual ability after macular hole surgery. *Am J Ophthalmol.* 2004;138:995-1002.
14. Tranos PG, Peter NM, Nath R, et al. Macular hole surgery without prone positioning. *Eye.* 2007;21:802-806.
15. Ghazi-Nouri SM, Tranos PG, Rubin GS, Adams ZC, Charteris DG. Visual function and quality of life following vitrectomy and epiretinal membrane peel surgery. *Br J Ophthalmol.* 2006;90:559-562.
16. Cahill MT, Stinnett SS, Banks AD, Freedman SF, Toth CA. Quality of life after macular translocation with 360 degrees peripheral retinectomy for age-related macular degeneration. *Ophthalmology.* 2005;112:144-151.
17. Pelli DG, Robson G, Wilkins AJ. The designed of a new letter chart for measuring contrast sensitivity. *Clin Vision Sci.* 1988;2:187-199.
18. Maeda N, Sato S, Watanabe H, et al. Prediction of letter contrast sensitivity using videokeratographic indices. *Am J Ophthalmol.* 2000;129:759-763.
19. Elliott DB, Bullimore MA, Bailey IL. Improving the reliability of the Pelli-Robson contrast sensitivity test. *Clin Vision Sci.* 1991;6:471-475.
20. Matsumoto C, Arimura E, Okuyama S, Takada S, Hashimoto S, Shimomura Y. Quantification of metamorphopsia in patients with epiretinal membranes. *Invest Ophthalmol Vis Sci.* 2003;44:4012-4016.
21. Arimura E, Matsumoto C, Okuyama S, Takada S, Hashimoto S, Shimomura Y. Retinal contraction and metamorphopsia scores in eyes with idiopathic epiretinal membrane. *Invest Ophthalmol Vis Sci.* 2005;46:2961-2966.
22. Suzkamo Y, Oshika T, Yuzawa M, et al. Psychometric properties of the 25-item National Eye Institute Visual Function Questionnaire (NEI VFQ-25), Japanese version. *Health Qual Life Outcomes.* 2005;3:65.
23. Hariprasad SM, Mieler WF, Grassi M, Green JL, Jager RD, Miller L. Vision-related quality of life in patients with diabetic macular oedema. *Br J Ophthalmol.* 2008;92:89-92.
24. Oshika T. Quantitative assessment of quality of vision (in Japanese). *Nippon Ganka Gakkai Zasshi.* 2004;108:770-807.
25. Ishii K, Kabata T, Oshika T. The impact of cataract surgery on cognitive impairment and depressive mental status in elderly patients. *Am J Ophthalmol.* 2008;146:404-409.
26. Belfort R, Campos M, Hoexter MQ, Belfort R Jr, Mari Jde J. The impact of photorefractive excimer laser keratectomy (PRK) and laser in situ keratomileusis (LASIK) on visual quality and life in patients with ametropias (in Portuguese). *Arq Bras Oftalmol.* 2008;71:83-89.
27. Nichols JJ, Twa MD, Mitchell GL. Sensitivity of the National Eye Institute Refractive Error Quality of Life instrument to refractive surgery outcomes. *J Cataract Refract Surg.* 2005;31:2313-2318.
28. Gupta OP, Brown GC, Brown MMA. Value-based medicine cost-utility analysis of idiopathic epiretinal membrane surgery. *Am J Ophthalmol.* 2008;145:923-928.
29. Miskala PH, Hawkins BS, Mangione CM, et al. and the Submacular Surgery Trials Research Group. Responsiveness of the National Eye Institute Visual Function Questionnaire to changes in visual acuity: findings in patients with subfoveal choroidal neovascularization: SST Report No. 1. *Arch Ophthalmol.* 2003;121:531-539.

30. Cassard SD, Patrick DL, Damiano AM, et al. Reproducibility and responsiveness of the VF-14: an index of functional impairment in patients with cataracts. *Arch Ophthalmol.* 1995;113:1508–1513.
31. Owsley C, Sloane ME. Contrast sensitivity, acuity, and the perception of "real-world" targets. *Br J Ophthalmol.* 1987;71:791–796.
32. Lennerstrand G, Ahlstrom CO. Contrast sensitivity in macular degeneration and the relation to subjective visual impairment. *Acta Ophthalmol (Copenh).* 1989;67:225–233.
33. Rubin GS, Roche KB, Prasada-Rao P, Fried LP. Visual impairment and disability in older adults. *Optom Vis Sci.* 1994;71:750–760.
34. Leat SJ, Woodhouse JM. Reading performance with low vision aids: relationship with contrast sensitivity. *Ophthalmic Physiol Opt.* 1993;13:9–16.
35. Carta A, Braccio L, Belpoliti M, et al. Self-assessment of the quality of vision: association of questionnaire score with objective clinical tests. *Curr Eye Res.* 1998;17:506–511.
36. Maguire M. Complications of Age-Related Macular Degeneration Prevention Trial Research Group. Baseline characteristics, the 25-Item National Eye Institute Visual Functioning Questionnaire, and their associations in the Complications of Age-Related Macular Degeneration Prevention Trial (CAPT). *Ophthalmology.* 2004;111:1307–1316.

Pharmacokinetics of Bevacizumab and Its Effect on Vascular Endothelial Growth Factor after Intravitreal Injection of Bevacizumab in Macaque Eyes

Taichiro Miyake,[1,2] *Osamu Sawada,*[1] *Masashi Kakinoki,*[1] *Tomoko Sawada,*[1] *Hajime Kawamura,*[1] *Kazumasa Ogasawara,*[2] *and Masahito Ohji*[1]

Purpose. To evaluate the pharmacokinetics of intravitreally injected bevacizumab in the systemic circulation and the aqueous humor and its effect on vascular endothelial growth factor (VEGF) in the aqueous humor.

Methods. Bevacizumab (1.25 mg/50 μL) was injected into the vitreous cavity of the right eyes of three cynomolgus macaques. Aqueous humor and serum were obtained from the macaques just before injection and on days 1, 3, and 7 and weeks 2, 4, 6, and 8 after injection. The bevacizumab and VEGF concentrations were measured using enzyme-linked immunosorbent assay.

Results. Aqueous VEGF concentrations ranged from 63.2 to 106 pg/mL (mean, 80.0 ± 22.6 pg/mL) before injection; decreased to <31.2 pg/mL, the lower limit of detection, in all eyes between 1 and 28 days after injection; and returned to the preinjection concentration at 42 days. Aqueous VEGF concentrations in the fellow eyes did not change throughout the experiment. Aqueous bevacizumab concentrations in the treated eyes reached a mean peak concentration of 49,500 ± 10,900 ng/mL the day after injection and gradually declined, whereas those in the untreated eyes peaked at 3 days, with a mean concentration of 18.5 ± 25.5 ng/mL, and declined to below 0.156 ng/mL, the limit of detection at 2 weeks. A maximum mean bevacizumab concentration of 1430 ± 186 ng/mL was achieved in the serum 1 week after injection.

Conclusions. Intravitreal injection of bevacizumab decreased the VEGF concentration in the treated eyes for at least 4 weeks and had no or a minimal effect on the untreated fellow eyes. (*Invest Ophthalmol Vis Sci.* 2010;51:1606–1608) DOI:10.1167/iovs.09-4140

Bevacizumab (Avastin; Genentech, South San Francisco, CA) is a full-length humanized monoclonal antibody to all isoforms of vascular endothelial growth factor (VEGF) and has been approved by the Food and Drug Administration for intravenous treatment of metastatic colorectal cancer. Recently, intravenous injection of bevacizumab was reported to be effective for treating age-related macular degeneration (AMD),[1,2] whereas intravitreal injection of bevacizumab has been used widely to treat various ocular diseases including AMD and proliferative diabetic retinopathy.[1–5] Although numerous reports about the efficacy of intravitreal injection of bevacizumab have been published, few studies have reported on the pharmacokinetics of bevacizumab. Bakri et al.[6] reported the pharmacokinetics of intravitreal bevacizumab in a rabbit model and clearly showed that the vitreous half-life of 1.25 mg intravitreal bevacizumab is 4.32 days in rabbit eyes, with minute amounts of bevacizumab detected in the serum and the fellow untreated eye. However, the study had some limitations because of differences in vitreous volume and anatomy of human eyes. Therefore, we used a primate model, which has several advantages in that the ocular volume and anatomy are similar to those of humans. We measured the VEGF and bevacizumab concentrations over time in the aqueous humor of the treated and the untreated eyes after intravitreal injection of bevacizumab in cynomolgus macaques and the pharmacokinetics of bevacizumab in the aqueous humor of the treated and untreated eyes and in the serum.

Methods

All treatments were conducted in agreement with the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research, and the animal research was approved by the Animal Experimentation Committee at Shiga University of Medical Science. Three male cynomolgus macaques, aged 8 to 9 years and weighing 3.9 to 5.5 kg, were anesthetized with 5 mg/kg intramuscular ketamine hydrochloride and 1 mg/kg intramuscular xylazine hydrochloride. Povidone iodine was placed on the conjunctiva of each eye. With the use of a 29-gauge needle, bevacizumab (1.25 mg/50 μL) was injected into the vitreous cavity of the right eye of each macaque. The left eyes received no intravitreal injections and served as controls. Both aqueous humor samples (200 μL) and venous blood samples (2 mL) were obtained from the macaque just before injection and 1, 3, and 7 days and 2, 4, 6, and 8 weeks after injection. Aqueous humor samples were obtained with a 29-gauge syringe. Anterior chamber depth recovered at all times when the samples were obtained. Serum was obtained by allowing the blood sample to clot overnight at 4°C followed by centrifugation. Samples were stored in a freezer at −80°C until analysis. The eyes were monitored before injection and 1, 3, and 7 days and then weekly after injection for signs of inflammation.

Measurement of VEGF

VEGF concentrations in the aqueous humor and the serum were measured with a commercial immunoassay (Quantikine Human VEGF Immunoassay; R&D Systems, Minneapolis, MN) according to the manufacturer's instructions. The limit of the detectable VEGF concentration was 31.2 pg/mL. We measured serum VEGF concentrations twice. However, we measured VEGF concentrations in the aqueous humor once because the sample volumes were small.

From the Departments of [1]Ophthalmology and [2]Pathology, Shiga University of Medical Science, Otsu, Shiga, Japan.

Supported in part by Grant 21592255 from the Ministry of Education, Culture, Sports, Science and Technology of Japan and a grant from the Ministry of Health, Labour and Welfare.

Submitted for publication June 13, 2009; revised August 14, 2009; accepted September 27, 2009.

Disclosure: **T. Miyake**, None; **O. Sawada**, None; **M. Kakinoki**, None; **T. Sawada**, None; **H. Kawamura**, None; **K. Ogasawara**, None; **M. Ohji**, None

Corresponding author: Taichiro Miyake, Department of Ophthalmology, Shiga University of Medical Science, Setatukinowa, Otsu, Shiga, Japan 520-2192; taitirou@belle.shiga-med.ac.jp.

Investigative Ophthalmology & Visual Science, March 2010, Vol. 51, No. 3

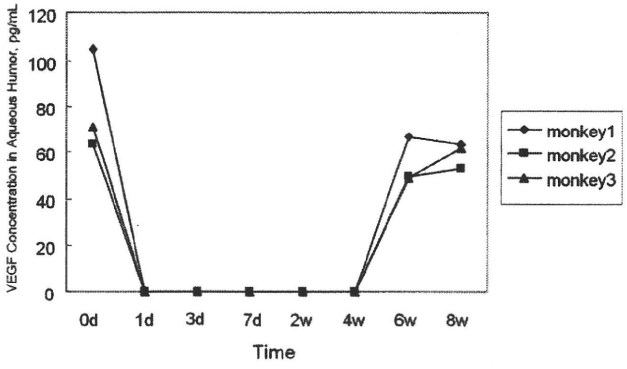

FIGURE 1. VEGF concentrations in the aqueous humor of the monkey eyes treated with bevacizumab. The 0 pg/mL VEGF concentration indicates concentrations below the lower limit of detection (31.2 pg/mL).

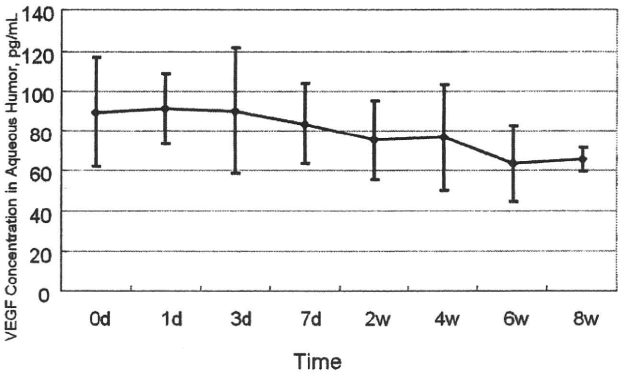

FIGURE 2. Mean VEGF concentrations in the aqueous humor of the fellow untreated eyes.

Bevacizumab Immunoassay

The concentration of bevacizumab was measured using an enzyme-linked immunosorbent assay, as previously described with slight modification.[7] Ninety-six-well plates were coated with recombinant human $VEGF_{165}$ (R&D Systems) at a concentration of 1 μg/mL overnight at 4°C (100 μL/well). After washing three times with phosphate-buffered saline (PBS) containing 0.05% Tween-20, the wells were blocked with 3% bovine serum albumin/PBS overnight at 4°C (200 μL/well). The wells then were washed five times with PBS containing 0.05% Tween-20 and stored dry at 4°C for later use. Aqueous humor or serum diluted in 0.1% bovine serum albumin/PBS was added to the plates overnight at 4°C (50 μL/well). Bevacizumab was detected by horseradish peroxidase-goat anti-human IgG (H+L) conjugate (Invitrogen Corporation, Carlsbad, CA) with a concentration of 1 μg/mL after a 3-hour incubation at room temperature. After five washes, color development was performed with 100-μL tetramethyl benzidine substrates (3,3′,5,5″-tetramethyl benzidine substrate), and the reaction was stopped by the addition of 1 M hydrogen chloride (100 μL). Optical density was measured at 450 nm with correction at 570 nm. A standard curve was prepared, with bevacizumab ranging from 15.6 to 1000 pg/mL. Because the sample volumes were small, we diluted them to 10 times and performed the measurement. Therefore, the limit of the detectable bevacizumab concentration was 0.156 ng/mL. We measured the bevacizumab concentration in each sample twice.

Statistical Analysis

All statistical analyses were carried out with a statistical analysis program (SAS 9.1.3; SAS Institute Japan, Tokyo, Japan).

RESULTS

VEGF concentrations in the aqueous humor of the right eyes ranged from 63.2 to 106 pg/mL (mean ± SD, 80.0 ± 22.6 pg/mL) before intravitreal injection of bevacizumab. One day after injection of bevacizumab, the VEGF concentrations in the aqueous humor decreased to <31.2 pg/mL, the lower limit of detection, in all treated eyes. The concentration below the lower limit was maintained until 4 weeks in all eyes (Fig. 1). VEGF concentrations in the aqueous humor of the fellow untreated eyes (left eyes) ranged from 57.9 to 108 pg/mL (mean, 89.4 ± 27.5 pg/mL) before intravitreal injection. There were no significant differences between the treated and the untreated eyes before intravitreal injection. VEGF concentrations in the aqueous humor of the fellow eyes did not change (Fig. 2). VEGF concentrations in the serum were <31.2 pg/mL, the limit of detection, before intravitreal injection of bevacizumab throughout the experiment.

Changes in the concentration of bevacizumab over time in the aqueous humor of the treated and the untreated eyes and in the serum after intravitreal injection are shown in Figure 3. Bevacizumab concentrations in the aqueous humor of the treated eyes peaked at 49,500 ± 10,900 ng/mL the day after injection and gradually declined. Bevacizumab also was detected in the untreated eyes; however, the levels were very low. Concentrations of bevacizumab in the aqueous humor of the untreated eyes peaked 3 days after injection, with a mean concentration 18.5 ± 25.5 ng/mL, and declined to <0.156 ng/mL, the lower limit of detection, at 2 weeks in all macaques. Bevacizumab was detected in the serum after intravitreal injection, though the concentrations were much lower than in the aqueous humor for 1 to 2 weeks after intravitreal injection. A maximum concentration of 1430 ± 186 ng/mL was achieved 1 week after injection and then gradually declined. However, the reduction rate was lower than that in the aqueous humor of the treated eyes, and the bevacizumab concentration in the serum was higher than that in the aqueous humor in the treated eyes at 4 weeks and thereafter. The bevacizumab concentration in the serum 8 weeks after injection was 67.1± 24.3 ng/mL, which was approximately 187 times higher than that in the aqueous humor of the treated eyes. The half-life of 1.25 mg intravitreally injected bevacizumab was 2.8 ± 0.6 days (n = 3; range, 2.3–3.5 days) in the aqueous humor and 12.3 ± 2.6 days (n = 3; range, 9.2–14.1 days) in the serum. The area under curve was 5680 ± 2336 (μg/mL × h) in the aqueous humor and 526.2 ± 17.1 (μg/mL × h) in the serum. No complications, such as uveitis or endophthalmitis, developed after the bevacizumab injections.

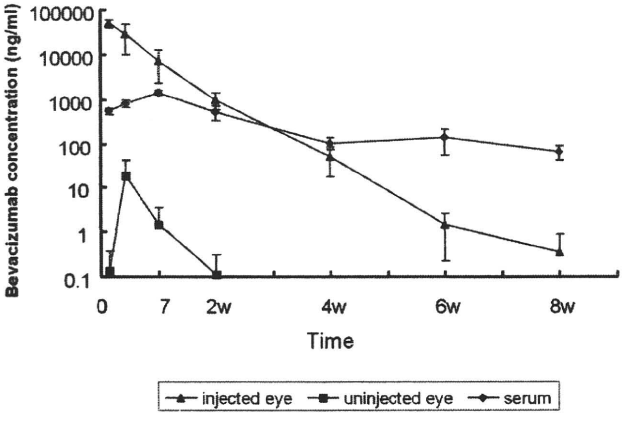

FIGURE 3. Concentrations of bevacizumab in the aqueous humor of the treated eye and in the serum after intravitreal injection.

Discussion

Because we used a macaque model and obtained aqueous humor samples repeatedly over time, we observed the VEGF levels at different time points in the same macaque eyes. To our best knowledge, this is the first study to report the time course of the VEGF level in the same macaques. Although macaque eyes are not the same as human eyes, VEGF levels in the aqueous humor of the macaques before injection were similar to those in human eyes.[5,7]

Concentrations of bevacizumab in macaques also were similar to those in humans.[7,8] Therefore, the current results could be applicable to human eyes. The only difference in the bevacizumab concentrations between macaques and humans was that the drug decreased in concentration in a shorter time in macaques than in humans. Krohne et al.[8] reported that the half-life of an intravitreal injection of 1.5 mg bevacizumab in humans was 9.82 days in the aqueous humor. However, in the present study, the half-life of 1.25 mg bevacizumab was 3.1 days in the aqueous humor. There are several explanations for this difference. First, we observed the bevacizumab concentrations at different time points in the same macaque eyes, whereas the same patients were not observed in the clinical study. Second, we used naive macaques in the present study, whereas the patients in the clinical study had some diseases. Measuring the VEGF and bevacizumab concentrations in the vitreous cavity rather than in the aqueous humor seems to be better for evaluating the intraocular concentration or the pharmacokinetics; however, it would be almost impossible to obtain vitreous samples from the same eyes repeatedly. Therefore, we measured VEGF and bevacizumab concentrations in the aqueous humor. The concentration in the aqueous humor can be useful because the VEGF level in the aqueous humor was reported to be significantly correlated with the VEGF level in the vitreous.[9] Funatsu et al.[10] measured VEGF and interleukin (IL)-6 levels in the aqueous humor, vitreous fluid, and plasma and reported a significant relationship between VEGF and IL-6 levels in the aqueous humor and vitreous fluid. The VEGF level in the vitreous fluid was about five to six times higher than in the aqueous humor. Because we clearly showed that the VEGF concentration in the aqueous humor decreased substantially after intravitreal injection of bevacizumab, the VEGF concentration in the vitreous also should decrease substantially after intravitreal injection of bevacizumab. In the present study, the VEGF level in the aqueous humor fell below the lower limit of detection after bevacizumab injection, similar to results reported in humans.[5] The decreased concentration was maintained for approximately 4 weeks and returned to a level similar to that before injection at 6 weeks after injection. Therefore, the effect of intravitreal injection of bevacizumab is expected to continue for approximately 1 month in macaques; although we do not know the exact length of time, the intravitreal injection of bevacizumab continued to be effective for at least 1 month in humans.[11]

Aqueous humor concentrations of bevacizumab gradually declined; however, low bevacizumab concentrations were detected over 8 weeks after the intravitreal injection, and the time course of the decreasing concentration in humans is longer than in macaques, indicating that the effect might continue longer in humans.[7,8] We previously reported that intravitreal injection of bevacizumab did not decrease the VEGF level in the aqueous humor of the fellow eyes and did not have as great a beneficial effect as a direct intravitreal injection of bevacizumab.[12] However, because that was a clinical study, we could not measure the VEGF concentration in the aqueous humor of the untreated fellow eyes before intravitreal injection of bevacizumab in the treated eye. Therefore, we could not measure the exact decrease in those eyes.

In the present study, the VEGF concentrations in the aqueous humor of the fellow eyes did not change throughout the experiments, although a minute amount of bevacizumab was detected in the fellow untreated eyes and peaked at 3 days with a concentration of 18.5 ng/mL. Avery et al.[3] reported that intravitreal injection of 6200 ng bevacizumab decreased fluorescein leakage in some cases. Because the vitreous volume is approximately 4 mL, an intravitreal injection of 6200 ng bevacizumab results in approximately 1500 ng/mL in the vitreous fluid. According to a previous study, the VEGF level in the vitreous fluid was approximately five to six times higher than in the aqueous humor.[10] Therefore, 1500 ng/mL in vitreous is at least >250 ng/mL in the aqueous humor. However, in the present study, only 18.5 ng/mL was detected, and it might have been too small to have an effect. Bevacizumab was detected in the serum after intravitreal injection, though the concentrations were much lower than in the aqueous humor until 2 weeks after injection. Intravenous injection of bevacizumab 2 mg/kg once weekly in macaques was not toxic after 26 weeks, and bevacizumab concentrations in the serum 1 week after one intravenous injection of 2 mg/mL bevacizumab were higher than 10,000 ng/mL (interview form for bevacizumab, Chugai Oncology, Tokyo, Japan; available only in Japanese). The maximum concentration in serum was 1430 ± 186 ng/mL, which is much lower than 10,000 ng/mL. Therefore 1.25 mg intravitreal injections of bevacizumab are not toxic systemically.

In conclusion, intravitreal injection of bevacizumab decreased the VEGF concentration in the treated eyes for approximately 4 weeks but had no or a minimal effect on the untreated fellow eyes in macaques.

References

1. Michels S, Rosenfeld PJ, Puliafito CA, Marcus EN, Vemlatraman AS. Systemic bevacizumab (Avastin) therapy for neovascular age-related macular degeneration: twelve-week results of an uncontrolled open-label clinical study. *Ophthalmology.* 2005;112:1035-1047.
2. Moshfeghi AA, Rosenfeld PJ, Puliafito CA, et al. Systemic bevacizumab (Avastin) therapy for neovascular age-related macular degeneration: twenty-four-week results of an uncontrolled open-label clinical study. *Ophthalmology.* 2006;113:2002-2011.
3. Avery RL, Pearlman J, Pieramici D, et al. Intravitreal bevacizumab (Avastin) in the treatment of proliferative diabetic retinopathy. *Ophthalmology.* 2006;113:1695-1705.
4. Spaide RF, Fisher YL. Intravitreal bevacizumab (Avastin) treatment of proliferative diabetic retinopathy complicated by vitreous hemorrhage. *Retina.* 2006;26:275-278.
5. Sawada O, Kawamura H, Kakinoki M, Ohji M. Vascular endothelial growth factor in aqueous humor before and after intravitreal injection of bevacizumab in eyes with diabetic retinopathy. *Arch Ophthalmol.* 2007;125:1363-1366.
6. Bakri SJ, Snyder MR, Reid JM, Pulido JS, Ezzat MK, Singh RJ. Pharmacokinetics of intravitreal bevacizumab (Avastin). *Ophthalmology.* 2007;114:855-859.
7. Zhu Q, Ziemssen F, Henke-Fahle S, et al. Vitreous levels of bevacizumab and vascular endothelial growth factor-α in patients with choroidal neovascularization. *Ophthalmology.* 2008;115:1750-1755.
8. Krohne TU, Eter N, Holz FG, Meyer CH. Intraocular pharmacokinetics of bevacizumab after a single intravitreal injection in humans. *Am J Ophthalmol.* 2008;146:508-512.
9. Aiello LP, Avery RL, Arrigg PG, et al. Vascular endothelial growth factor in ocular fluid of patients with diabetic retinopathy and other retinal disorders. *N Engl J Med.* 1994;331:1480-1487.
10. Funatsu H, Yamashita H, Noma H, et al. Aqueous humor levels of cytokines are related to vitreous levels and progression of diabetic retinopathy in diabetic patients. *Graefes Arch Clin Exp Ophthalmol.* 2005;243:3-8.
11. Funk M, Kriechbaum K, Prager F, et al. Intraocular concentrations of growth factors and cytokines in retinal vein occlusion and the effect of therapy with bevacizumab. *Invest Ophthalmol Vis Sci.* 2009;50:1025-1032.
12. Sawada O, Kawamura H, Kakinoki M, Ohji M. Vascular endothelial growth factor in fellow eyes of eyes injected with intravitreal bevacizumab. *Graefes Arch Clin Exp Ophthalmol.* 2008;246:1379-1381.

VITRECTOMY FOR EXUDATIVE AGE-RELATED MACULAR DEGENERATION WITH VITREOUS HEMORRHAGE

TAIJI SAKAMOTO, MD, PHD,* SHWU-JIUAN SHEU, MD, PHD,†
NOBORU ARIMURA, MD,* SEIJI SAMESHIMA, MD,* MASAHIKO SHIMURA, MD, PHD,‡
AKINORI UEMURA, MD, PHD,§ HIROKI KAWANO, MD,* TSUNG-TIEN WU, MD,†
TOSHIAKI KUBOTA, MD, PHD,¶ RIKA SOHMA, MD,¶ YOSHIHIRO NODA, MD, PHD**

Purpose: The purpose of this study was to study the effect of pars plana vitrectomy (PPV) for age-related macular degeneration with vitreous hemorrhage on choroidal neovascularization (CNV).

Methods: A retrospective interventional case series in which 92 eyes with age-related macular degeneration with vitreous hemorrhage that received PPV were studied. Among them, 60 eyes without pre- or posttreatment other than PPV were selected. Choroidal neovascularization was expressed as the incidence of bleeding 6 months before and after PPV. The status of CNV after PPV was compared and classified as worsened, remained, regressed, disappeared, or unclassified. The influence of posterior vitreous detachment was examined.

Results: The incidence of bleeding was reduced dramatically after PPV (1.11 ± 0.44 in preoperative 6 months vs. 0.03 ± 0.18 in postoperative 6 months, $P < 0.0001$). The status of CNV improved in most cases; 40 of 54 classifiable eyes (74.1%) were categorized as "regressed" or "disappeared." Postoperative visual acuity was significantly better than preoperative visual acuity ($P < 0.0001$). The status of CNV subsided more in those eyes without posterior vitreous detachment than in those with posterior vitreous detachment (odds ratio, 1.02; 95% confidence interval, −0.01−2.08; $P = 0.054$).

Conclusion: The activity of CNV was reduced after PPV in eyes with age-related macular degeneration with vitreous hemorrhage. Visual acuity significantly improved, with only rare severe complications. The involvement of vitreomacular traction in the patho-physiology of CNV in age-related macular degeneration is possible.

RETINA 30:856–864, 2010

Age-related macular degeneration (AMD) is the leading cause of severe visual loss in developed countries.[1–4] Although the pathogenesis of the disease is not fully characterized, it is clear that the defect lies in the outer retina and retinal pigment epithelium and that genetic predisposition plays a major role in its development.[5–7]

Although the outer retinal layers are the site for primary lesions in AMD, it has recently been shown that the vitreous may play a role in the progression of AMD.[8–16] A higher incidence of posterior vitreous attachment has been observed during AMD operations.[8,12] Other studies of the vitreous using ultrasound suggest that complete posterior vitreous detachment (PVD) occurs less frequently in AMD in an age-matched healthy population and that a higher incidence of vitreomacular traction (VMT)/vitreomacular adhesion (VMA) is detected in AMD.[9,10] Optical coherence tomography (OCT) has suggested that there is a higher rate of VMT in exudative AMD.[11] In addition, Lee et al[14] showed a higher incidence of vitreous

From the *Department of Ophthalmology, Kagoshima University School of Dental and Medical Sciences, Kagoshima, Japan, † Kaohsiung Veterans General Hospital, School of Medicine, National Yang-Ming University, Taiwan, People's Republic of China, ‡NTT Tohoku Hospital, Sendai, Japan, §Kagoshima City Hospital, Kagoshima, Japan, the ¶University of Occupational and Environmental Health, Kitakyushu, Japan, and the **Department of Ophthalmology, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan.

Supported in part by a grant from the Research Committee on Chorioretinal Degeneration and Optic Atrophy, Ministry of Health, Labor, and Welfare; by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, and Culture of Japan; and by Grant VGHKS 98-063 from Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan.

The authors declare no conflict of interest.

Reprint requests: Taiji Sakamoto, MD, Department of Ophthalmology, Kagoshima University Graduate School of Medical and Dental Science, Sakuragaoka 8-35-1, Kagoshima 890-8520, Japan; e-mail: tsakamot@m3.kufm.kagoshima-u.ac.jp

adhesion in exudative AMD in a paired-eye study. Regardless of these reports, the real influence of VMT/VMA on AMD is still unclear.

Theoretically, there is another way to prove the hypothesis. If VMT/VMA is critical in the progression of exudative AMD, the activity of exudative AMD should settle down after PVD. Indeed, Weber-Krause and Eckardt[9] found that choroidal neovascularization (CNV) disappeared after spontaneous PVD in two cases. Furthermore, Ikeda et al[15] reported that CNV activity was significantly reduced after pars plana vitrectomy (PPV). Therefore, the logical approach is to perform prophylactic PPV to determine the role of VMT/VMA in AMD. However, in this era of antivascular endothelial growth factor (anti-VEGF) therapy, this approach is not justified in most cases.

Nonetheless, there are many AMD cases that require PPV for other reasons, such as vitreous hemorrhage. To our knowledge, there is no detailed study about the effect of PPV on eyes with AMD with vitreous hemorrhage. Therefore, this study was intended primarily to see the effect of PPV on eyes with AMD with vitreous hemorrhage and to further evaluate the possible roles of VMT/VMA by comparing eyes with and without complete PVD.

Subjects and Methods

A consecutive case series in which patients with AMD with vitreous hemorrhage and CNV, who received PPV from January 2005 to September 2008 and who were followed-up for at least 6 months postoperatively at the following hospitals, were studied. The hospitals included were Kagoshima University Hospital, Kagoshima, Japan; University of Occupational and Environmental Health Hospital, Kitakyushu, Japan; Kagoshima City Hospital, Kagoshima, Japan; Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan; and NTT Tohoku Hospital, Sendai, Japan. The data were obtained from medical records and analyzed at the Kagoshima University and Kyushu University. Institutional review board approval for this study was obtained at each hospital.

The patients underwent a complete ophthalmologic examination, including visual acuity testing with standardized refraction using decimal charts, slit-lamp biomicroscopy, fluorescein angiography (FA), and OCT (one of the following at each hospital: OCT3000, Zeiss, Dublin, CA; OCT mark II, Topcon, Tokyo, Japan).

The retina specialists at each hospital determined the surgical indication. In brief, the indications were primarily to remove dense media opacity resulting from vitreous hemorrhage. Eyes with retinal detachment caused by any reason other than AMD and highly myopic eyes (≤ -6.0 diopters) were excluded from the study, as were eyes with apparent diabetic retinopathy, hypertensive retinopathy, or retinal vein occlusion. A standard three-port PPV was performed, and phacoemulsification or intraocular lens implantation was also performed when needed. In the eyes without complete PVD, PVD was produced during surgery. Intravitreous triamcinolone injection was not performed at the end of or after the surgery. In three cases with retinal breaks, silicone oil tamponade was performed. The presence of complete PVD was determined based on the preoperative ultrasonography or intraoperative findings.

The details of the surgical protocols varied between hospitals, but the basic procedure was similar. Under paraocular or general anesthesia, a standard 20-gauge PPV was performed. Three standard sclerotomies were created. Cataract surgery or intraocular lens insertion was performed when needed. Core vitrectomy was performed, and the posterior vitreous cortex was separated from the retina by active aspiration with a vitrectomy probe or a soft cannulated extrusion needle around the optic disk. Premacular membrane was not removed intentionally. This procedure was performed gently and carefully so as not to damage the posterior vitreous cortex. After surgical PVD, the residual vitreous cortex was resected, and endolaser photocoagulation or fluid-gas exchange was performed when needed. The tamponade with SF_6, C_3F_8, or silicone oil was performed when needed. The presence of spontaneous PVD was determined by each surgeon from the intraoperative findings. The intraoperative findings were recorded immediately after surgery, and these records were reviewed postoperatively.

The type of CNV in each case was determined by FA and/or indocyanine green angiography, which was performed before PPV or within 4 weeks after PPV. It was classified as "idiopathic polypoidal choroidal vasculopathy (IPCV)," "AMD," or "unclassifiable" on the basis of our previous reports.[17,18]

The incidence of hemorrhage was determined by the funduscopic examinations. In case the size of subretinal bleeding increased or a subretinal bleed appeared in a new area, it was regarded as one instance of bleeding. A case in which a vitreous hemorrhage occurred was also regarded as one instance of bleeding. The sum of these events represented the total incidence of bleeding. If the exact incidence could not be known because of dense hemorrhage or obscure preoperative records, the total incidence was regarded as one.

The status of CNV was determined by fundus examination, FA, and/or OCT. Because the first observable time to detect CNV after surgery varied in each case, the last findings before vitreous hemorrhage and those of the final examination within 1 year were compared. If there were no data of previous vitreous hemorrhage, the findings of the first examination after PPV were applied instead of those before vitreous hemorrhage. On the basis of these results, CNV status was classified into four categories—"worsened," "remained," "regressed," or "disappeared"—in agreement with two or more examiners of each hospital in a masked fashion, as reported previously.[17,18] The undetermined cases were grouped as "unclassified."

Age-Related Macular Degeneration and Idiopathic Polypoidal Choroidal Vasculopathy

Although AMD is found in all races, IPCV is more common in the Asian population than in whites. Thus, the subgroup analysis was performed in these two groups. The preoperative visual acuity, postoperative visual acuity, incidence of PVD, and status of CNV of each patient based on FA and/or IA findings were compared.

Statistical Analysis

For statistical analysis, decimal fractions of visual acuity were converted to a logarithmic scale (the logarithm of the minimal angle of resolution). According to results of Holladay, blindness was set at 0.00125/2.9 (decimal/logarithm of the minimal angle of resolution), light perception at 0.0025/2.6, hand movements at 0.005/2.3, and counting fingers at 0.014/1.85.[19,20] Preoperative versus postoperative values were compared using the Wilcoxon rank-sum test. To evaluate the influence of complete PVD on the course of CNV after PPV, the eyes with and without complete PVD were compared. Characteristics of the patients were analyzed using the Mann-Whitney U test and the chi-square test. The curative results were scored as follows: worsened, 0; remained, 1; regressed, 2; disappeared, 3; and unclassified, missing value. The relative merit was estimated by the ordered logistic regression model. A P value <0.05 was considered significant.

Results

Data were obtained for 92 eyes from 92 Asian patients, of whom 30 were women and 62 were men. The ages ranged from 49 years to 86 years, with an average of 69.1 ± 9.2 years (median, 69 years). Forty-seven were left eyes and 45 were right eyes. The average follow-up period was 18.3 ± 10.9 months. Forty-one eyes were classified as AMD (44.6%), 33 eyes as IPCV (35.9%), and 18 eyes as unclassified (19.6%). The previous treatments before PPV consisted of intravitreous bevacizumab in 4 eyes, single intravitreal triamcinolone in 6 eyes, intravitreal gas plus tissue plasminogen activator in 13 eyes, and transpupillary thermal therapy in 2 eyes. Intraoperative complications involving retinal detachment were seen in three eyes. Cataract surgery was performed at the same time in 25 eyes (Table 1).

For the following analysis, those eyes that received any specific treatment for AMD, such as the intravitreous/periocular bevacizumab or triamcinolone acetonide injection, were excluded. Those eyes with

Table 1. Characteristics of Patients With and Patients Without PVD

	βPVD (+)		PVD (−)		P	
	Total (n = 40)	PPV Alone (n = 26)	Total (n = 50)	PPV Alone (n = 36)	Total	PPV Alone
Age (years)	70 (50–85)	70 (51–85)	69 (49–86)	69 (50–86)	0.492*	0.376*
Female sex, no. (%)	14 (35)	10 (38)	16 (32)	11 (31)	0.764†	0.516†
Types of CNV, no.						
AMD:IPCV:others	19:15:6	14:8:4	21:18:11	14:14:8	0.690†	0.498†
VA before PPV						
Decimal, median (range)	HM (LP to 20/50)	HM (LP to 20/50)	HM (LP to 20/40)	HM (LP to 20/40)	—	—
LogMAR, mean ± SD	2.04 ± 0.60	2.10 ± 0.59	2.04 ± 0.61	2.01 ± 0.65	0.972*	0.540*
VA after PPV						
Decimal, median (range)	0.05 (LP 20/30)	0.04 (LP 20/30)	0.02 (LP 20/12)	0.02 (HM 20/12)	—	—
LogMAR, mean ± SD	1.37 ± 0.58	1.45 ± 0.55	1.44 ± 0.74	1.36 ± 0.67	0.264*	0.954*

HM, hand movements; IPCV, idiopathic polypoidal choroidal vasculopathy; logMAR, logarithm of minimum angle of resolution; LP, light perception: PPV alone, cases without any additional treatment or postoperative retinal detachment; VA, visual acuity.
*Mann-Whitney *U* test.
†Chi-square test.

postoperative complications were also excluded. As a result, data were analyzed for 64 eyes from 64 Asian patients, of whom 21 were women and 43 were men. The ages ranged from 50 years to 86 years, with an average of 69.5 ± 9.5 years (median, 70 years). The average follow-up period was 19.6 ± 11.4 months. Twenty-nine eyes were classified as AMD (45.3%), 22 eyes as IPCV (34.4%), and 13 eyes as unclassified (20.3%; Table 1).

Visual Acuity

Preoperative visual acuity ranged from light perception to 20/40, median of hand movements, and the logarithm of the minimal angle of resolution was 2.05 ± 0.62 (average ± standard deviation). Postoperative visual acuity ranged from light perception to 1.5, median of 0.04, and the logarithm of the minimal angle of resolution was 1.40 ± 0.61. Postoperative visual acuity was significantly better than preoperative visual acuity ($P < 0.0001$, Wilcoxon rank-sum test; Figure 1).

Incidence of Bleeding

During 6 months before PPV, the incidence of bleeding was 1.11 ± 0.44 (average ± standard deviation; median, 1; range, 0–3). This was significantly reduced to 0.03 ± 0.18 (median, 0; range, 0–1) during the 6 months after PPV ($P < 0.0001$, Wilcoxon rank-sum test; Table 2).

Status of Choroidal Neovascularization

After PPV, the status of CNV was as follows: "worsened" in 4 eyes (6.3%), "remained" in 10 eyes (15.6%), "regressed" in 19 eyes (29.7%), and "disappeared" in 21 eyes (32.8%). Ten eyes (15.6%) were "unclassified" (Table 2) because of poor FA quality, persistent subretinal hemorrhage, or scar. Therefore, among the 54 classifiable eyes, 40 eyes (74.1%) showed that CNV settled down.

Posterior Vitreous Detachment

Complete PVD was observed in 26 eyes, whereas artificial PVD was produced in 36 eyes during the surgery. In the remaining two eyes, complete PVD could not be confirmed because of massive hemorrhage.

To evaluate the influence of PVD on the course of CNV after PPV, the eyes with and without complete PVD were compared (Table 1). There was no significant difference between the two groups in terms of age, sex, types of CNV, visual acuity before and after PPV, or incidence of bleeding. In the eyes with complete PVD, 3 eyes were classified as "worsened" (11.5%), 5 eyes as "remained" (19.2%), 8 eyes as "regressed" (30.8%), 6 eyes as "disappeared" (23.1%), and 4 eyes as "unclassified" (15.4%), whereas in eyes without PVD, 1 eye was classified as "worsened" (2.8%), 4 eyes as "remained" (11.1%), 11 eyes as "regressed" (30.6%), 15 eyes as "disappeared" (41.7%), and 5 eyes as "unclassified" (13.9%). The ordered logistic regression model showed a marginal result that the status of CNV subsided more significantly in those eyes without complete PVD than in

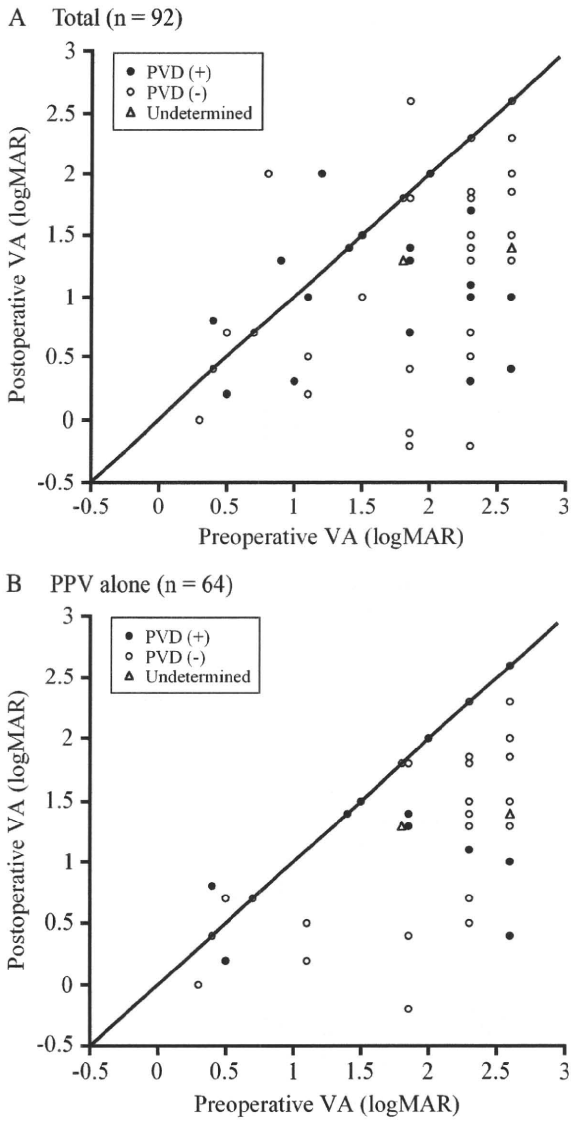

Fig. 1. Scattergram showing best-corrected preoperative visual acuity and postoperative visual acuity of eyes with AMD with vitreous hemorrhage. **A.** Results of all cases. **B.** Results of cases without additional treatment, such as intravitreous bevacizumab or triamcinolone. The cases with postoperative retinal detachment were also excluded. Points lying under the diagonal line represent improvement in visual acuity. Most of the eyes showed an improvement in visual acuity after PPV regardless of complete PVD.

Table 2. Comparisons of Bleeding Incidence and CNV Status in Eyes With and Eyes Without PVD

	PVD (+)		PVD (–)		*P*	
	Total (n = 40)	PPV Alone (n = 26)	Total (n = 50)	PPV Alone (n = 36)	Total	PPV Alone
Incidence of bleeding, no.						
Before PPV (times in 6 months)						
4	1	0	0	0	—	—
3	1	0	1	1	—	—
2	8	5	5	2	—	—
1	29	20	43	32	—	—
0	1	1	1	1	0.147*	0.544*
After PPV (times in 6 months)						
1	1	0	5	2	—	—
0	39	26	45	34	0.159*	0.711*
Status of CNV, no.						
Worsened	4	3	1	1	—	—
Remained	6	5	6	4	—	—
Regressed	16	8	15	11	—	—
Disappeared	9	6	21	15	0.031†	0.054†
Unclassified	5	4	7	5	—	—

PPV alone, cases without any additional treatment or postoperative retinal detachment.
*Mann-Whitney *U* test.
†Ordered logistic regression model.

those with complete PVD (odds ratio, 1.02; 95% confidence interval, −0.01 to 2.08; $P = 0.054$; Figure 2). In the analysis of all 90 eyes, including those that received any additional treatment, the difference was statistically significant (odds ratio, 2.55; 95% confidence interval, 1.09–5.97; $P = 0.031$; Figure 2).

Age-Related Macular Degeneration and Idiopathic Polypoidal Choroidal Vasculopathy

Although the average age differed between the groups, there was no statistically significant difference in the preoperative visual acuity, postoperative visual acuity, or ratio of PVD. This was also the case for the incidence of bleeding and the status of CNV (Table 3).

Case Presentation

A 55-year-old Japanese man was referred to the Kagoshima University Hospital because of IPCV of his right eye. IA showed typical polypoidal lesions with retinal pigment epithelial detachment (Figure 3A, arrow). Optical coherence tomography showed retinal pigment epithelial detachment and adhesion of the

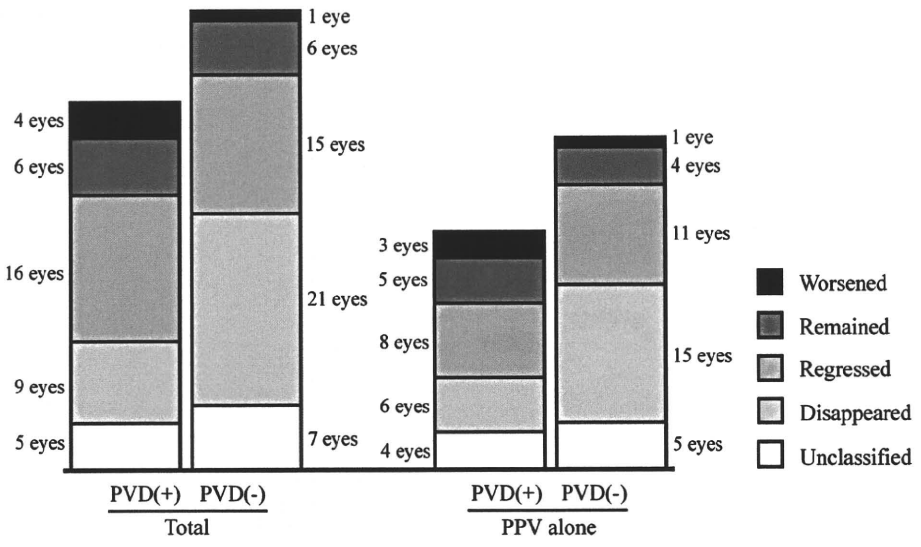

Fig. 2. The status of CNV after PPV. Left, Results of all cases. Right, Results of cases without additional treatment, such as intravitreous bevacizumab or triamcinolone. The cases with postoperative retinal detachment were also excluded. The status of CNV before and after PPV was compared in each case, and the change was categorized as "worsened," "disappeared," regressed," "disappeared," or "unclassified." The ordered logistic regression models showed that the status of CNV subsided more significantly in those eyes without preexisting PVD (—) than in those with PVD (+): $P = 0.031$ in all cases (Total) and $P = 0.054$ in selected cases (PPV alone).

posterior vitreous surface to the retinal surface (Figure 3B, arrowheads). After 2 months, subretinal hemorrhage occurred (Figure 3C), progressing to vitreous hemorrhage, and visual acuity deteriorated to hand movements. Pars plana vitrectomy was performed, and visual acuity recovered gradually. Four months after PPV, both the polypoidal lesions and the retinal pigment epithelial detachment had disappeared (Figure 3, D and E). Visual acuity recovered to 20/12, and neither polypoidal nor CNV lesion was observed except for some scaring 10 months after PPV (Figure 3F).

Discussion

In this study of AMD with vitreous hemorrhage, we found that the activity of CNV subsided significantly after PPV based on two different evaluations: the incidence of bleeding and the status of CNV. It was more evident in eyes without complete PVD than in those with complete PVD. Although the postoperative visual acuity did not reach a satisfactory level.

Hemorrhage caused by CNV is one of the important signs of advanced AMD, and bleeding is a final symptom of AMD. Therefore, the present findings might have reflected the natural course of advanced AMD rather than the therapeutic effect of PPV; however, this is unlikely because the incidence of bleeding was dramatically reduced within a short period of time after PPV. The incidence of bleeding 6 months before and after PPV decreased from an average of 1.11 to 0.03 ($P < 0.0001$). There was a concern that a new hemorrhage might be overlooked or masked by an older, larger subretinal hemorrhage, resulting in an underestimation of postoperative bleeding. On the other hand, it is highly possible that the preoperative incidence was underestimated because approximately one-third of the patients did not visit the hospital until vitreous hemorrhage occurred, and their preoperative incidence of bleeding was classified as one but could be higher. Therefore, the real difference between pre- and postoperative incidence is likely greater than the present result. Previously, it has been described that the activity of CNV in AMD subsides after vitrectomy, although these were anecdotal or small case series.[12,15] Considering these facts together, it is possible that PPV reduces the activity of CNV in eyes with AMD with vitreous hemorrhage, at least to a certain extent.

It is not clear why and how PPV affected the activity of CNV in eyes with AMD. The first possibility is that

Table 3. Characteristics of the Patients With AMD, IPCV, and Others

	AMD		IPCV		Others		*P*	
	Total (n = 40)	PPV Alone (n = 28)	Total (n = 33)	PPV Alone (n = 22)	Total (n = 17)	PPV Alone (n = 12)	Total	PPV Alone
Age (years)	73 (54–86)	73 (54–86)	65 (49–85)	67 (50–85)	69 (53–86)	69 (53–86)	0.015*	0.202*
Female sex, no. (%)	15 (38)	10 (36)	8 (24)	5 (23)	7 (41)	6 (50)	0.366†	0.265†
PVD, no. (%)	19 (48)	14 (50)	15 (45)	8 (36)	6 (35)	4 (33)	0.690†	0.498†
VA before PPV (logMAR)	1.99 ± 0.59	2.06 ± 0.53	2.13 ± 0.53	2.13 ± 0.60	1.96 ± 0.74	1.85 ± 0.83	0.580*	0.607*
VA after PPV (logMAR)	1.44 ± 0.56	1.44 ± 0.54	1.27 ± 0.75	1.39 ± 0.70	1.60 ± 0.74	1.33 ± 0.69	0.244*	0.919*
Incidence of bleeding, no. (times/6 mo)								
Before PPV	1.15 ± 0.36	1.07 ± 0.26	1.27 ± 0.80	1.09 ± 0.61	1.18 ± 0.39	1.25 ± 0.45	0.958*	0.644*
After PPV	0.05 ± 0.22	0	0.03 ± 0.17	0.05 ± 0.21	0.18 ± 0.39	0.08 ± 0.29	0.127*	0.909*
Status of CNV, no.								
Worsened	2	2	1	0	2	2	—	—
Remained	4	3	5	4	3	2	—	—
Regressed	16	10	14	8	1	1	—	—
Disappeared	14	10	13	10	3	1	1.000‡	0.660‡
Unclassified	4	3	0	0	8	6	—	—

VA and incidence of bleeding are expressed as mean ± SD.

LogMAR, logarithm of minimum angle of resolution; VA, visual acuity; PPV alone, cases without any additional treatment or postoperative retinal detachment.

*Kruskal-Wallis variance analysis.

†Chi-square test.

‡Ordered logistic regression model.

COLOR

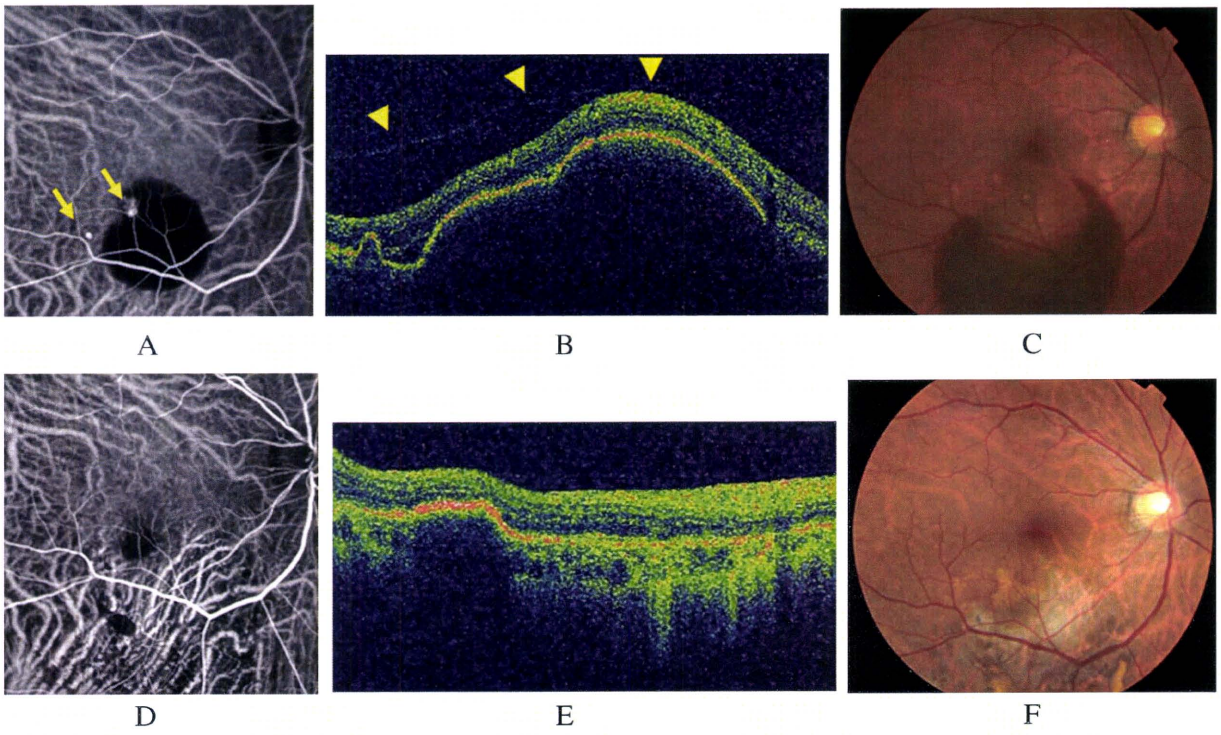

Fig. 3. Clinical course of the case with IPCV (55-year-old Japanese man). Indocyanine green angiography showed the typical polypoidal lesions with the retinal pigment epithelial detachment (**A,** arrow). Optical coherence tomography showed the retinal pigment epithelial detachment and the adhesion of posterior vitreous to the retinal surface (**B,** arrowheads). After 2 months, subretinal hemorrhage occurred progressing into vitreous hemorrhage, and visual acuity deteriorated into hand movements (**C,** the day before vitreous hemorrhage). Then, PPV was performed, and visual acuity recovered gradually. Four months after PPV, both the polypoidal lesions and the retinal pigment epithelial detachment disappeared (**D, E**). Visual acuity recovered to 20/12, and neither polypoidal nor choroidal neovascularization lesion was observed except for the scar 10 months after PPV (**F**).

the activity of AMD subsided as a result of the release of VMT/VMA by PPV. So far, there have been many reports that complete PVD was less frequent in exudative AMD than in nonexudative AMD or age-matched controls.[8–16] These results, obtained using ultrasound, OCT, or intraoperative findings, showed that complete PVD was found in 34% to 66% of AMD cases.[11,12] In this study, complete PVD was found in 44% of the eyes. Because the present data were obtained from eyes with different conditions (vitreous hemorrhage) and the methods of examination were different, it is understandable that the incidence differed from that of the previous reports. Recently, mechanisms of how VMT/VMA causes the deterioration of AMD have been explained hypothetically.[8–16,21–25] Increases in the mechanical forces associated with abnormal VMT/VMA may result in the secretion of signaling factors by the Miiller cells with both paracrine and autocrine effects. This process may lead to a cascade of inflammatory factors and local vascular changes, which may include vascular leakiness and subsequent cystoid macular edema. In addition, in eyes with CNV, this can set up a vicious cycle in which the inflammation, the reactive gliosis, and the tractional forces result in worsening the chronic exudation of the underlying disease. Furthermore, it has been suggested that the presence of adherent vitreous over the macula will not allow VEGF and other cytokines to be cleared away into the vitreous cavity; thus, vitrectomy or PVD might vastly increase the clearance of these factors.[14,26] To prove this hypothesis clearly, a study of prophylactic vitrectomy for eyes with AMD with VMT/VMA may be a logical method. However, this method is not justifiable at the moment because anti-VEGF therapy is widely accepted as an effective treatment for AMD.[27] Furthermore, surgery in such eyes can result in complications, and vitrectomy may also complicate anti-VEGF treatment because it may shorten the half-life of intravitreal anti-VEGF drugs.[27] To avoid this problem, in this study, we retrospectively reviewed the status of CNV in AMD with vitreous hemorrhage during the perisurgical period. The eyes were divided into two groups: eyes with complete PVD and eyes without complete PVD. The status of CNV improved more significantly and more evidently in those eyes without complete PVD than in those with

complete PVD. The results indicate that CNV in AMD without PVD is more inclined to PPV therapy. Certainly, eyes without complete PVD do not always have pathologic VMT/ VMA, but they apparently have more chances to have VMT/VMA than those with complete PVD. This finding supports the idea that VMT/VMA is one of the deteriorating factors of AMD.

The other possibility is that physiologic changes might reduce the activity of CNV after PPV. Regardless of the existence of PVD, the incidence of bleeding and the activity of CNV in AMD with vitreous hemorrhage were significantly reduced after PPV. Pars plana vitrectomy has various physiologic consequences in the vitreous cavity.[26] For example, oxygen transport to an ischemic retina is improved, and the clearance of various molecules, including VEGF, is increased. From this study, the overall effect is likely to make CNV regress after PPV.

It is of interest to note that PPV could significantly increase visual acuity without causing serious complications. Because the dense media opacity was removed by PPV, this significant improvement in visual acuity is not surprising. The most serious complication in this series was proliferative vitreoretinopathy, but it was observed only in 3 cases (3.3%). Other complications, such as cataract, could be corrected by the additional surgery. Although the final visual acuity might not necessarily be satisfactory, the benefit/risk ratio is acceptably high, justifying PPV for AMD with vitreous hemorrhage.

There are several limitations in this study. It was performed in a retrospective manner, and no randomization was applied. The other limitation lies in the method used to evaluate the CNV status. In this study, CNV was not always observable soon after surgery, and in many cases, subretinal hemorrhage was present, in part, even after surgery. Thus, the first observable time differed depending on the case, and to evaluate status accurately, all eyes should be examined at equal timing after surgery. In this study, the CNV status was determined by comparing the preoperative or the first findings after surgery and those at a later time (~6–12 months). This limitation should be remembered while interpreting the results, especially regarding the effect of preexisting PVD. In addition, IPCV is more common in the Asian population than in whites,[28–30] and thus, generalization of the results should be done with caution.

There are various factors related to the progression of AMD, and the genetic factor is supposed to be the most crucial. Fundamental pathologic mechanisms of AMD must have already begun for tractional forces to achieve a change for the worse, because VMT alone is not able to induce AMD. The high coincidence of VMT and CNV and the observation of CNV after PPV in the present cases should lead us to consider vitreous changes when diagnosing and treating patients with AMD. For example, when anti-VEGF therapy is ineffective on an eye with AMD with strong VMT, PPV is a second option for treatment. When all these data are accumulated and the characteristics of these eyes are well understood, the development of a pharmacologic agent to induce PVD might be of benefit for this condition.

Key words: age-related macular degeneration, choroidal neovascularization, pars plana vitrectomy, polypoidal choroidal vasculopathy, posterior vitreous detachment.

References

1. Coleman HR, Chan CC, Ferris FL III, Chew EY. Age-related macular degeneration. Lancet 2008;372:1835–1845.
2. Bunce C, Wormald R. Causes of blind certifications in England and Wales: April 1999–March 2000. Eye (Lond) 2008;22: 905–911.
3. Vingerling JR, Dielemans I, Hofman A, et al. The prevalence of age-related maculopathy in the Rotterdam Study. Ophthalmology 1995;102:205–210.
4. Munoz B, West SK, Rubin GS, et al. Causes of blindness and visual impairment in a population of older Americans: the Salisbury Eye Evaluation Study. Arch Ophthalmol 2000;118: 819–825.
5. Haines JL, Hauser MA, Schmidt S, et al. Complement factor H variant increases the risk of age-related macular degeneration. Science 2005;308:419–421.
6. Edwards AO, Ritter R III, Abel KJ, Manning A, Panhuysen C, Farrer LA. Complement factor H polymorphism and age-related macular degeneration. Science 2005;308:421–424.
7. Hageman GS, Anderson DH, Johnson LV, et al. A common haplotype in the complement regulatory gene factor H (HF1/ CFH) predisposes individuals to age-related macular degeneration. Proc Natl Acad Sci U S A 2005;102:7227–7232.
8. Lambert HM, Capone A Jr, Aaberg TM, Sternberg P Jr, Mandell BA, Lopez PF. Surgical excision of subfoveal neovascular membranes in age-related macular degeneration. Am J Ophthalmol 1992;113:257–262.
9. Weber-Krause B, Eckardt U. Incidence of posterior vitreous detachment in eyes with and without age-related macular degeneration. An ultrasonic study [in German]. Ophthalmologe 1996;93:660–665.
10. Ondes F, Yilmaz G, Acar MA, Unlu N, Kocaoglan H, Arsan AK. Role of the vitreous in age-related macular degeneration. Jpn J Ophthalmol 2000;44:91–93.
11. Krebs I, Brannath W, Glittenberg C, Zeiler F, Sebag J, Binder S. Posterior vitreomacular adhesion: a potential risk factor for exudative age-related macular degeneration? Am J Ophthalmol 2007;144:741–746.
12. Mojana F, Cheng L, Bartsch DU, et al. The role of abnormal vitreomacular adhesion in age-related macular degeneration: spectral optical coherence tomography and surgical results. Am J Ophthalmol 2008;146:218–227.
13. Schulze S, Hoerle S, Mennel S, et al. Vitreomacular traction and exudative age-related macular degeneration. Acta Ophthalmol 2008;86:468–469.

14. Lee SJ, Lee CS, Koh HJ. Posterior vitreomacular adhesion and risk of exudative age-related macular degeneration: paired eye study. Am J Ophthalmol 2009;147:621–626.
15. Ikeda T, Sawa H, Koizumi K, et al. Pars plana vitrectomy for regression of choroidal neovascularization with age-related macular degeneration. Acta Ophthalmol Scand 2000;78: 460–464.
16. Robison CD, Krebs I, Binder S, et al. Vitreomacular adhesion in active and end-stage age-related macular degeneration. Am J Ophthalmol 2009;148:79–82.
17. Hirakawa M, Tanaka M, Tanaka Y, et al. Age-related maculopathy and sunlight exposure evaluated by objective measurement. Br J Ophthalmol 2008;92:630–634.
18. Okubo A, Ito M, Sameshima M, et al. Pulsatile blood flow in the polypoidal choroidal vasculopathy. Ophthalmology 2005; 112:1436–1441.
19. Holladay JT. Proper method for calculating average visual acuity. J Refract Surg 1997;13:388–391.
20. Schulze-Bonsel K, Feltgen N, Burau H, Hansen L, Bach M. Visual acuities "hand motion" and "counting fingers" can be quantified with the Freiburg visual acuity test. Invest Ophthalmol Vis Sci 2006;47:1236–1240.
21. Sahni J, Stanga P, Wong D, Harding S. Optical coherence tomography in photodynamic therapy for subfoveal choroidal neovascularisation secondary to age related macular degeneration: a cross sectional study. Br J Ophthalmol 2005;89:316–320.
22. De La Paz MA, Itoh Y, Toth CA, Nagase H. Matrix metalloproteinases and their inhibitors in human vitreous. Invest Ophthalmol Vis Sci 1998;39:1256–1260.
23. Schmidt JC, Mennel S, Horle S, Meyer CH. High incidence of vitreomacular traction in recurrent choroidal neovascularisation after repeated photodynamic therapy. Br J Ophthalmol 2006;90:1361–1362.
24. Meyer CH, Mennel S. Vitreomacular traction, macular hole formation, and subfoveal choroidal neovascularization in a patient with age-related macular degeneration. Eye 2006; 20:1090–1092.
25. Karatas M, Ramirez JA, Ophir A. Diabetic vitreopapillary traction and macular oedema. Eye 2005;19:676–682.
26. Stefánsson E. Physiology of vitreous surgery. Graefes Arch Clin Exp Ophthalmol 2009;247:147–163.
27. Freeman WR, Falkenstein I. Avastin and new treatments for AMD: where are we? Retina 2006;26:853–858.
28. Sho K, Takahashi K, Yamada H, et al. Polypoidal choroidal vasculopathy: incidence, demographic features, and clinical characteristics. Arch Ophthalmol 2003;121:1392–1396.
29. Wen F, Chen C, Wu D, Li H. Polypoidal choroidal vasculopathy in elderly Chinese patients. Graefes Arch Clin Exp Ophthalmol 2004;242:625–629.
30. Liu Y, Wen F, Huang S, et al. Subtype lesions of neovascular age-related macular degeneration in Chinese patients. Graefes Arch Clin Exp Ophthalmol 2007;245:1441–1445.