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Intravitreal Injection of Ranibizumab for Recovery of Macular Function in Eyes With Subfoveal Polypoidal Choroidal Vasculopathy

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Purpose. To evaluate changes in macular function in eyes with polypoidal choroidal vasculopathy (PCV) after intravitreal ranibizumab (IVR) treatment.

Methods. Twenty-three eyes from 23 patients with treatment-naïve subfoveal PCV received three monthly injections of IVR, followed by as-needed injections. Visual acuity (VA); retinal thickness (measured with optical coherence tomography); macular sensitivity (measured with microperimetry); and focal macular electroretinograms (fmERGs) were evaluated both before the initiation of therapy and after 3 and 12 months.

Results. Before treatment, cystoid macular edema was observed in five eyes, serous retinal detachments in 13 eyes, and serosanguinous pigment epithelial detachments in 18 eyes. IVR treatment resulted in substantial morphological improvements and consequent marked reductions in foveal thickness ($P = 0.008$). Although logarithm of the minimum angle of resolution (logMAR) VA did not improve significantly over the 12-month study period ($P = 0.623$), the amplitude of the fmERG photopic negative response and macular sensitivity within 4° had increased significantly at 3 months ($P = 0.004$, $P = 0.026$, respectively). This trend persisted until the end of the 12-month monitoring period. Among the eyes with preexisting serous retinal detachments, those in which the detachments had resolved completely at 3 months also exhibited greater increases in fmERG a-wave amplitudes ($P = 0.048$).

Conclusions. IVR therapy resulted in morphological improvements and the partial recovery of macular function in eyes with subfoveal PCV. This therapy may improve photoreceptor function by resolving serous retinal detachments.

Keywords: polypoidal choroidal vasculopathy, electroretinography, age related macular degeneration, microperimetry, ranibizumab

In eyes with exudative AMD, intravitreal ranibizumab (IVR) therapy often induces rapid regression of classic choroidal neovascularization (CNV) and exudative changes, leading to improved visual acuity (VA).[1,2] However, there are reports that IVR has limited effects on vascular lesions associated with polypoidal choroidal vasculopathy (PCV).[3–6] In a recent study by Hikichi et al., IVR therapy achieved complete resolution of any polypoidal lesions in only 40% of eyes with PCV.[5,7] To date, the ability of IVR therapy to improve visual function in eyes with PCV is still uncertain. Efficacy and Safety of Verteporfin Added to Ranibizumab in the Treatment of Symptomatic Macular Polypoidal Choroidal Vasculopathy (EVEREST; NCT00674323) reports that eyes with PCV gained an average of 9.2 letters after 6 months of IVR treatment.[8] Another recent investigation by Matsumiya et al. reports no improvement in VA in eyes with PCV after three monthly IVR injections.[6]

VA is typically measured prior to any treatment to gauge the limits of treatment efficacy prospectively. However, standard VA measurements reflect only foveal function. Notably, because PCV can involve the larger macula, foveal function may not accurately reflect macular function in PCV. Eyes with PCV often have extensive branching vascular networks that terminate in polypoidal lesions and/or accompanying subfoveal abnormalities. These can include large serosanguinous pigment epithelial detachments (PED), extensive serous retinal detachments, and/or subretinal hemorrhage in the macular area.[9,10] Unfortunately, physicians sometimes encounter PCV patients who show no visual improvement after IVR therapy, despite remarkable morphological improvements. Additionally, although some patients report visual improvements, these were not accompanied by improved VA.

Microperimetry allows for functional evaluation of the larger macular area beyond the fovea.[11,12] During the test, an auto-tracking feature corrects for small shifts in the measurement position caused by saccadic eye movements. Focal macular ERG (fmERG) may also be useful because it allows for focal measurements of objective macular function.[13] fmERG can also provide meaningful results in patients with poor fixation or low VA. Fundus position can be monitored using an infrared camera, and stimuli can be placed manually over the fovea. Microperimetry is useful in patients with AMD,[14–22] and fmERG has been beneficial in evaluating the extent of any macular edema associated with diabetes and/or retinal vein occlusion. Terasaki et al. demonstrated a correlation between fmERG-

detected functional changes and foveal thickness in patients with diabetic macular edema.[23] More recently, we demonstrated the usefulness of fmERG in evaluating macular function in cases of macular edema associated with retinal vein occlusion.[24,25]

Although several investigators evaluated the efficacy of IVR in the treatment of PCV, all relied solely upon VA for the evaluation of retinal function.[6,7,26–29] However, some studies reported the successful use of fmERG in the evaluation of AMD patients, some of whom also had PCV.[30–32] In eyes with PCV, the efficacy of IVR therapy can only be determined by evaluating the larger macula, rather than the fovea alone. Here, we evaluated the efficacy of IVR therapy in eyes with subfoveal PCV through macular functional testing, including VA, microperimetry and fmERG. The correlations between visual function and PCV-associated morphological changes in the macula were also examined.

Methods

This prospective study was approved by the Institutional Review Board at Kyoto University Graduate School of Medicine (E-1054) and adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from each patient before any study procedures were performed. The study included 23 eyes from 23 patients with treatment-naïve subfoveal PCV. All subjects received injections of IVR at Kyoto University Hospital between December 2010 and April 2012. Patients with symptomatic subfoveal PCV with exudative or hemorrhagic features involving the macula were recruited for the study. PCV was diagnosed on the basis of indocyanine green angiography results showing polypoidal lesions and a branching vascular network that terminated in polypoidal swelling. Eyes with other macular abnormalities (e.g., AMD, pathologic myopia, idiopathic CNV, presumed ocular histoplasmosis, angioid streaks, and other secondary CNV) or a history of prior treatment for PCV were excluded from this study. Pseudophakic eyes were included, but eyes with a history of vitrectomy were excluded.

Prior to treatment at the initial study visit, each patient underwent a complete ophthalmic examination, including best-corrected VA (Landolt chart); slit-lamp biomicroscopy; indirect fundus ophthalmoscopy; optical coherence tomography (OCT); fluorescein and indocyanine green angiography; microperimetry; and fmERG. Patients meeting all inclusion and exclusion criteria received three monthly injections of IVR, followed by as-needed injections. After the initial 3 months of treatment, additional injections were given when VA declined more than 0.1 logarithm of the minimum angle of resolution (logMAR) along with signs of exudation on OCT or angiography, when retinal thickness increased >100 μm, and when subretinal fluid, subretinal hemorrhage, or active CNV persisted or developed.

Intravitreal injections were performed in a sterile manner, and prophylactic topical antibiotics were used for 1 week after each injection. Patients returned to our clinic for monthly follow-up visits for 1 year. VA, OCT, slit-lamp biomicroscopy, and indirect ophthalmoscopy were performed at each visit. Additional evaluations (microperimetry, fmERG) were carried out 3 and 12 months after the first IVR injection.

Fluorescein and Indocyanine green angiography were carried out using a confocal laser scanning system (HRA-2; Heidelberg Engineering, Heidelberg, Germany). At each scheduled visit, the entire macular area was examined with OCT (Spectralis HRA+OCT; Heidelberg Engineering). Horizontal and vertical images (averaged 100 times), centered on the fovea, were obtained at each visit and were used to measure foveal thickness. A trained grader manually measured foveal thickness at the foveal center, which was defined as the distance between the inner surface of the neurosensory retina and the subfoveal RPE. We adopted the mean foveal thickness obtained from horizontal and vertical scans.

Retinal sensitivity within the macular area was examined with a fundus-monitored microperimeter (Micro Perimeter MP-1; Nidek, Gamagori, Japan). A 4-2 staircase strategy with Goldmann III size stimuli was used to examine 57 stimulus locations within the central 10° region. Stimuli were placed according to the measurement points of the Humphrey 10-2 visual field test. Additional points throughout the macula were also examined. The illumination of the white background was set at 1.27 cd/m^2. The differential luminance, defined as the difference between the stimulus and background luminance, was 127 cd/m^2 at 0 dB stimulation. The maximum stimulus attenuation was 20 dB. The stimulus duration was 200 ms, and the fixation target varied in size (2° cross for central fixation, 4° or 6° cross for paracentral fixation) according to patient VA. There were 17 and 37 measurement points within the central 4° and 8° areas, respectively.

The fmERG recording procedure is described in detail elsewhere.[24,25] Briefly, after maximal dilatation of both eyes, a Burian–Allen bipolar contact lens electrode (Hansen Ophthalmic Laboratories, Iowa City, IA) was placed in the conjunctival sac of each eye under topical anesthesia. A chloride silver electrode was attached to the left earlobe to serve as the ground electrode. The fmERGs were elicited by a 15° circular stimulus carefully positioned over the macular area, using a prototype system (ER-80; Kowa, Tokyo, Japan). The prototype system (Kowa) consisted of an infrared camera and a stimulation system (Mayo Co., Nagoya, Japan). The luminance values for the white stimulus light and background were 181.5 cd/m^2 and 6.9 cd/m^2, respectively.

The 15° circular stimulus was carefully and constantly centered on the fovea, as observed through the infrared camera. The fmERG was recorded using a 5-Hz rectangular stimuli (100 ms light on, 100 ms light off). Eyes with PCV were examined first, before the fellow eyes. All recordings (200 responses/session) were performed in triplicate to confirm reproducibility; 600 responses were averaged by the signal processor (Neuropack MEB-2204; Nihon Kohden, Tokyo, Japan). The fmERG response was digitized at 10 kHz with a band-pass filter of 5 to 500 Hz for a-wave, b-wave, and photopic negative response (PhNR) recordings. The a-wave amplitude was measured from baseline to the peak of the a-wave, and the b-wave amplitude was measured from the trough of the a-wave to the peak of the b-wave. Based on our previous reports, PhNR amplitude was measured from the peak of the b-wave to the trough of the PhNR (Fig. 1). Latency was defined as the time from the beginning of stimulation to the peak of each component.

Best-corrected VA was measured using a Landolt chart and converted to the logarithm of the minimum angle of resolution (logMAR) for all analyses. All parameters obtained prior to IVR therapy and at 3 and 12 months after treatment initiation were compared using repeated-measures' analysis of variance and post hoc tests with the Bonferroni correction. The parameters of eyes in which serous retinal detachments had resolved completely after treatment were compared with the others using the unpaired *t*-test with Bonferroni's correction to counteract the effect of multiple comparisons. The reproducibility of the fmERG was evaluated by calculating the intraclass correlation coefficient (ICC) from the 23 fellow (non-PCV) untreated eyes. Measure reproducibility was evaluated with baseline and 3-month data. The data are presented as mean ± standard deviation. All statistical analyses were performed using statistical analysis software (PASW Statistics 17; SPSS,

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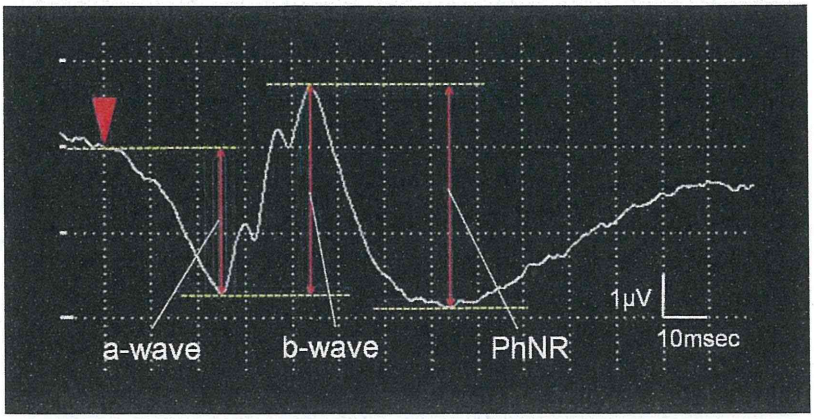

FIGURE 1. A typical fmERG obtained from a healthy eye. The *red arrowhead* indicates the beginning of the stimulus.

Inc., Chicago, IL). A P value of less than 0.05 was considered statistically significant.

RESULTS

Twenty-three eyes from 23 patients (18 men and 5 women) with subfoveal PCV were included. The average age was 74.4 ± 6.9 years (range, 63–88 years). All patients were Japanese. Table 1 summarizes the baseline VA, foveal thickness, mean retinal sensitivities (as measured with the MP-1), and fmERG parameters. Before the initiation of IVR therapy, all eyes had exudative changes with a branching vascular network terminating in polypoidal lesions. The greatest linear dimension was 2812 ± 1550 μm, and foveal thickness averaged 257 ± 165 μm. Serosanguinous PED was seen in 18 eyes (78%); serous retinal detachment, 13 eyes (57%); and cystoid macular edema, in 5 eyes (22%).

After three monthly scheduled IVR doses, most eyes showed a reduction in exudative abnormalities. Serosanguinous PED remained in nine eyes (39%); serous retinal detachment remained in four eyes (17%); and cystoid macular edema remained in one eye (4%). Of the 13 eyes with preexisting serous retinal detachment, 10 achieved complete resolution. Subretinal fluid was observed at 3 months in one eye without serous retinal detachment at baseline. The eye's foveal thickness had decreased significantly to 164 ± 78 μm (P = 0.015), even though there was no significant improvement in VA (P = 0.444). However, there were significant improvements in retinal sensitivity within 4° (P = 0.041, Fig. 2) and significant increases in PhNR amplitude at 3 months (P = 0.003, Fig. 2). The latency of the fmERG components (a-wave, b-wave, PhNR) did not change significantly from baseline values (see Supplementary Fig. S1).

The mean number of IVR injections over the 12-month follow-up period averaged 6.1 ± 2.8 injections (range, 3–11 injections). Two patients withdrew from the study before the end of the 12-month period because of systemic problems. One individual suffered lymphoma at 10 months, and the other required treatment for chronic heart failure at 11 months. Although the VA did not change, the foveal thickness, retinal sensitivity, and PhNR amplitude improvements seen at 3 months remained at 12 months (Table 1, Fig. 2; see Supplementary Fig. S2). Moreover, serosanguinous PED remained in nine eyes (43%); serous retinal detachment remained in 5 eyes (24%); and cystoid macular edema remained in 3 eyes (14%).

Next, we examined how the exudative changes affected macular function before and after the three initial IVR injections. Table 2 shows the changes in VA, macular sensitivity, and fmERG parameters associated with IVR therapy that did (n = 10 eyes, Fig. 3) or did not (n = 13 eyes, Fig. 4) exhibit complete resolution of preexisting serous retinal detachments. The changes in VA were similar in both groups. Macular sensitivity tended to increase more in eyes with retinal detachments that resolved completely, but this difference was

TABLE 1. VA, Foveal Thickness, Retinal Sensitivity, and fmERG of Eyes With Subfoveal PCV Before and After Treatment With Ranibizumab

	Before Treatment	3 Months	12 Months	P Value*
Visual acuity, logMAR	0.31 ± 0.32	0.28 ± 0.31	0.30 ± 0.34	0.623
Foveal thickness, μm	257 ± 165	164 ± 78	175 ± 70	0.008
Mean retinal sensitivity examined with microperimetry, dB				
Center	3.5 ± 3.5	5.9 ± 5.1	6.7 ± 4.4	0.024
Within 4°	5.1 ± 4.0	7.4 ± 4.5	7.6 ± 3.8	0.026
Within 8°	6.8 ± 4.6	8.6 ± 4.6	8.9 ± 3.6	0.061
Amplitude of fmERG, μV				
a-wave	0.81 ± 0.38	0.77 ± 0.42	0.86 ± 0.28	0.820
b-wave	1.46 ± 0.71	1.73 ± 0.82	1.73 ± 0.61	0.185
PhNR	1.31 ± 0.71	1.89 ± 0.89	1.68 ± 0.74	0.004
Latency of fmERG, ms				
a-wave	24.1 ± 2.9	24.7 ± 2.5	24.1 ± 2.0	0.831
b-wave	45.9 ± 3.9	44.3 ± 2.9	44.7 ± 3.4	0.077

* Repeated ANOVA.

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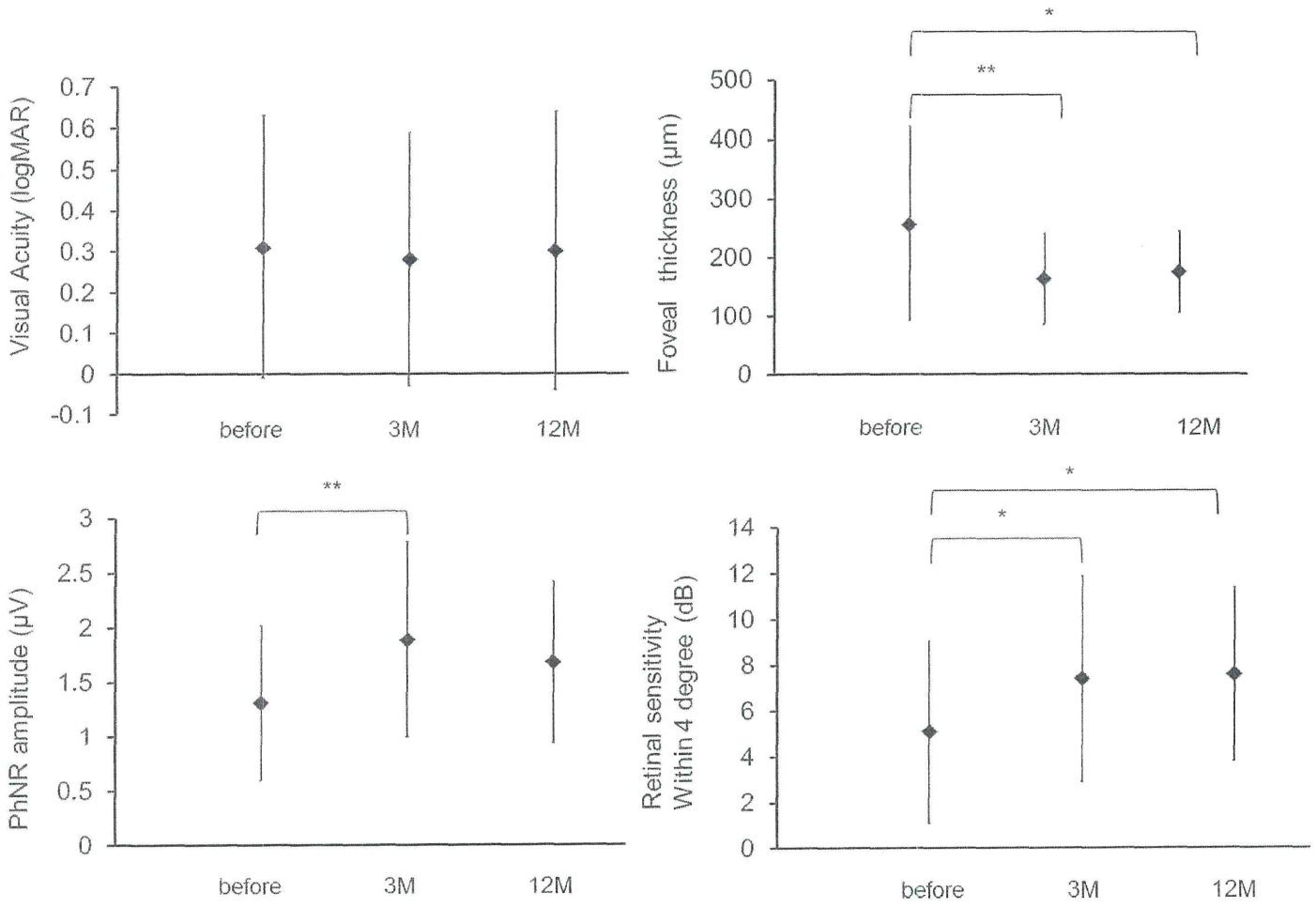

FIGURE 2. Visual acuity, foveal thickness, amplitude of the fmERG, PhNR, and mean retinal sensitivity after initiating treatment with IVR were examined within a 4° field. The values shown represent baseline, 3-month, and 12-month time points. $^{*}P < 0.05$. $^{**}P < 0.01$ in a post hoc test using Bonferroni's correction. *Error bars*: SD.

TABLE 2. Changes in VA, Retinal Sensitivity, and fmERG Parameters After Three Monthly Treatments of Subfoveal PCV With Ranibizumab

	Complete Resolution of Preexisting Serous Retinal Detachment (n = 10)	Remaining Eyes (n = 13)	P Value*
Change in visual acuity, logMAR	−0.05 ± 0.13	−0.02 ± 0.25	0.751
Change in retinal sensitivity, dB			
Center point	4.2 ± 5.8	0.9 ± 5.4	0.528
Within 4°	4.5 ± 3.3	0.6 ± 4.9	0.129
Within 8°	4.0 ± 2.8	0.1 ± 4.3	0.069
Change in amplitude of fmERG, μV			
a-wave	0.19 ± 0.44	−0.21 ± 0.28	0.048
b-wave	0.62 ± 0.52	0.01 ± 0.65	0.072
PhNR	0.79 ± 0.80	0.42 ± 0.73	0.792
Change in latency of fmERG, ms			
a-wave	4.9 ± 12.4	0.9 ± 6.7	0.422
b-wave	10.7 ± 25.4	−6.9 ± 18.3	0.134

* Unpaired *t*-test with Bonferroni correction.

not statistically significant ($P = 0.069$, Table 2). However, these eyes did show a significantly greater improvement in a-wave amplitudes than did the other eyes ($P = 0.048$).

The fmERG measurements obtained from these patients were reproducible.

We calculated the ICCs from fmERG recordings obtained from the 23 untreated eyes before and after IVR treatment of the fellow eye. Initial VA in these contralateral eyes was 0.12 ± 0.43 (slightly less than 20/25). At the initial visit, the a-wave, b-wave, and PhNR amplitudes were 1.24 ± 0.68 μV, 2.58 ± 1.21 μV, and 2.65 ± 1.14 μV, respectively. At 3 months, the a-wave, b-wave, and PhNR amplitudes were 1.41 ± 0.70 μV, 2.91 ± 1.33 μV, and 2.88 ± 1.29 μV, respectively. The latencies of the a-wave, b-wave, and PhNR were 23.2 ± 1.3 ms, 42.9 ± 2.3 ms, and 76.5 ± 7.7 ms, respectively, as measured at the initial visit. At 3 months, the latencies of the a-wave, b-wave, and PhNR were 23.7 ± 1.6 ms, 44.1 ± 2.7 ms, and 74.8 ± 6.4 ms, respectively. Table 3 shows the ICCs for a-wave, b-wave, and PhNR amplitudes. While the ICC of PhNR latency was relatively low (0.411), all other parameter ICCs were >0.7.

DISCUSSION

Despite substantial morphological improvements, VA did not improve significantly after IVR therapy for the treatment of PCV. Only a slight improvement in VA was observed, probably because the baseline VA was relatively good (better than 0.5 on a Landolt chart [Snellen equivalent better than 20/40]) in 14 of the 23 patients. In addition, since VA only represents foveal function, this measurement may not accurately reflect improved function in other parts of the macula. Because PCV is frequently accompanied by an extensive branching vascular network, a large serosanguinous PED or an extensive serous retinal detachment in the macular area, the physician must examine all areas of the macula (rather than just the central fovea) when evaluating treatment efficacy. Macular sensitivity, as measured in these patients using microperimetry and fmERG, revealed significant functional recovery after IVR therapy.

We report 2 main findings in this study. First, the improvement in macular function occurred rapidly, after only three monthly IVR injections. This improvement was maintained, with additional as-needed IVR injections, for the entire 12-month study period. Although the efficacy of anti-VEGF agents in improving VA was limited, the associated reduction in exudative changes likely facilitated the recovery of macular function. Recently, Tomita et al. reported the substantial regression of polypoidal lesions, along with good visual recovery, in PCV patients treated with photodynamic therapy in combination with IVR.[33] Because vascular component regression was limited with IVR monotherapy, further long-term studies with combination therapies are needed.

We also observed that the fmERG a-wave amplitude showed considerable patient-to-patient variation. On average, the mean change from baseline was greater for the b-wave or PhNR as compared with the a-wave amplitude (Table 1). However, those eyes in which preexisting serous retinal detachments resolved completely exhibited greater a-wave recovery than the eyes with incomplete resolution (Table 2). Interestingly, complete resolution was also associated with significantly smaller a-waves at baseline (0.61 ± 0.44 μV vs. 0.96 ± 0.26 μV, $P = 0.025$). This indicates that PCV-associated serous retinal detachments directly affect the photoreceptors and that the resolution of serous retinal detachments can facilitate the recovery of a-wave amplitudes and, thus, photoreceptor function. The cases shown in Figures 3 and 4 demonstrate the fmERG improvement and show how this improvement was dependent upon macular morphology.

In our previous study, the fmERG reproducibility of the a-wave was insufficient, which led us to conclude that PhNR amplitude was a more reproducible fmERG measure.[24] However, in the current study, we decreased the stimulus time (from 150 ms to 100 ms) and increased the stimulus frequency (from 2 to 5 Hz) for fmERG recordings. With these modifications, we achieved equivalent reproducibility for all waves. We therefore believe that the a-wave, b-wave, and PhNR measurements can be performed accurately and repeatedly.

TABLE 3. ICC for Each Parameter of fmERG of Untreated Contralateral Eyes

Parameter	ICC
A-wave amplitude	0.711
B-wave amplitude	0.760
PhNR amplitude	0.745
A-wave latency	0.716
B-wave latency	0.715
PhNR latency	0.411

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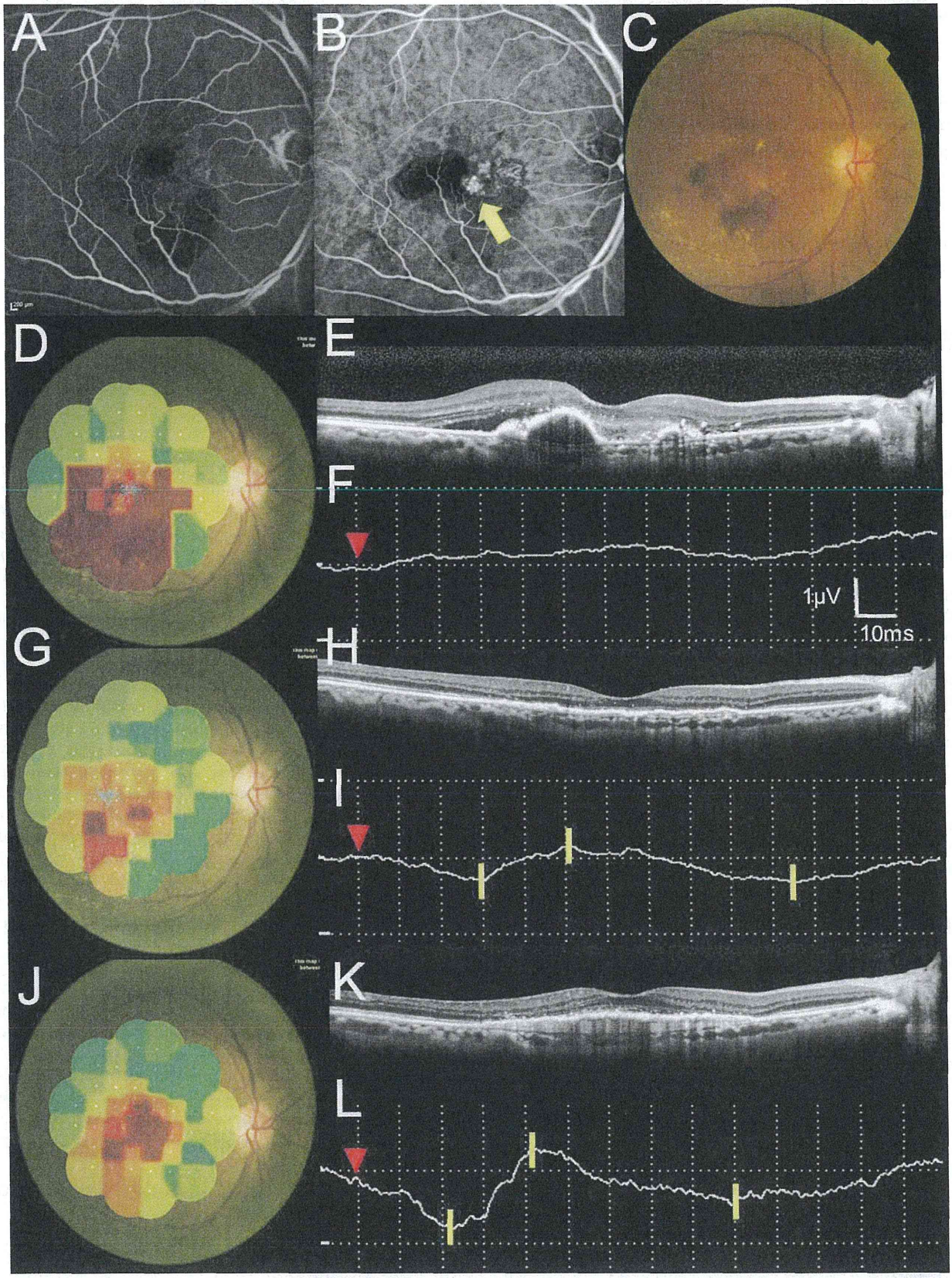

FIGURE 3. Complete resolution of serous retinal detachment following intravitreal injections of ranibizumab in an eye with PCV. The patient was an 81-year-old man with an 8-month history of decreased visual acuity (0.5 on the Landolt chart) in the right eye. The baseline fluorescein angiogram (**A**), indocyanine green angiogram (**B**), and fundus photograph (**C**) are shown. The indocyanine green angiogram showed a branching vascular network that terminated in polypoidal lesions (*yellow arrow*). Baseline, 3-month, and 12-month retinal sensitivity maps ([**D**, **G**, **J**], respectively); horizontal foveal OCT scans ([**E**, **H**, **K**], respectively); and fmERGs ([**F**, **I**, **L**], respectively) are shown.

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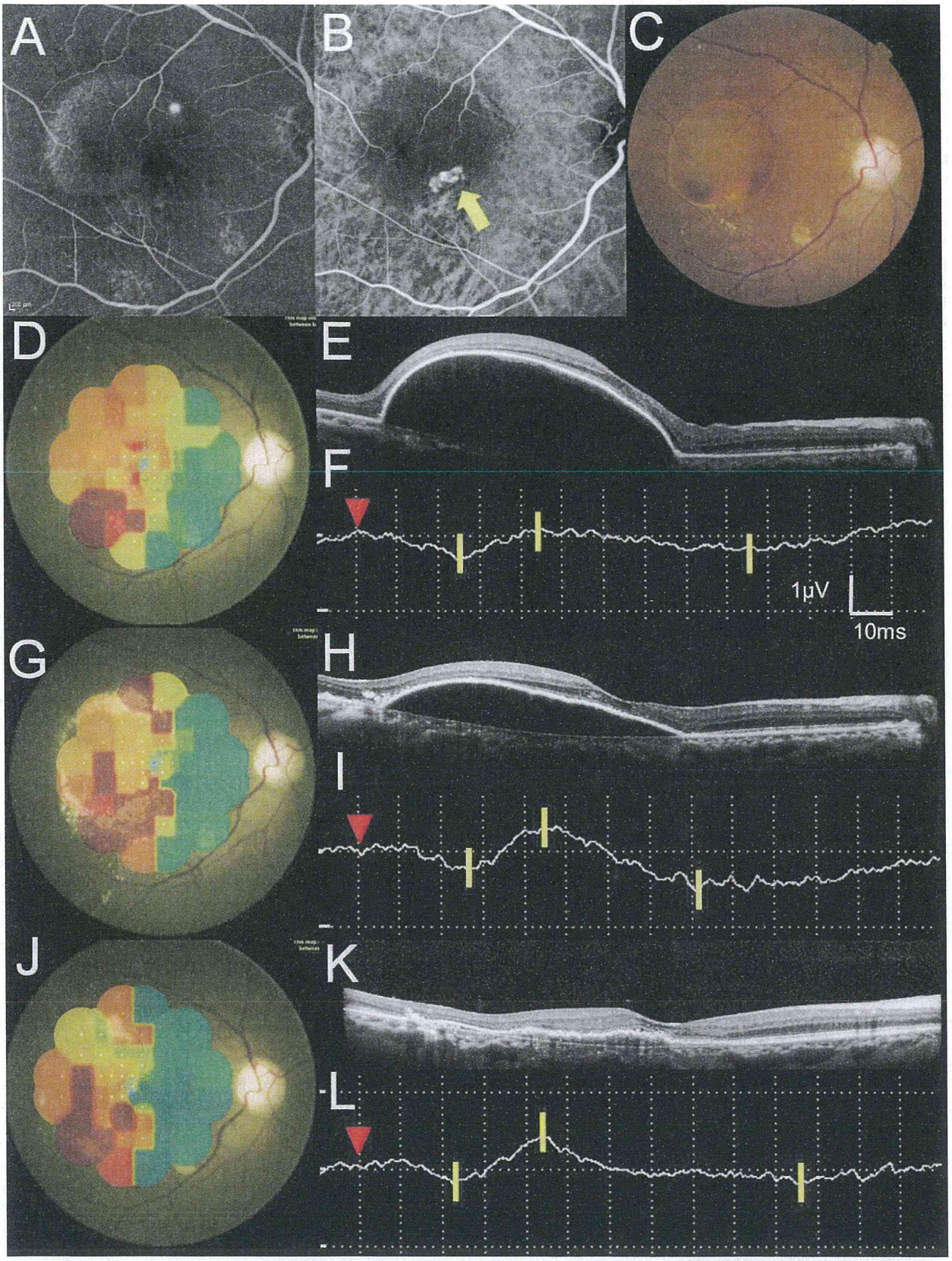

FIGURE 4. Resolution of a serosanguinous PED following intravitreal injections of ranibizumab. The patient was a 71-year-old man with a 6-month history of decreased visual acuity (0.3 on the Landolt chart) in the right eye. The baseline fluorescein angiogram (**A**), indocyanine green angiogram (**B**), and fundus photograph (**C**) are shown. The indocyanine green angiogram showed a branching vascular network that terminated in polypoidal lesions (*yellow arrow*). Baseline, 3-month, and 12-month retinal sensitivity maps ([**D**, **G**, **J**], respectively); horizontal foveal OCT scans ([**E**, **H**, **K**], respectively); and fmERGs ([**F**, **I**, **L**], respectively) are shown.

The main limitations of the current study are the small sample size and lack of healthy control data. VA was measured with methods that are less sensitive than those used previously less (e.g., Landolt chart versus Early Treatment Diabetic Retinopathy Study [ETDRS] chart), which might have interfered with the statistical significance of our results. The noncomparative design of this study also rendered it impossible to determine whether IVR monotherapy can adequately treat PCV. Despite these limitations, the treated eyes did show morphological improvements and increased macular function after only three monthly injections. Macular function did not worsen, even after 12 months. Because fmERG and microperimetry reflect the function of the entire macular area, rather than the fovea alone, they may be beneficial functional indices for use in PCV patients with neovascular lesions and extensive exudative changes. Finally, our findings suggest that IVR therapy allows for the recovery of photoreceptor function. This effect appears to be mediated by the reabsorption of subretinal fluid in eyes with extensive serous retinal detachment secondary to PCV.

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