



One-year outcome of combination therapy with intravitreal anti-vascular endothelial growth factor and photodynamic therapy in patients with pachychoroid neovascularopathy

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Abstract

Purpose To identify the functional outcome and evaluate the morphologic changes of patients with pachychoroid neovascularopathy (PNV) undergoing intravitreal anti-vascular endothelial growth factor (VEGF) combined with photodynamic therapy (PDT) at the 1-year follow-up.

Methods We retrospectively studied all the treatment-naïve PNV patients who were scheduled to undergo combination therapy between September 2017 and November 2018. All the patients received three consecutive monthly injections of 0.5 mg/0.05 mL ranibizumab as loading doses. Full-dose PDT was performed within 1 week of the first injection. Retreatment was allowed if evidence of clinical deterioration or the presence of fluid on spectral-domain optical coherence tomography examination performed at the 1-month follow-up was noted. The best-corrected visual acuity (BCVA) was compared before treatment and at 3, 6, and 12 months after the initial treatment. Changes in the central foveal thickness (CFT), central choroidal thickness (CCT), and retreatment rate during the maintenance phase were also evaluated.

Results Eleven eyes were enrolled in this study. Significantly, better BCVA was observed at 12 months than at baseline ($P = 0.010$). The mean CFT significantly decreased from 331 ± 93 to 237 ± 72 μm at 12 months ($P < 0.001$). The mean CCT also significantly decreased from 361 ± 74 to 310 ± 83 μm at 12 months ($P < 0.001$). The mean number of injections per eye was 3.9 ± 1.3 during the follow-up period. A total of 45.5% (5 / 11) of the patients required retreatment during the maintenance phase.

Conclusion Anti-VEGF combined with full-dose PDT was well tolerated and appeared to be effective treatment for patients with treatment-naïve PNV. Combination therapy might also reduce the treatment burden with fewer injections in patients with PNV.

Keywords Intravitreal injection · Pachychoroid neovascularopathy · Photodynamic therapy · Vascular endothelial growth factor

Introduction

Choroidal neovascularization (CNV) is a severe complication that induces vision loss in chorioretinal diseases [1]. Type 1 NV is the most common subtype of neovascularization in age-related macular degeneration (AMD) and is characterized by

pathologic angiogenesis below the retinal pigment epithelium (RPE) [2, 3]. Other conditions that are commonly associated with type 1 NV include the pachychoroid disease spectrum [4–6]. Pachychoroid neovascularopathy (PNV), included in the pachychoroid-related spectrum, is characterized by type 1 NV caused by a pachychoroid-driven process involving choroidal vascular hyperpermeability (CVH) manifested by thickened choroid and dilated choroidal vessels (pachyvessels) [7].

AMD is most frequently treated with anti-vascular endothelial growth factor (VEGF) agents that have demonstrated efficacy in improving visual acuity outcomes [8, 9]. The pathophysiology of PNV has been defined as type 1 NV overlying large choroidal vessels, often misinterpreted as AMD. Therefore, it is predicted that anti-VEGF agents would be useful for the treatment of PNV. In fact, many studies have

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reported the efficacy of intravitreal injection of anti-VEGF for PNV [10, 11]. However, the need for frequent visits and the burden of injections are issues that require resolution.

Photodynamic therapy (PDT) is known to decrease the choroidal thicknesses to suppress CVH [12]. Therefore, it is expected that anti-VEGF agents combined with PDT may be effective with reduced number of injections in patients with PNV. However, combined therapy for PNV have not been identified. The purpose of this report was to identify the functional outcome and assess morphologic changes of patients with PNV undergoing intravitreal anti-VEGF combined with PDT at the 1-year follow-up.

Patients and methods

We retrospectively reviewed the medical records of 11 eyes from 10 treatment-naïve Japanese patients with PNV treated with anti-VEGF combined with PDT at the Yokohama City University Medical Center between September 2017 and November 2018. This study design was approved by the institutional review board at the Yokohama City University Medical Center. It also followed the tenets of the Declaration of Helsinki.

The inclusion criteria were the presence of PNV determined by clinical, spectral-domain optical coherence tomography (SD-OCT), fluorescein angiography (FA), indocyanine green angiography (ICGA), and OCT angiography (OCTA) findings. PNV was defined as a form of type 1 NV, occurring over the areas of pachyvessels that exceeded the choroidal diameter seen in normal eyes, with exudative changes such as fluid (subretinal fluid, intraretinal fluid, and sub-RPE fluid), fibrin, and hemorrhage [6]. In areas overlying pachyvessels, attenuation of choriocapillaris and dilation of Haller vessels were observed even if central choroidal thickness (CCT) are less than 300 μm . All the patients had no polypoidal lesions before the treatment and also no history of central serous chorioretinopathy (CSC) in the past. Patients who had a history of previous treatment for PNV (i.e., laser photocoagulation, PDT, the intravitreal injection of anti-VEGF agents, or intravitreal steroids) were excluded from this study.

All eyes received three consecutive monthly intravitreal injections of 0.5 mg/0.05 mL ranibizumab (Lucentis®; Novartis Pharma AG, Basel, Switzerland, and Genentech, South San Francisco, CA, USA) combined with PDT as an induction treatment. Full-dose PDT was performed within 1 week of the first intravitreal injection. Verteporfin was administered over 10 min. Fifteen minutes after the intravenous infusion started, a 689-nm laser was applied for 83 s to deliver 50 J/cm². The greatest linear dimension (GLD) was determined to cover the

abnormality vascular network. During the maintenance phase, retreatment of anti-VEGF injection was allowed if recurrent fluid accumulation and fibrin on OCT imaging; clinically detectable hemorrhage; or visual acuity loss were seen. Single anti-VEGF combined with PDT was considered if persistent exudative findings were seen in spite of two consecutive monthly injections.

The main outcome measure was the best-corrected visual acuity (BCVA) between the pre- and postoperative BCVA at 3, 6, and 12 months after the initial treatment. The BCVA was converted to the logarithm of the minimum angle of resolution (logMAR) equivalent for the statistical analysis. The secondary outcome was the comparison of the change in the central foveal thickness (CFT) and central choroidal thickness (CCT) at baseline, 3, 6, and 12 months. The recurrence rate and mean number of injections during the follow-up periods were also analyzed. Digital simultaneous FA and ICGA (SPECTRALIS Product Family Version 5.3; Heidelberg Engineering, Germany) and SD-OCT (Heidelberg Spectralis HRA + OCT; Heidelberg Engineering, Germany) have been used to evaluate these changes.

The pre- and postoperative visual acuity was compared using one-way ANOVA. CFT and CCT were also evaluated using the one-way ANOVA. The statistical analyses were performed using the Ekuseru-Toukei 2012 (Social Survey Research Information, Tokyo, Japan). *P* value < 0.05 was considered to denote statistical significance.

Results

The baseline characteristics and clinical data for each patient before and after treatment are shown in Table 1. Of the 10 patients included in the series, 8 were men and 2 were women. The patient age ranged 61–82 years (mean age, 71.9 \pm 6.7 years). The mean GLD was 2138 \pm 674 μm .

The mean logMAR visual acuity at the baseline was 0.12 \pm 0.17. The mean logMAR BCVA values at 3, 6, and 12 months after the initial injection were 0.10 \pm 0.16, 0.03 \pm 0.18, and 0.01 \pm 0.13, respectively. The postoperative BCVA at 12 months, but not at 3 and 6 months, showed a significant improvement, compared with the preoperative visual acuity (*P* = 1.000, *P* = 0.076, and *P* = 0.010 at 3, 6, and 12 months, respectively) (Fig. 1).

The mean baseline CFT was 331 \pm 93 μm . The mean CFT at 3, 6, and 12 months after the initial treatment was 219 \pm 95, 231 \pm 89, and 237 \pm 72 μm , respectively. The mean CFT at 3, 6, and 12 months showed significant decreasing, compared with those at baseline (*P* < 0.001, respectively) (Fig. 2).

The mean CCT at baseline was 361 \pm 74 μm . The mean CCT at 3, 6, and 12 months after the initial injection was 286

Table 1 The baseline characteristics and clinical data for each patient before and after treatment

Case	Patient	R/ L	Age	Gender	CFT(μm)		CCT(μm)			GLD (μm) of injection	Number of injection	Switching of injection	Additional PDT	Best-corrected visual acuity					
					Baseline		Baseline							Baseline					
					3 months	6 months	12 months	3 months	6 months					12 months	3 months	6 months	12 months		
1	1	L	69	F	192	170	168	155	485	444	437	441	1730	3		20/16	20/25	20/16	20/16
2	2	L	65	M	476	454	451	344	287	246	265	217	1900	7	1	20/25	20/16	20/16	20/12
3	3	L	68	M	234	151	163	190	289	134	145	190	1900	3		20/16	20/25	20/16	20/20
4	4	L	71	M	265	183	205	233	309	245	296	283	2750	4		20/30	20/25	20/20	20/16
5	5	R	71		342	170	173	299	362	277	287	318	2190	5		20/50	20/50	20/63	20/40
6	6	R	76	M	245	141	158	172	420	282	293	365	2020	3		20/40	20/32	20/25	20/20
7	7	R	77	M	469	193	203	210	421	358	351	327	3900	3		20/25	20/16	20/20	20/16
8	8	R	61	F	382	346	321	378	419	381	397	394	2210	5		20/40	20/30	20/25	20/25
9	9	L	82	M	341	206	219	219	361	282	323	323	1530	3		20/25	20/20	20/20	20/20
10	10	R	69	M	389	196	286	203	379	323	344	358	1750	4		20/16	20/16	20/12	20/16
11	11	L	82	M	310	200	197	207	238	179	172	172	1640	3		20/32	20/40	20/16	20/30

R right, L left, F female, M male, CFT central foveal thickness, CCT central choroidal thickness, GLD greatest linear dimension, PDT photodynamic therapy

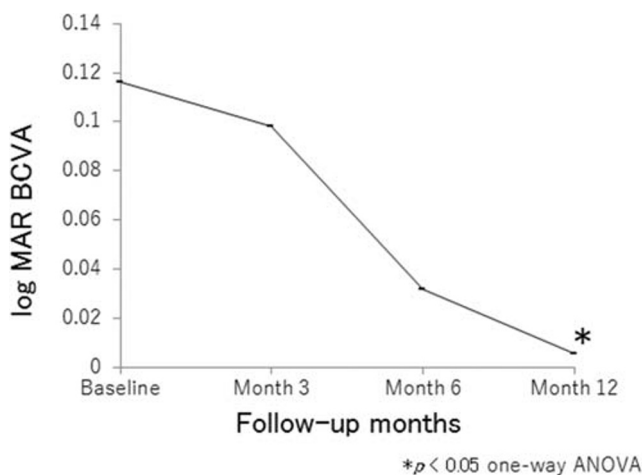


Fig. 1 Changes in best-corrected visual acuity (BCVA) during the 12-month follow-up period. The postoperative BCVA at 12 months, but not at 3 and 6 months, had improved significantly, compared with the preoperative visual acuity ($P = 1.000$, $P = 0.076$, and $P = 0.010$ at 3, 6, and 12 months, respectively)

± 89 , 301 ± 87 , and $310 \pm 83 \mu\text{m}$, respectively. The mean CCT at 3, 6, and 12 months had also decreased significantly compared with those at baseline ($P < 0.001$, respectively) (Fig. 3).

In the maintenance phase, 5 of the 11 eyes (45.5%) exhibited recurrence during the maintenance phase. The mean number of injections per eye was 3.9 ± 1.3 during the follow-up period. Only 1 eye showed persistent fluid in spite of continuous injections; therefore, anti-VEGF was switched from ranibizumab to aflibercept, and PDT was additionally administered.

No incidence of serious ocular adverse effects, such as endophthalmitis, rhegmatogenous retinal detachment, or any nonocular adverse events, occurred. Figures 4 and 5 show the cases of PNV treated with anti-VEGF combined with PDT.

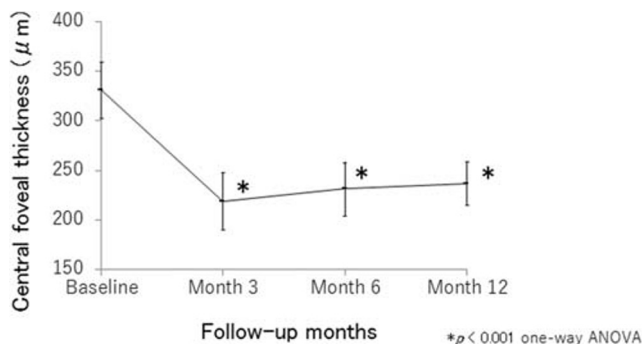


Fig. 2 Changes in the central foveal thickness (CFT) during the 12-month follow-up period. The mean CFT at 3, 6, and 12 months decreased significantly, compared with those at baseline ($P < 0.001$, respectively)

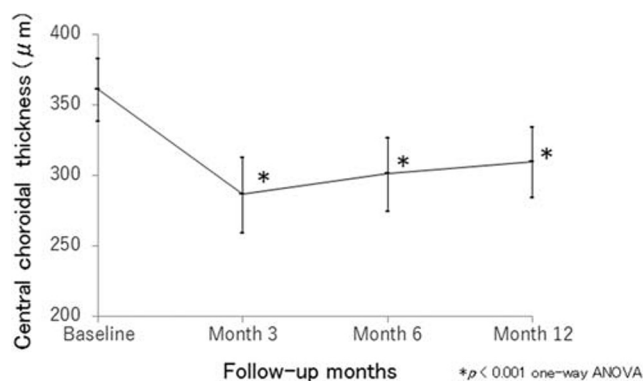


Fig. 3 Changes in the central choroidal thickness (CCT) during the 12-month follow-up period. The mean CCT at 3, 6, and 12 months decreased significantly, compared with those at baseline ($P < 0.001$, respectively)

Discussion

Our study demonstrated that ranibizumab combined with full-dose PDT was well tolerated and had efficacy in improving vision for treatment-naïve PNV during the 1-year follow-up examination. Furthermore, combined therapy showed improving exudative findings and reduced CCT with low rate of retreatment. There were few previous reports to investigate the functional outcome and morphologic changes of anti-VEGF combined with PDT in treatment-naïve patients with PNV [13].

The etiology of PNV has not been identified and has often mimicked AMD. However, patients with PNV are reported to have no evidence of AMD, such as soft drusen or fundus tessellation [7]. Furthermore, a recent report described that PNV was genetically different from neovascular AMD [14]. The current understanding of the pathogenesis of PNV involves the pachychoroid-related spectrum of diseases [4–6] including CSC [15, 16] and polypoidal choroidal vasculopathy (PCV) [5, 7]. PNV occurs due to a pachychoroid-driven process involving choroidal congestion and CVH [7]. These changes can cause compression of the choriocapillaris, leading to a progression of type 1 NV through ischemic mechanism related to increased VEGF. Therefore, it is reasonable that anti-VEGF agents would be effective in suppressing type 1 NV due to PNV, resulting in improved exudative findings.

Furthermore, regarding PCV, part of the pachychoroid disease spectrum, Maruko et al. reported that PDT has reduced choroidal thickening [12]. The additional performance of PDT decreases the choroidal thickness, potentially leading to the suppression of CVH and mechanical pressure of pachyvessels to the RPE itself. Therefore, we expected the synergistic effect of anti-VEGF agents and PDT for PNV treatment.

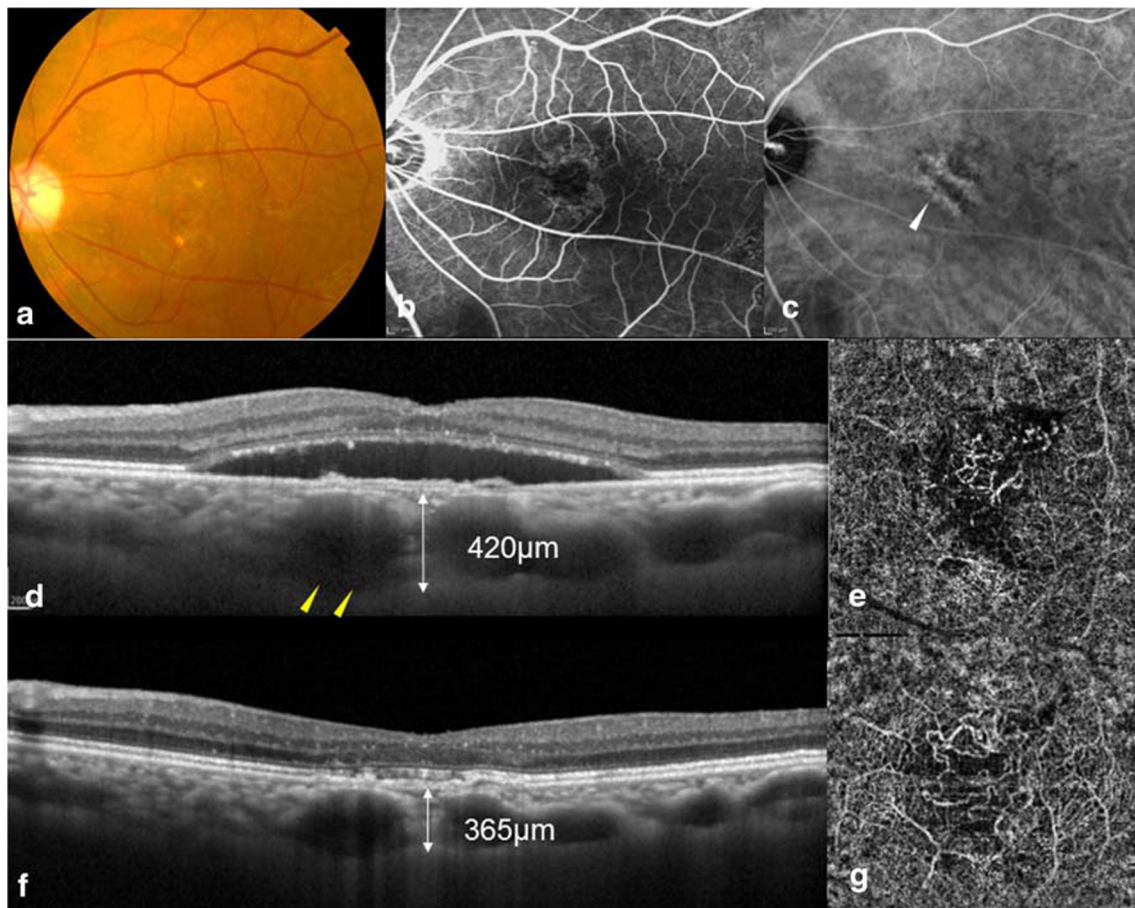


Fig. 4 The case of a 76-year-old man who was no recurrence in the maintenance phase. **a** Color fundus photograph shows the area of RPE alteration in the macula. The best-corrected visual acuity (BCVA) was 20/40. **b** Early-phase fluorescein angiography reveals hyperfluorescent area corresponding to type 1 neovascularization (NV). **c** Early-phase indocyanine green angiography exhibits dilated choroidal vessels (white arrowhead). **d** Optical coherence tomography (OCT) at baseline shows type 1

NV with pachyvevessels (yellow arrowheads). The choroidal thickness (CCT) was 420 μm . **e** OCT angiography (OCTA) shows the flow signal of NV clearly. Combined therapy using ranibizumab was performed. **f** One year after the initial treatment, OCT shows the decrease of CCT to 365 μm without exudative changes. **g** OCTA shows persistent flow signal of NV. The patient's BCVA improved to 20/20

Some patients with PNV need frequent anti-VEGF retreatment in the maintenance phase. A previous report has described that 64% (35 of 54 eyes) required additional treatment with anti-VEGF (ranibizumab and aflibercept) after the maintenance phase during the 12-month follow-up [10]. Another study has reported that 59% (13 of 22 eyes) needed additional treatment with anti-VEGF monotherapy [11]. In this study, 45.5% (5 of 11 eyes) showed that recurrence during the maintenance phase was lower than that in previous studies. The EVEREST II trial for PCV patients showed that the combined therapy of ranibizumab and PDT was superior to ranibizumab monotherapy in BCVA with fewer injections (4 versus 7 during 1 year) [17]. The Fujisan study in Japan also showed that initial PDT group led to significantly fewer additional ranibizumab treatments in the maintenance phase than

later PDT group [18]. Combination therapy, especially using PDT as the initial treatment, may help reduce the treatment burden not only in patients with PCV but also in those with PNV.

The limitations of this study include its retrospectively nature and its small sample size. Furthermore, there was the lack of a control group of patients who had anti-VEGF monotherapy. The results of the current study require validation by further comparative studies involving a larger sample size. Finally, genetic differences between Japanese and Caucasian patients may underlie. Therefore, results in this study are possible to apply to a relatively homogenous Asian population; however, the same results may not apply to Caucasian patients with the same lesions.

In conclusion, ranibizumab combined with full-dose PDT was well tolerated and a highly effective treatment option in

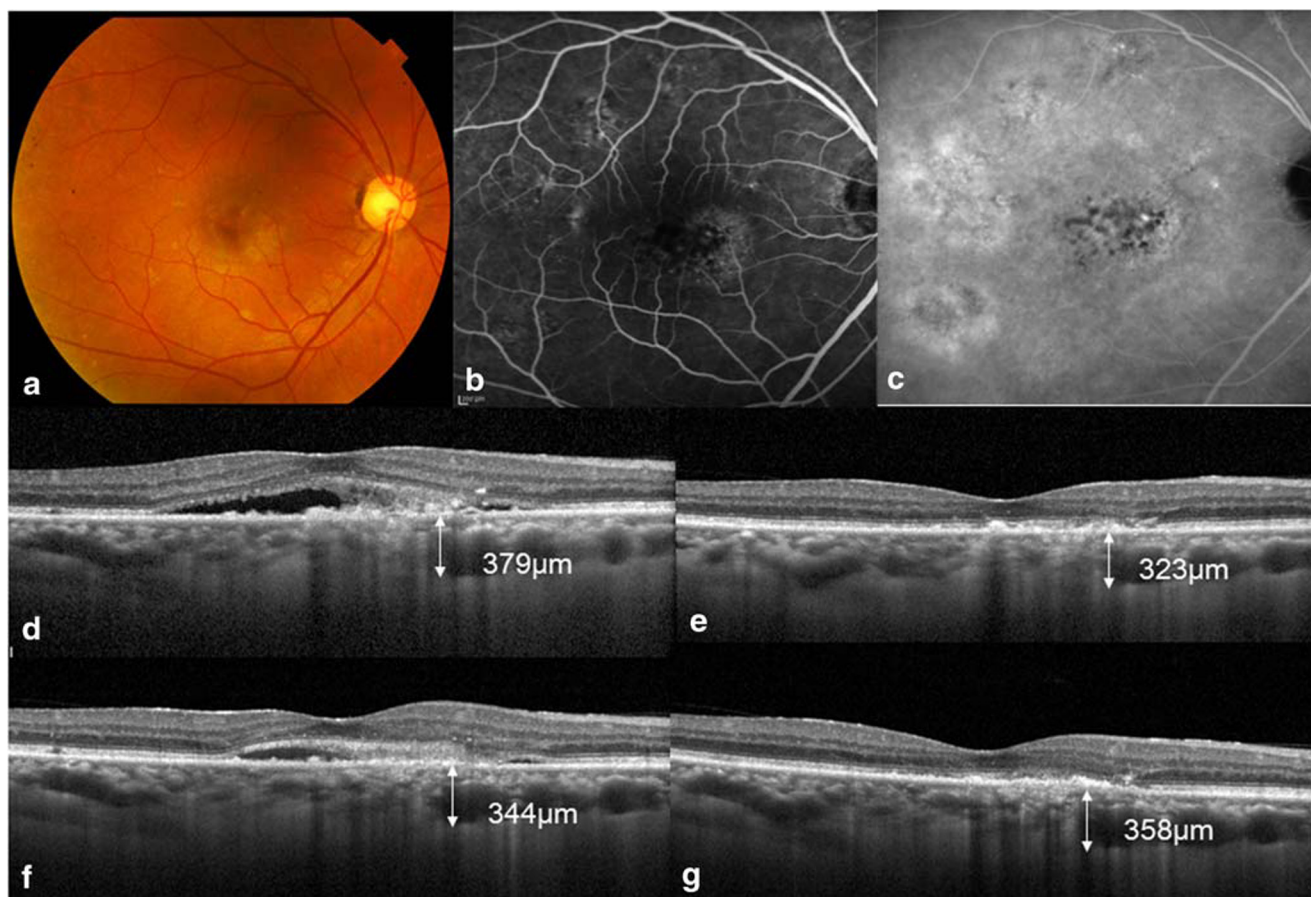


Fig. 5 A 69-year-old man who required one additional treatment with ranibizumab due to the poor response. **a** Color fundus photograph shows the area of RPE alteration in the macula. The best-corrected visual acuity (BCVA) was 20/16. **b** Early-phase fluorescein angiography demonstrates hyperfluorescent area corresponding to type 1 neovascularization (NV). **c** Late-phase indocyanine green angiography shows focal hyperfluorescent spots with choroidal vascular hyperpermeability. **d** Optical coherence tomography (OCT) at baseline shows type 1 NV, and choroidal thickness is 379 μm .

Combined therapy using ranibizumab was performed. **e** Three months after the initial treatment, OCT shows the decrease of central choroidal thickness to 323 μm without exudative changes. The BCVA was maintained at 20/16. **f** Seven months after the initial treatment, subretinal fluid recurred, and additional ranibizumab was administered. **g** Twelve months after the initial treatment, OCT shows no exudative changes, and choroidal thickness was 358 μm . The patient's BCVA was maintained at 20/16

treatment-naïve patients with PNV. Combination therapy might also reduce the treatment burden with fewer injections in patients with PNV.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the Yokohama City University and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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