



CLINICAL INVESTIGATION

One-year outcomes of half-fluence photodynamic therapy combined with intravitreal injection of aflibercept for pachychoroid neovascularopathy without polypoidal lesions

Hidetaka Matsumoto¹ · Ryo Mukai¹ · Yuka Kikuchi¹ · Masahiro Morimoto¹ · Hideo Akiyama¹

Received: 4 June 2019 / Accepted: 8 January 2020 / Published online: 3 February 2020
© Japanese Ophthalmological Society 2020

Abstract

Purpose To evaluate the 1-year efficacy of half-fluence photodynamic therapy (HFPDT) combined with intravitreal aflibercept injection on treatment-naïve pachychoroid neovascularopathy (PNV) without polypoidal lesions.

Study design Retrospective, interventional case series

Patients and methods We retrospectively studied 21 eyes with treatment-naïve PNV and assessed the best-corrected visual acuity (BCVA), central macular thickness (CMT), central choroidal thickness (CCT), pachyvessel vertical diameter, and choroidal neovascularization thickness (CNVT) at the fovea over a 12-month period.

Results The median BCVA was 0.15 at baseline, 0.00 ($P < .05$) at 3 months, 0.05 at 6 months, and -0.08 ($P < .05$) at 12 months. The BCVA was significantly improved at 3 months and 12 months as compared with the baseline BCVA. The median CMT was 230 μm at baseline, 140 μm ($P < .01$) at 3 months, 150 μm ($P < .01$) at 6 months, and 150 μm ($P < .01$) at 12 months. The median CCT was 386 μm at baseline, 347 μm ($P < .01$) at 3 months, 331 μm ($P < .01$) at 6 months, and 352 μm ($P < .01$) at 12 months. The median pachyvessel vertical diameter was 309 μm at baseline, 246 μm ($P < .01$) at 3 months, 232 μm ($P < .01$) at 6 months, and 242 μm ($P < .01$) at 12 months. The median CNVT was 28 μm at baseline, 17 μm ($P < .01$) at 3 months, 19 μm ($P < .05$) at 6 months, and 21 μm ($P < .05$) at 12 months. The CMT, CCT, pachyvessel vertical diameter, and CNVT were significantly decreased at 3, 6, and 12 months as compared with those at baseline. Whilst 17 eyes (81.0%) showed no signs of CNV recurrence during the 12-month period, 4 eyes (19.0%) required additional combination therapy.

Conclusions HFPDT combined with intravitreal aflibercept injection may effectively improve BCVA and ameliorate exudative changes in eyes with PNV without polypoidal lesions for up to 1 year.

Keywords Pachychoroid neovascularopathy (PNV) · anti-vascular endothelial growth factor (anti-VEGF) · photodynamic therapy (PDT) · optical coherence tomography (OCT)

Introduction

Recently, pachychoroid spectrum diseases have been described as a new clinical entity composed of macular disorders [1]. “Pachychoroid” is defined as an abnormal increase in choroidal thickness often showing dilated choroidal vessels [1]. Type 1 choroidal neovascularization (CNV)

can reportedly develop in long-standing central serous chorioretinopathy (CSC), a typical pachychoroid spectrum disease, and masquerade as neovascular age-related macular degeneration (AMD) [2, 3]. Pang and Freund proposed “pachychoroid neovascularopathy (PNV)” in 2015 as a diagnosis in eyes with features of type 1 neovascularization and choroidal thickening in the absence of characteristic AMD or degenerative changes [4].

Intravitreal injection of an antivascular endothelial growth factor (VEGF) agent is a first-line therapy for neovascular AMD. We previously reported the efficacy of a treat-and-extend regimen using intravitreal aflibercept injection for PNV and type 1 neovascular AMD [5]. Our study revealed that management of PNV required significantly fewer intravitreal aflibercept injections than did type 1 neovascular

Corresponding Author: Hidetaka Matsumoto

✉ Hidetaka Matsumoto
hide-m@gunma-u.ac.jp

¹ Department of Ophthalmology, Gunma University School of Medicine, 3-39-15 Showa-machi, Maebashi, Gunma 371-8511, Japan

AMD [5]. However, treatment of PNV without polypoidal lesions required significantly more injections than did PNV with polypoidal lesions, so-called polypoidal choroidal vasculopathy (PCV) [5]. Lee et al also reported that PNV eyes without polypoidal lesions were refractory to anti-VEGF monotherapy [6].

Photodynamic therapy (PDT) using verteporfin was developed to treat CNV in neovascular AMD. Previous studies revealed PDT combined with intravitreal injection of an anti-VEGF agent to be effective against PCV [7, 8]. Moreover, combination therapy can reduce the adverse events associated with PDT such as subretinal hemorrhage [9]. PDT has also become a treatment option for CSC because PDT can reduce choroidal hyperpermeability and thickness, preventing fluid leakage from the retinal pigment epithelium (RPE) into the subretinal space [10]. When PDT is applied for CSC, the exposure fluence or exposure time or the amount of verteporfin is reduced to prevent complications such as RPE atrophy, choroidal ischemia, secondary CNV, and sudden visual acuity decreases [11, 12].

The aim of this study, using a 1-year follow-up period, was to evaluate the efficacy of half-fluence PDT (HFPDT) combined with intravitreal aflibercept injection in patients with PNV without polypoidal lesions.

Patients and methods

We performed this study, which complied with the guidelines of the Declaration of Helsinki, with approval from our institutional review board. We retrospectively studied 21 eyes of 21 patients with previously untreated PNV with exudative changes. The patients received HFPDT combined with an intravitreal aflibercept injection during the period from February 2017 through October 2018 and were followed up for at least 12 months at Gunma University Hospital.

All the patients with PNV underwent a complete ophthalmologic examination, including slit-lamp biomicroscopy with a noncontact fundus lens (SuperField lens; Volk Optical); color fundus photography and fundus autofluorescence (FAF) (Canon CX-1; Canon); fluorescein angiography (FA) and indocyanine green angiography (ICGA); and optical coherence tomography (OCT) with an angle of 30 degrees (Spectralis HRA + OCT; Heidelberg Engineering); and swept-source OCT (SS-OCT) (DRI OCT-1 Triton; Topcon Corp and PLEX Elite 9000; Carl Zeiss Meditec).

The DRI OCT-1 Triton and PLEX Elite 9000 incorporate a tunable laser with a 1050-nm central wavelength and acquire 100,000 A-scans/second. The DRI OCT-1 Triton has an axial resolution of 8 μm and a lateral resolution of 20 μm , whilst the respective resolutions of the PLEX Elite 9000 are 6.5 μm and 20 μm . We obtained B-mode images of

the horizontal and vertical line scans (12 mm) through the fovea by using the DRI OCT-1 Triton. Next, we performed OCT angiography volume scanning, with the scans containing 300 x 300 pixels in an area of 3 x 3 mm, by using the PLEX Elite 9000. OCT angiography is based on an optical microangiography algorithm.

In this study, the diagnosis was PNV if all the following criteria were met: (1) CNV without polypoidal lesions was diagnosed or suspected by FA and ICGA in the affected eye. (2) A shallow irregular RPE detachment at the site of CNV was observed on the OCT B-mode images, whilst CNV findings were detected in the slab from the outer retina to the choriocapillaris on OCT angiography [13]. (Shallow irregular RPE detachment was originally described as the so-called “double-layer sign” in PCV, containing branching vascular networks feeding polypoidal lesions [14].) (3) The clinical and anatomic features of the pachychoroid phenotype were pathologically dilated outer choroidal vessels on the OCT images and regional choroidal vascular hyperpermeability on the ICGA images. Central choroidal thickness (CCT) was not included among the criteria for the pachychoroid phenotype because CCT is affected by age and refractive error [15]. Furthermore, eyes with normal CCT can exhibit extrafoveal choroidal thickening at CNV sites [16]. The absence of drusen was also excluded from the criteria for the pachychoroid phenotype because pachychoroid-associated drusen, so-called pachydrusen, can be seen in pachychoroid spectrum diseases [17, 18].

All the eyes were treated with HFPDT combined with an intravitreal injection of aflibercept (2 mg/0.05 mL). HFPDT was performed 2 days after the aflibercept injection. The patients received a verteporfin injection at 6 mg/m² body surface area and then underwent PDT with a light fluence of 25 J/cm² using a Visulas PDT system 690S (Carl Zeiss Japan) for 83 seconds. The greatest linear dimension (GLD) of the PNV lesion was determined according to the ICGA, B-mode OCT, and OCTA. The diameter of the PDT treatment spot size was the GLD plus 1000 μm . After receiving this combination therapy, the patients were followed up every 1 to 2 months. When the exudative changes recurred, the same combination therapy was again performed.

Best-corrected visual acuity (BCVA), central macular thickness (CMT), CCT, pachyvessel vertical diameter, and CNV thickness (CNVT) at the fovea were examined at every visit. The BCVA was determined with a manifest refraction and recorded as decimal values and converted to logarithm of the minimal angle of resolution (logMAR) units. The CMT, CCT, pachyvessel vertical diameter, and CNVT were measured on the B-mode images using the computer-based caliper measurement tool in the OCT system. CMT was defined as the distance between the internal limiting membrane and the top of the RPE at the fovea. CCT was defined as the distance between the Bruch membrane and the

margin of the choroid and sclera under the fovea. Pachyvessel vertical diameter was defined as the vertical diameter of the most dilated pachyvessel within 1000 μm of the fovea on the horizontal B-scan OCT through the fovea. CNVT was defined as the distance between the bottom of the RPE and the Bruch membrane at the fovea. The data for CMT, CCT, pachyvessel vertical diameter, and CNVT were recorded independently by 2 examiners masked to the patients' information, and if the measurement difference exceeded 15% of the mean of the 2 values, there was open adjudication with the senior author.

For statistical analysis, the Wilcoxon signed rank test was used to compare the differences between the BCVA, CMT, CCT, pachyvessel vertical diameter, and CNVT at baseline versus the other time points. The data analyses were performed using Excel 2016 (Microsoft) with add-in software Statcel4 [19]. Probability values less than .05 were considered to indicate significant differences. All data are presented as medians (minimums, maximums).

Results

The patients in this study were all Japanese and comprised 17 men (81%) and 4 women (19%). The median patient age was 66 (45, 84) years. The respective GLD values were 2069 (714, 3571) μm . Fifteen eyes had subfoveal CNV, and the other 6, juxta or extrafoveal CNV. None of the patients in this study had serous RPE detachment under the fovea. The clinical data before treatment are presented in Table 1. The BCVA changes during the 12-month period are shown in Figure 1a. The median BCVA was 0.15 (-0.08, 0.70) at baseline, 0.00 (-0.08, 0.52) ($P < .05$) at 3 months, 0.05 (-0.08,

0.52) at 6 months, and -0.08 (-0.08, 0.70) ($P < .05$) at 12 months. The BCVA was significantly improved at 3 and 12 months as compared with the BCVA at baseline. The CMT changes during the 12-month study period are shown in Figure 1b. The median CMT was 230 (140, 418) μm at baseline, 140 (82, 233) μm ($P < .01$) at 3 months, 150 (86, 220) μm ($P < .01$) at 6 months, and 150 (83, 220) μm ($P < .01$) at 12 months. The CMT showed significant reductions at 3, 6, and 12 months as compared with the CMT at baseline. The CCT changes during the 12 months of treatment are shown in Figure 1c. The median CCT was 386 (191, 611) μm at baseline, 347 (131, 522) μm ($P < .01$) at 3 months, 331 (122, 572) μm ($P < .01$) at 6 months, and 352 (92, 581) μm ($P < .01$) at 12 months. The CCT showed significant reductions at 3, 6, and 12 months as compared with the CCT at baseline. The changes in pachyvessel vertical diameter during the 12-month study period are shown in Figure 1d. The median pachyvessel vertical diameter was 309 (102, 394) μm at baseline, 246 (77, 344) μm ($P < .01$) at 3 months, 232 (77, 339) μm ($P < .01$) at 6 months, and 242 (73, 330) μm ($P < .01$) at 12 months. The pachyvessel vertical diameter was significantly decreased at 3, 6, and 12 months as compared with that at baseline. The CNVT values at the fovea during the 12-month treatment period are shown in Figure 1e. The median CNVT was 28 (0, 74) μm at baseline, 17 (0, 59) μm ($P < .01$) at 3 months, 19 (0, 59) μm ($P < .05$) at 6 months, and 21 (0, 64) μm ($P < .05$) at 12 months. The CNVT was significantly decreased at 3, 6, and 12 months as compared with the CNVT at baseline. Four patients (19.0 %) showed CNV recurrence after the initial PDT plus aflibercept treatment and received additional combination therapy during the 12-month period: 1 additional treatment for 3 eyes and 3 additional treatments for 1 eye. Three of the 4 eyes with recurrence had the highest CNVT values (51, 65, and 74 μm) at baseline among the 21 eyes with PNV. The other 17 patients (81.0%) showed no signs of CNV recurrence during the 12-month period. A representative case is shown in Figure 2. None of the patients experienced severe adverse events, such as cerebral infarction, myocardial infarction, infectious endophthalmitis, rhegmatogenous retinal detachment, and subretinal hematoma.

Table 1 Demographic and clinical characteristics of patients with PNV

No. of patients	21
No. of eyes	21
Male/female	17/4
Age, y	66 (45, 84)
Best-corrected visual acuity, logMAR	0.15 (-0.08, 0.70)
Central macular thickness, μm	230 (140, 418)
Central choroidal thickness, μm	386 (191, 611)
Vertical diameter of pachyvessel, μm	309 (102, 394)
Choroidal neovascularization (CNV) thickness, μm	28 (0, 74)
Greatest linear dimension, μm	2069 (714, 3571)
Subfoveal CNV/juxtafoveal CNV	15/6

Age, best-corrected visual acuity, central macular thickness, central choroidal thickness, vertical diameter of pachyvessel, choroidal neovascularization thickness, and greatest linear dimension are shown as medians (minimums, maximums)

Discussion

We retrospectively investigated 21 eyes with treatment-naïve PNV given HFPDT combined with intravitreal injection of aflibercept. The BCVA was significantly improved at 3 and 12 months after the treatment as compared with the BCVA at baseline. The CMT, CCT, pachyvessel vertical diameter, and CNVT showed significant reductions at 3, 6, and 12 months after the treatment as compared with those at

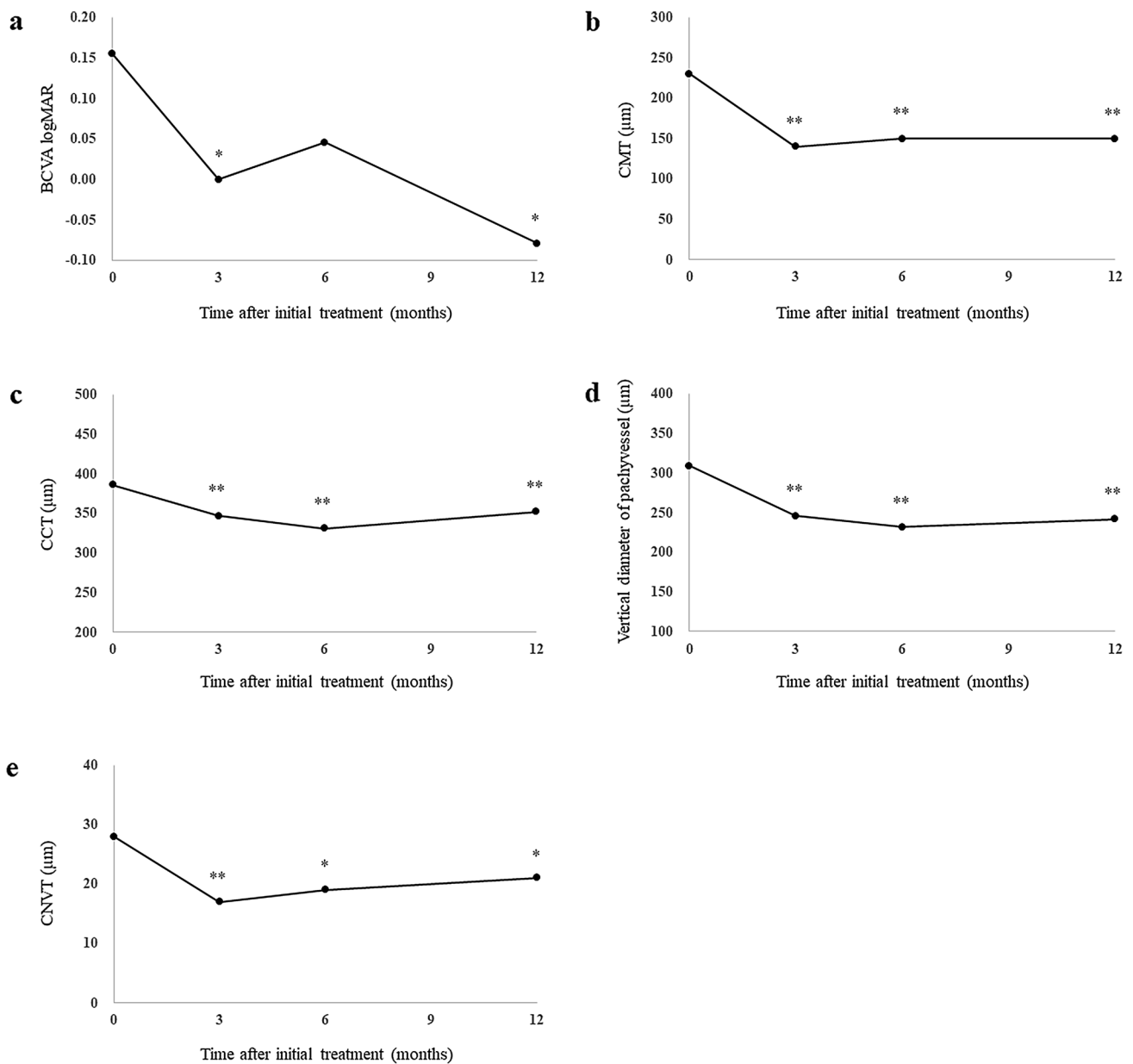


Fig. 1 **a** Changes in best-corrected visual acuity (BCVA) in previously treatment-naïve pachychoroid neovascularopathy during the 12-month period after half-fluence photodynamic therapy combined with intravitreal aflibercept injection. The BCVA was significantly improved at 3 and 12 months as compared with the BCVA at baseline. **b** Changes in central macular thickness (CMT) during the 12-month period after the combination therapy. The CMT was significantly decreased at 3, 6, and 12 months as compared with the CMT at baseline. **c** Changes in central choroidal thickness (CCT) during the 12-month period after administration of the combination therapy.

The CCT was significantly decreased at 3, 6, and 12 months as compared with the CCT at baseline. **d** Changes in pachyvessel vertical diameter during the 12-month period after administration of the combination therapy. The pachyvessel vertical diameter was significantly decreased at 3, 6, and 12 months as compared with that at baseline. **e** Changes in choroidal neovascularization thickness (CNVT) during the 12-month period after administration of the combination therapy. The CNVT was significantly decreased at 3, 6, and 12 months as compared with the CNVT at baseline. All data are shown as medians. * $P < .05$, ** $P < .01$

baseline. Seventeen of the 21 patients (81.0%) showed no signs of CNV recurrence during the 12-month period.

Miyake et al investigated the phenotypic/genetic differences between neovascular AMD and PNV including PCV [20]. They reported patients with PNV to be significantly

younger than those with neovascular AMD [20]. They also noted that genetic susceptibility to AMD was significantly lower in PNV than in neovascular AMD [20]. Hata et al studied the difference in intraocular VEGF concentrations between neovascular AMD and PNV, including PCV [21].

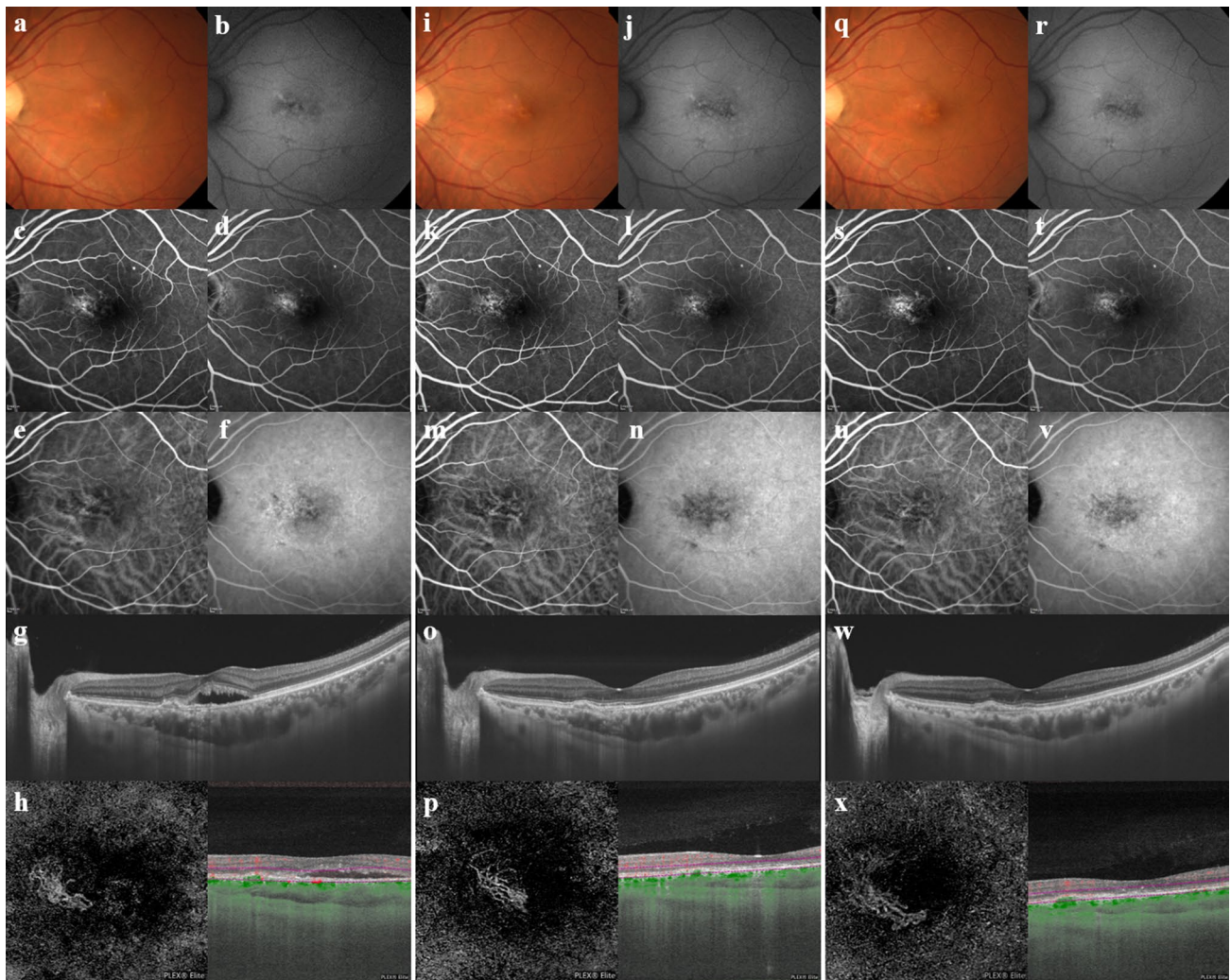


Fig. 2 Images from a 62-year-old man with previously treatment-naïve pachychoroid neovascularopathy. The best-corrected visual acuity in the left eye was -0.08 logMAR units during the 12-month follow-up period. **a-h** Images obtained at baseline. **a** Color fundus photograph showing retinal pigment epithelium (RPE) degeneration at the macular area. **b** Fundus autofluorescence showing a mixture of hyperautofluorescence and hypoautofluorescence according to RPE degeneration. **c** and **d** Fluorescein angiographic images (**c** 50 sec, **d** 5 min.) showing window defects and some leakage from the RPE. **e** and **f** Indocyanine green angiographic images (**e** 1 min, **f** 10 min) showing no apparent choroidal neovascularization. **g** Horizontal optical coherence tomography (OCT) B-scan through the fovea showing dilated outer choroidal vessels and shallow irregular RPE detachment accompanied by serous retinal detachment. The central macular thickness (CMT), central choroidal thickness (CCT), vertical diameter of the most dilated pachyvessel, and choroidal neovascularization thick-

ness (CNVT) were 290, 330, 320, and 37 μm , respectively. **h** OCT angiographic image (3×3 mm) showing CNV in the slab from the outer retina to the choriocapillaris. **i-p** Images obtained 3 months after half-fluence photodynamic therapy combined with intravitreal aflibercept injection. **k** and **l** Fluorescein angiographic images (**k** 50 sec, **l** 5 min.) showing no leakage from the RPE. **o** Horizontal OCT B-scan through the fovea showing no serous retinal detachment. The CMT, CCT, pachyvessel vertical diameter, and CNVT were 165, 274, 284, and 32 μm , respectively. **p** OCT angiographic image showing CNV. **q-x** Images obtained 12 months after administration of combination therapy. **s** and **t** Fluorescein angiographic images (**s** 50 sec, **t** 5 min.) showing no leakage from the RPE. **w** Horizontal OCT B-scan through the fovea, showing no serous retinal detachment. The CMT, CCT, pachyvessel vertical diameter, and CNVT were 174, 246, 245, and 30 μm , respectively. **x** OCT angiographic image showing CNV

They reported the mean VEGF concentration to be lower in PNV than in neovascular AMD [21]. These reports suggest that the mechanisms of CNV development might differ between neovascular AMD and PNV. PNV, by definition, is a disease that develops from type 1 neovascularization associated with choroidal thickening [1]. Impairment of

the choroidal circulation might have a major impact on the development of CNV in PNV. Therefore, achieving good long-term outcomes may require not only treating the CNV but also decreasing the choroidal thickness.

Previous studies revealed that the regression rate of polypoidal lesions in PCV is higher with aflibercept than with

ranibizumab [22–24]. In addition, aflibercept is reportedly effective for the treatment of neovascular AMD with RPE detachment refractory to ranibizumab [25]. Therefore, aflibercept is thought to be more effective than ranibizumab for lesions under the RPE. Aflibercept also reportedly affects the choroidal circulation more than does ranibizumab. Julien et al investigated choroidal changes in monkey eyes after intravitreal injection of aflibercept or ranibizumab [26]. They reported the reductions of choriocapillaris endothelium thickness and the number of fenestrations to be more pronounced after intravitreal aflibercept injections than after intravitreal ranibizumab injections [26]. Moreover, several studies have shown that aflibercept reduces choroidal thickness more than does ranibizumab [27, 28].

PDT is also effective for CNV occlusion and diminishing choroidal thickness [29]. Maruko et al investigated choroidal thickness change after combination therapy with intravitreal ranibizumab and PDT in eyes with recurrent PCV [30]. They reported that the subfoveal choroidal thickness, which was increased at the time of recurrence, returned to the baseline level after choroidal thinning in response to PDT treatment [30]. Kim et al investigated long-term changes in subfoveal choroidal thickness after PDT and the relationships of these changes with chronic CSC recurrence [31]. They reported incomplete absorption or recurrence of subretinal fluid after PDT to be associated with greater subfoveal choroidal thickness [31].

Reduced-fluence PDT is a treatment option for CSC. Reduced-fluence PDT can decrease choroidal thickness, whilst the risks of complications such as RPE atrophy, choroidal ischemia, secondary CNV, and sudden visual acuity decrease are lower than with full fluence PDT [11, 32]. In addition, combination therapy with intravitreal anti-VEGF and PDT for neovascular AMD can reduce the adverse events associated with PDT such as subretinal hemorrhage [9]. In the current study, we treated PNV with intravitreal injection of aflibercept combined with HFPDT. Our results demonstrated this combination therapy to be effective for achieving CNV regression, decreasing choroidal thickness, and diminishing pachyvessels. However, eyes with high CNVT values at baseline tended to require additional treatments. Therefore, CNVT assessment might be important for predicting the efficacy of combination therapy for PNV.

The limitations of our study include its retrospective nature, single-center design, small number of patients, and relatively short follow-up period. CMT, CCT, and CNVT were measured manually, although it should be noted that all measurements were performed by highly experienced investigators masked to the patients' clinical and demographic information. The patients were all Japanese, so the results may not be generalizable to other racial and ethnic groups.

In conclusion, HFPDT combined with intravitreal aflibercept injection may be effective, for up to 1 year, for

improving BCVA and ameliorating exudative changes in eyes with PNV without polypoidal lesions. This combination regimen is a potential treatment option for PNV without polypoidal lesions.

Acknowledgements Author contributions are as follows: design and conduct of the study (H.M., R.M., M.M.); data collection (H.M., Y.K.), management (H.M.), and analysis (H.M., R.M.); interpretation of the results (H.M.); preparation of the article (H.M.); review and approval of the manuscript for submission (R.M., H.A.).

Conflicts of interest H. Matsumoto, None; R. Mukai, None; Y. Kikuchi, None; M. Morimoto, None; H. Akiyama, None.

References

- Gallego-Pinazo R, Dolz-Marco R, Gómez-Ulla F, Mrejen S, Freund KB. Pachychoroid diseases of the macula. *Med Hypothesis Discov Innov Ophthalmol*. 2014;3:111–5.
- Fung AT, Yannuzzi LA, Freund KB. Type 1 (sub-retinal pigment epithelial) neovascularization in central serous chorioretinopathy masquerading as neovascular age-related macular degeneration. *Retina*. 2012;32:1829–37. <https://doi.org/10.1097/IAE.0b013e3182680a66>.
- Yannuzzi LA, Freund KB, Goldbaum M, Scarsellati-Sforzolini B, Guyer DR, Spaide RF, et al. Polypoidal choroidal vasculopathy masquerading as central serous chorioretinopathy. *Ophthalmology*. 2000;107:767–77.
- Pang CE, Freund KB. Pachychoroid neovascularopathy. *Retina*. 2015;35:1–9. <https://doi.org/10.1097/IAE.0000000000000331>.
- Matsumoto H, Hiroe T, Morimoto M, Mimura K, Ito A, Akiyama H. Efficacy of treat-and-extend regimen with aflibercept for pachychoroid neovascularopathy and Type 1 neovascular age-related macular degeneration. *Jpn J Ophthalmol*. 2018;62:144–50. <https://doi.org/10.1007/s10384-018-0562-0>.
- Lee JH, Lee WK. One-year results of adjunctive photodynamic therapy for type 1 neovascularization associated with thickened choroid. *Retina*. 2016;36:889–95. <https://doi.org/10.1097/IAE.0000000000000809>.
- Koh A, Lai TYY, Takahashi K, Wong TY, Chen LJ, Ruamvi-boonsuk P, et al. Efficacy and safety of ranibizumab with or without verteporfin photodynamic therapy for polypoidal choroidal vasculopathy: a randomized clinical trial. *JAMA Ophthalmol*. 2017;135:1206–13. <https://doi.org/10.1001/jamaophthamol.2017.4030>.
- Koh A, Lee WK, Chen LJ, Chen SJ, Hashad Y, Kim H, et al. EVEREST study: efficacy and safety of verteporfin photodynamic therapy in combination with ranibizumab or alone versus ranibizumab monotherapy in patients with symptomatic macular polypoidal choroidal vasculopathy. *Retina*. 2012;32:1453–64. <https://doi.org/10.1097/IAE.0b013e31824f91e8>.
- Sato T, Kishi S, Matsumoto H, Mukai R. Combined photodynamic therapy with verteporfin and intravitreal bevacizumab for polypoidal choroidal vasculopathy. *Am J Ophthalmol*. 2010;149(947–54):e1. <https://doi.org/10.1016/j.ajo.2009.12.038>.
- Chan WM, Lam DS, Lai TY, Tam BS, Liu DT, Chan CK. Choroidal vascular remodelling in central serous chorioretinopathy after indocyanine green guided photodynamic therapy with verteporfin: a novel treatment at the primary disease level. *Br J Ophthalmol*. 2003;87:1453–8.
- Kim YK, Ryou NK, Woo SJ, Park KH. Comparison of visual and anatomical outcomes of half-fluence and half-dose photodynamic therapy in eyes with chronic central serous chorioretinopathy.

- Graefes Arch Clin Exp Ophthalmol. 2015;253:2063–73. <https://doi.org/10.1007/s00417-014-2926-6>.
12. Shiode Y, Morizane Y, Kimura S, Hosokawa M, Kawata T, Doi S, et al. Comparison of halving the irradiation time or the verteporfin dose in photodynamic therapy for chronic central serous chorioretinopathy. *Retina*. 2015;35:2498–504. <https://doi.org/10.1097/IAE.0000000000000621>.
 13. Dansingani KK, Balaratnasingam C, Klufas MA, Sarraf D, Freund KB. Optical coherence tomography angiography of shallow irregular pigment epithelial detachments in pachychoroid spectrum disease. *Am J Ophthalmol*. 2015;160(1243–54):e2. <https://doi.org/10.1016/j.ajo.2015.08.028>.
 14. Sato T, Kishi S, Watanabe G, Matsumoto H, Mukai R. Tomographic features of branching vascular networks in polypoidal choroidal vasculopathy. *Retina*. 2007;27:589–94. <https://doi.org/10.1097/01.iae.0000249386.63482.05>.
 15. Ikuno Y, Kawaguchi K, Nouchi T, Yasuno Y. Choroidal thickness in healthy Japanese subjects. *Invest Ophthalmol Vis Sci*. 2010;51:2173–6. <https://doi.org/10.1167/iovs.09-4383>.
 16. Lee WK, Baek J, Dansingani KK, Lee JH, Freund KB. Choroidal morphology in eyes with polypoidal choroidal vasculopathy and normal or subnormal subfoveal choroidal thickness. *Retina*. 2016;36(Suppl 1):S73–82. <https://doi.org/10.1097/IAE.0000000000001346>.
 17. Spaide RF. Disease expression in nonexudative age-related macular degeneration varies with choroidal thickness. *Retina*. 2018;38:708–16. <https://doi.org/10.1097/IAE.0000000000001689>.
 18. Matsumoto H, Mukai R, Morimoto M, Tokui S, Kishi S, Akiyama H. Clinical characteristics of pachydrusen in central serous chorioretinopathy. *Graefes Arch Clin Exp Ophthalmol*. 2019;257:1127–32. <https://doi.org/10.1007/s00417-019-04284-4>.
 19. Yanai H, Shteinberg A, Porat Z, Budovsky A, Braiman A, Ziesche R, et al. Cellular senescence-like features of lung fibroblasts derived from idiopathic pulmonary fibrosis patients. *Aging (Albany NY)*. 2015;7:664–72. <https://doi.org/10.18632/aging.100807>.
 20. Miyake M, Ooto S, Yamashiro K, Takahashi A, Yoshikawa M, Akagi-Kurashige Y, et al. Pachychoroid neovascularopathy and age-related macular degeneration. *Sci Rep*. 2015;5:16204. <https://doi.org/10.1038/srep16204>.
 21. Hata M, Yamashiro K, Ooto S, Oishi A, Tamura H, Miyata M, et al. Intraocular vascular endothelial growth factor levels in pachychoroid neovascularopathy and neovascular age-related macular degeneration. *Invest Ophthalmol Vis Sci*. 2017;58:292–8. <https://doi.org/10.1167/iovs.16-20967>.
 22. Gomi F, Oshima Y, Mori R, Kano M, Saito M, Yamashita A, et al. Initial versus delayed photodynamic therapy in combination with ranibizumab for treatment of polypoidal choroidal vasculopathy: the Fujisan Study. *Retina*. 2015;35:1569–76. <https://doi.org/10.1097/IAE.0000000000000526>.
 23. Yamamoto A, Okada AA, Kano M, Koizumi H, Saito M, Maruko I, et al. One-year results of intravitreal aflibercept for polypoidal choroidal vasculopathy. *Ophthalmology*. 2015;122:1866–72. <https://doi.org/10.1016/j.ophtha.2015.05.024>.
 24. Cho HJ, Kim KM, Kim HS, Han JJ, Kim CG, Lee TG, et al. Intravitreal aflibercept and ranibizumab injections for polypoidal choroidal vasculopathy. *Am J Ophthalmol*. 2016;165:1–6. <https://doi.org/10.1016/j.ajo.2016.02.019>.
 25. Patel KH, Chow CC, Rathod R, Mieler WF, Lim JJ, Ulanski LJ 2nd, et al. Rapid response of retinal pigment epithelial detachments to intravitreal aflibercept in neovascular age-related macular degeneration refractory to bevacizumab and ranibizumab. *Eye (Lond)*. 2013;27:663–7; quiz 8. <https://doi.org/10.1038/eye.2013.31>.
 26. Julien S, Biesemeier A, Taubitz T, Schraermeyer U. Different effects of intravitreally injected ranibizumab and aflibercept on retinal and choroidal tissues of monkey eyes. *Br J Ophthalmol*. 2014;98:813–25. <https://doi.org/10.1136/bjophthalmol-2013-304019>.
 27. Yamazaki T, Koizumi H, Yamagishi T, Kinoshita S. Subfoveal choroidal thickness after ranibizumab therapy for neovascular age-related macular degeneration: 12-month results. *Ophthalmology*. 2012;119:1621–7. <https://doi.org/10.1016/j.ophtha.2012.02.022>.
 28. Koizumi H, Kano M, Yamamoto A, Saito M, Maruko I, Sekiryu T, et al. Subfoveal choroidal thickness during aflibercept therapy for neovascular age-related macular degeneration: twelve-month results. *Ophthalmology*. 2016;123:617–24. <https://doi.org/10.1016/j.ophtha.2015.10.039>.
 29. Maruko I, Iida T, Sugano Y, Saito M, Sekiryu T. Subfoveal retinal and choroidal thickness after verteporfin photodynamic therapy for polypoidal choroidal vasculopathy. *Am J Ophthalmol*. 2011;151(594–603):e1. <https://doi.org/10.1016/j.ajo.2010.10.030>.
 30. Maruko I, Iida T, Oyamada H, Sugano Y, Ojima A, Sekiryu T. Choroidal thickness changes after intravitreal ranibizumab and photodynamic therapy in recurrent polypoidal choroidal vasculopathy. *Am J Ophthalmol*. 2013;156:548–56. <https://doi.org/10.1016/j.ajo.2013.03.041>.
 31. Kim YK, Ryoo NK, Woo SJ, Park KH. Choroidal thickness changes after photodynamic therapy and recurrence of chronic central serous chorioretinopathy. *Am J Ophthalmol*. 2015;160(72–84):e1. <https://doi.org/10.1016/j.ajo.2015.04.011>.
 32. Shin JY, Woo SJ, Yu HG, Park KH. Comparison of efficacy and safety between half-fluence and full-fluence photodynamic therapy for chronic central serous chorioretinopathy. *Retina*. 2011;31:119–26. <https://doi.org/10.1097/IAE.0b013e3181e378f2>.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.