Title	Five-year visual outcomes after anti-VEGF therapy with or without photodynamic therapy for polypoidal choroidal vasculopathy
Author(s)	Miyata, Manabu; Ooto, Sotaro; Yamashiro, Kenji; Tamura, Hiroshi; Hata, Masayuki; Ueda-Arakawa, Naoko; Yoshikawa, Munemitsu; Numa, Shogo; Tsujikawa, Akitaka
Citation	British Journal of Ophthalmology (2018), Online First
Issue Date	2018-6-6
URL	http://hdl.handle.net/2433/235951
Right	This article has been accepted for publication in 'British Journal of Ophthalmology' following peer review. The definitive copyedited, typeset version [Contributor please insert complete citation information when available] is available online at: https://bjo.bmj.com/content/early/2018/09/29/bjophthalmol-2018-311963; This is not the published version. Please cite only the published version. この論文は出版社版でありません。引用の際には出版社版をご確認ご利用ください。
Type	Journal Article
Textversion	author

Five-Year Visual Outcomes after Anti-VEGF Therapy with or without Photodynamic Therapy for Polypoidal Choroidal Vasculopathy

Manabu Miyata, Sotaro Ooto, Kenji Yamashiro, Hiroshi Tamura, Masayuki Hata, Naoko Ueda-Arakawa, Munemitsu Yoshikawa, Shogo Numa, Akitaka Tsujikawa

Department of Ophthalmology and Visual Sciences, Kyoto University Graduate School of Medicine, Kyoto, Japan

Correspondence:
Manabu Miyata, MD, PhD
Department of Ophthalmology and Visual Sciences, Kyoto University Graduate School of Medicine,
Shogoin Kawahara-cho 54, Sakyo-ku, Kyoto 606-8507, Japan
Tel.: 011-81-75-751-3248
Fax: 011-81-75-752-0933
E-mail: miyatam@kuhp.kyoto-u.ac.jp

Contributors:
All authors have made substantive intellectual contributions in the study, including study design, data acquisition and/or the analysis or interpretation of data and final review of the manuscript.

Funding:
This work was supported in part by a grant-in-aid for scientific research (number 26861451) from the Japan Society for the Promotion of Science, Tokyo, Japan, and the Innovative Techno-Hub for Integrated Medical Bio-Imaging of the Project for Developing Innovation Systems from the Ministry of Education, Culture, Sports, Science and Technology (MEXT), Tokyo, Japan. None of these organizations had any role in the design or conduct of this research.

Competing Interests:
All authors attest that they meet the current ICMJE criteria for authorship.

Word Count:
2500

SYNOPSIS

Anti-vascular endothelial growth factor therapy alone and combination with photodynamic therapy for polypoidal choroidal vasculopathy yields similar 5-year visual outcomes and retinal structural changes; however, macular atrophy tends to be more frequent with combination treatment.

ABSTRACT

Background/Aims: To evaluate the 5-year visual and anatomical outcomes after anti-vascular endothelial growth factor (VEGF) therapy alone or in combination with photodynamic therapy (PDT), followed by pro re nata (PRN) anti-VEGF therapy with or without PDT, for polypoidal choroidal vasculopathy (PCV).

Methods: This retrospective, observational study included 61 consecutive patients with treatment-naïve symptomatic PCV who were followed for 5 years. Twenty eyes (20 patients) initially received PDT and intravitreal injection of ranibizumab (IVR), followed by a PRN regimen of anti-VEGF therapy with or without PDT (combination group), while 41 eyes (41 patients) initially received only IVR every 3 months, followed by a PRN regimen of anti-VEGF monotherapy (IVR group). Macular atrophy including the fovea was confirmed using colour fundus photography and spectral-domain optical coherence tomography.

Results: In both groups, the visual acuity (VA) at 1 year was better than the baseline VA, whereas the 3-, 4-, and 5-year VA values were similar to the baseline VA. There was no significant difference in the 5-year VA, 5-year central retinal thickness, and incidence of macular atrophy between the two groups (P=0.63, 0.72, and 0.06, respectively). In the combination group, the 5-year VA was correlated with the 5-year incidence of macular atrophy (P=0.02, r=0.51).

Conclusions: A PRN regimen for PCV may have a limited effect for the long-term maintenance of improved VA. Macular atrophy may occur more frequently with combination therapy and is possibly associated with the 5-year VA. Thus, combination therapy should be carefully selected for patients susceptible to macular atrophy.

INTRODUCTION

Symptomatic polypoidal choroidal vasculopathy (PCV), characterized by branching vascular networks terminating in polypoidal lesions, is similar to exudative age-related macular degeneration (AMD), although it is considered a separate entity since its description in 1982.[1, 2] Some pathologicak studies have shown that vascular endothelial growth factors (VEGFs) are involved in symptomatic PCV development.[3, 4] Therefore, like AMD, symptomatic PCV is treated by intravitreal injection of anti-VEGF agents such as pegaptanib, ranibizumab, and aflibercept.[5]

Photodynamic therapy (PDT) with or without intravitreal anti-VEGF therapy is also used to treat symptomatic PCV and has favourable effects on visual acuity (VA).[6-8] In the EVEREST study, the 6-month rate of complete polyp regression was higher for patients treated with PDT combined with intravitreal injection of ranibizumab (IVR) than in those treated with IVR alone (77.8% vs. 28.6%, P<0.001).[9] Thrombosis of polypoidal lesions following PDT and inhibition of VEGF production and vascular permeability via IVR may produce synergetic effects for symptomatic PCV treatment. Further, the prospective, randomised, double-masked, multicentre EVEREST II study showed that the 12-month VA was better for patients who received combination therapy of ranibizumab with PDT than for those who received ranibizumab alone.[10] However, the invasive effect of PDT on the retina and choroid remains concerning.[11]

In clinical settings, anti-VEGF agents are often administered for PCV on a pro re nata (PRN) basis, with or without PDT. However, in the long term, VA was reported to decrease in patients with AMD who received PRN anti-VEGF therapy.[12] In the present study, we assessed the 5-year visual and anatomical outcomes after initial antii-VEGF therapy alone or in combination with PDT, followed by anti-VEGF therapy with or without PDT on a PRN basis, in patients with PCV.

METHODS

This retrospective study was approved by the institutional review board at Kyoto University Graduate School of Medicine, Kyoto, Japan. All study protocols adhered to the tenets of the Declaration of Helsinki. All patients provided written informed consent for treatment. The institutional review board waived the need for informed patient consent for a retrospective review of medical records.

Subjects

We reviewed the medical records of treatment-naïve eyes affected by symptomatic PCV in consecutive patients who were followed for 5 years after receiving initial combination therapy of PDT and IVR (Lucentis; Novartis, Buläch, Switzerland) or IVR

alone between April 2009 and October 2011 at Kyoto University Hospital. The combination group included patients initially treated with a combination of PDT and IVR, followed by a PRN regimen of anti-VEGF therapy [ranibizumab or aflibercept (Eylea; Bayer, Basel, Switzerland)] with or without PDT. The IVR group included patients initially treated with IVR every 3 months, followed by a PRN regimen of anti-VEGF monotherapy. The inclusion criteria were as follows: presence of exudative or haemorrhagic features involving the macula and a follow-up period of 5 years, with at least one visit per year after the initial treatment. The exclusion criteria were as follows: intraocular surgery, including cataract surgery and vitrectomy, during the 5-year follow-up period; high myopia with an axial length (AL) of ≥26.50 mm (or a refractive value of ≤−6.00 D in patients without AL data); and the presence or a history of other eye diseases. When both eyes of a patient were eligible, the eye treated first was included. If both eyes had received treatment on the same day, the right eye was included.

Before treatment for PCV, all patients had undergone a comprehensive ophthalmic examination, including measurement of the best corrected VA using a decimal VA (Landolt) chart; measurement of AL using partial coherence interferometry (IOLMaster; Carl Zeiss Meditec, Inc., Dublin, CA, USA) or A-mode echo analysis (UD-8000; Tomey Corp., Nagoya, Japan) in cases where measurement with the IOLMaster was not possible; colour fundus photography (TRC-NW8F; Topcon Corp., Tokyo, Japan); spectral domain optical coherence tomography (SD-OCT; Spectralis HRA+OCT, Heidelberg Engineering, Heidelberg, Germany; or RS-3000 Advance, Nidek Corp., Gamagori, Japan); and fundus fluorescein angiography and indocyanine green angiography (ICGA; Heidelberg Retina Angiography 2; Heidelberg Engineering). PCV was diagnosed if a branching vascular network terminating in polypoidal swelling was detected by retinal specialists on ICGA images.

Measurement of the central retinal thickness and greatest linear dimension

The central retinal thickness was defined as the distance between the inner surface of the internal limiting membrane and Bruch's membrane beneath the fovea, and it was measured on SD-OCT images by one investigator (MM) using the scanner’s built-in tool. The average distance calculated from measurements acquired in horizontal and vertical scans was used for analysis. The greatest linear dimension (GLD) was measured on ICGA images using the Heidelberg Retina Angiography 2 built-in software.

Confirmation of macular atrophy

Macular atrophy involving the fovea was confirmed by two investigators (MM, SN) on the basis of colour fundus photography and SD-OCT findings at baseline and 5 years after treatment (Fig. 1). The criteria for atrophy diagnosis were as follows: thinning of the retinal pigment epithelium (RPE) band on OCT, increased signal transmission in the choroid on OCT[13], and no contradicting findings on colour fundus photography. Hyper-refractivity on near-infrared fundus photography was referred. After the confirmation of a good interobserver agreement, the values recorded by one investigator (MM) were used as representative variables.

Intravitreal injection and photodynamic therapy

Intravitreal injections were administered in a sterile manner. Prophylactic topical antibiotics were regularly applied for 3 days before injection and 3 days to 1 week after injection. Three to 4 days after the intravitreal injection, normal-fluence PDT was administered using a 689-nm diode laser unit (Visulas PDT system 690S; Carl Zeiss) and intravenous verteporfin (Visudyne; Novartis, Basel, Switzerland) in accordance with the guidelines for PDT in AMD.[14] All polypoidal lesions, including the entire branching vascular network detected by ICGA, and the choroidal neovascularization detected by fluorescein angiography, were included. Serous pigment epithelium detachments were not included in the lesion areas when underlying choroidal neovascularization was confirmed to be absent.

Retreatment criteria

The retreatment criteria were identical to those reported previously.[7, 15] Briefly, additional combination therapy or PDT was administered as required for exudative OCT findings, such as the development or persistence of subretinal fluid, subretinal haemorrhage, or active choroidal neovascularization, 3 months after PDT. Additional anti-VEGF therapy for exudative findings was administered as required during monthly follow-up visits.

Genotyping

Genotyping data were available for 18 and 35 patients in the combination and IVR groups, respectively. Genomic DNA was extracted from peripheral blood samples using a DNA extraction kit (QuickGene-610 L; Fujifilm, Minato, Tokyo, Japan). Genes encoding age-related maculopathy susceptibility protein 2 (*ARMS2*) A69S rs10490924 and complement factor H I62V rs800292 were genotyped by the TaqMan single-nucleotide polymorphism assay method using the ABI PRISM 7700 system (Applied Biosystems, Foster City, CA, USA).

Statistical analysis

The data are presented as mean ± standard deviation or number of eyes, as applicable. All VA values were converted to fractional or logarithm of the minimum angle of resolution (logMAR) values, where applicable. All statistical analyses were performed using SPSS version 21 software (IBM Corp., Armonk, NY, USA). The datasets were compared using the *t*-test, chi-square test, or chi-square trend test, as appropriate. Correlations between the 5-year logMAR VA and other parameters were determined using Spearman's rank correlation coefficient analysis. Multiple stepwise regression analyses were performed using the 5-year logMAR VA as a dependent variable and baseline parameters (Spearman's correlation coefficients with *P*-values of <0.10) as independent variables. The first combination therapy in the combination group and the three initial monthly loading treatments in the IVR group were excluded from the number of retreatments. Combination therapy with PDT and intravitreal anti-VEGF injection was considered a single session of retreatment. To determine the reliability of the measurements, intra-class correlation coefficients (ICCs) for interobserver agreement regarding the macular atrophy values recorded by the two investigators were calculated. A *P*-value of <0.05 was considered statistically significant.

Subgroup analysis of patients aged ≥70 years at baseline

The mean patient age in the combination group was significantly higher than that in the IVR group. Because patient age could influence the treatment outcome, subgroup analyses including patients aged ≥70 years at baseline were performed to detect differences between the combination group and an age-matched IVR group. The 5-year course of VA and number of retreatments in both groups were also analysed.

RESULTS

In total, 61eyes of 61 consecutive patients were included; 20 eyes of 20 patients and 41 eyes of 41 patients were divided into the combination and IVR groups, respectively (Table 1). There was no significant difference in VA between the two groups at baseline or at 1, 2, 3, 4, and 5 years after treatment (Fig. 2). In the combination group, the 1-year VA was better than the baseline VA (*P*=0.003), whereas, the VA values at 2, 3, 4, and 5 years were not different from the baseline value. In the IVR group, VA at 1 and 2 years was better than the baseline VA (*P*=0.003 and 0.02, respectively), whereas, that at 3, 4, and 5 years was similar to the baseline VA. The number of retreatments in the first year was higher in the IVR group than in the combination group (Fig. 2, *P*=0.02). However, there was no significant intergroup difference in the number of retreatments in the subsequent 4 years. The patient age differed between

the two groups at baseline (*P*<0.001); none of the baseline parameters, including sex, AL, central retinal thickness, genotype, GLD, and macular atrophy, showed significant differences between the two groups. The incidence of macular atrophy was marginally higher in the combination group than in the IVR group (*P*=0.06). ICC (2, 1) for interobserver agreement regarding macular atrophy assessment was 0.95, indicating excellent agreement.

Univariate analysis revealed that the 5-year VA was significantly correlated with the baseline VA (*P*=0.04, r=0.47) and 5-year incidence of macular atrophy (*P*=0.02, r=0.51) in the combination group and age (*P*<0.001, r=0.53), the baseline VA (*P*<0.001, r=0.58), and the baseline GLD (*P*=0.003, r=0.45) in the IVR group (Table 2). Multivariate analysis revealed that the 5-year VA was strongly correlated with the 5-year incidence of macular atrophy (*P*=0.03, β=0.47) in the combination group and the baseline VA (*P*<0.001, β=0.51) in the IVR group (Table 2).

Subgroup analysis of patients aged ≥70 years at baseline

The subgroup analysis included 20 and 23 patients from the combination and IVR groups, respectively (Table 3). Although the results concerning VA were similar to those of the overall group analyses, the total number of retreatments during the 5-year period was significantly lower in the combination group than in the IVR group (*P*=0.04). The number of retreatments in the first and third years was higher in the IVR group than in the combination group (Fig. 2; *P*=0.02 and 0.003, respectively), with no significant intergroup differences in the number of retreatments in the second, fourth, and fifth years.

DISCUSSION

In the present study, the 1-year VA after both combination therapy and anti-VEGF monotherapy was better than the corresponding baseline VA for patients with PCV. However, in both groups, there was no significant improvement in VA at 3, 4, and 5 years. PRN anti-VEGF therapy, which is often administered in clinical practice, with or without PDT did not achieve a long-term improvement in VA, although the visual outcome was superior to that expected in patients with untreated disease.[16] Moreover, combination therapy could reduce the number of additional treatments in patients aged ≥70 years.

In a previous 6-year study, the 3-year VA after PRN anti-VEGF therapy for patients with PCV was similar to the baseline VA.[17] Similarly, a 3-year study assessing a PRN regimen for PCV reported that the post-treatment improvement in VA persisted until a year after treatment, with VA deterioration.[18] These findings are consistent with those of the present study. Multicentre prospective studies of AMD

have suggested that a PRN regimen is inferior to a monthly injection regimen with regard to the persistence of improved VA.[19, 20] The SEVEN-UP study reported that the 7-year VA decreased relative to the baseline VA in patients with AMD treated on a PRN basis.[12] In clinical practice, PRN monotherapy has a limited effect in terms of the long-term maintenance of improved VA in patients with PCV. Therefore, monthly injections or a treat-and-extend regimen would be preferable in this scenario.

Some retrospective noncomparative studies reported VA improvements at 1 year in patients with PCV treated by PRN combination therapy with PDT and IVR.[6-8] However, the improvement was not sustained in the second year.[8] These results are consistent with the present findings. In contrast, a retrospective non-comparative study reported a sustained improvement in VA at 3 years after initial combination treatment with PDT and intravitreal bevacizumab injection, followed by PDT and intravitreal bevacizumab on a PRN basis.[21] The EVEREST II study reported that combination therapy was superior to IVR monotherapy in terms of the 12-month visual outcomes and number of injections.[10] Thus, data regarding the long-term outcomes of these regimens are desirable.

Macular atrophy is a frequent finding in eyes with wet AMD both before and after anti-VEGF therapy.[13] In the CATT study, newly developed atrophy was observed in 26% eyes after a 2-year regimen of monthly IVR and 15% eyes after PRN IVR treatment.[22] There is no evidence suggesting that PDT increases the risk of macular atrophy, excluding high myopia.[23] In the present study, newly developed macular atrophy including the fovea was observed in 45% eyes in the combination group and 22% eyes in the IVR group (P=0.06). PDT damages the choriocapillary endothelium within a short interval.[24] We consider that the damage may affect macular atrophy development in the long term. The 5-year incidence of macular atrophy including the fovea was significantly correlated with the 5-year VA in our combination group. These results suggest that combination therapy should be carefully chosen for patients who are potentially susceptible to macular atrophy, and that it is better to administer PDT in regions excluding the fovea.

The baseline GLD was associated with the 5-year VA in our IVR group. Tsujikawa et al. reported that the post-treatment VA in patients with PCV was worse in the presence of large vascular lesions measuring more than one disc area.[25] Our findings for the IVR group are consistent with these findings,[25] and those of another 3-year study.[18] However, GLD was not associated with VA in our combination group; this suggests that the effect of IVR monotherapy on the 5-year VA may be limited for eyes with PCV exhibiting an increased GLD before treatment.

The present study has some limitations. First is the retrospective design. To our knowledge, there is only one prospective trial on this subject, i.e. the EVEREST

study, which recently reported its 12-month data.[10] Second, the mean patient age in the combination group was significantly higher than that in the IVR group, although we performed a subgroup analysis and found no significant influence of age on the findings.

In conclusion, our findings suggest that a PRN regimen for PCV may have a limited effect for the long-term maintenance of improved VA. Macular atrophy may occur more frequently with combination therapy and is possibly associated with 5-year VA. Thus, combination therapy should be carefully selected for patients who susceptible to macular atrophy.

REFERENCES

1. Yannuzzi LA, Sorenson J, Spaide RF, et al. Idiopathic polypoidal choroidal vasculopathy (IPCV). *Retina* 1990;**10**:1-8.
2. Imamura Y, Engelbert M, Iida T, et al. Polypoidal choroidal vasculopathy: a review. *Surv. Ophthalmol.* 2010;**55**:501-15.
3. Terasaki H, Miyake Y, Suzuki T, et al. Polypoidal choroidal vasculopathy treated with macular translocation: clinical pathological correlation. *Br. J. Ophthalmol.* 2002;**86**:321-27.
4. Matsuoka M, Ogata N, Otsuji T, et al. Expression of pigment epithelium derived factor and vascular endothelial growth factor in choroidal neovascular membranes and polypoidal choroidal vasculopathy. *Br. J. Ophthalmol.* 2004;**88**:809-15.
5. Hata M, Tsujikawa A, Miyake M, et al. Two-year visual outcome of ranibizumab in typical neovascular age-related macular degeneration and polypoidal choroidal vasculopathy. *Graefes Arch. Clin. Exp. Ophthalmol.* 2015;**253**:221-27.
6. Lee YH, Lee EK, Shin KS, et al. Intravitreal ranibizumab combined with verteporfin photodynamic therapy for treating polypoidal choroidal vasculopathy. *Retina* 2011;**31**:1287-93.
7. Tomita K, Tsujikawa A, Yamashiro K, et al. Treatment of polypoidal choroidal vasculopathy with photodynamic therapy combined with intravitreal injections of ranibizumab. *Am. J. Ophthalmol.* 2012;**153**:68-80.
8. Hata M, Tsujikawa A, Miyake M, et al. Two-year visual outcome of polypoidal choroidal vasculopathy treated with photodynamic therapy combined with intravitreal injections of ranibizumab. *Graefes Arch. Clin. Exp. Ophthalmol.* 2015;**253**:189-97.
9. Koh A, Lee WK, Chen LJ, 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.
10. Koh A, Lai TYY, Takahashi K, 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.
11. Yodoi Y, Tsujikawa A, Otani A, et al. Chorioretinal anastomosis after photodynamic therapy for polypoidal choroidal vasculopathy: CRA after PDT for PCV. *Int. Ophthalmol.* 2008;**28**:297-9.
12. Rofagha S, Bhisitkul RB, Boyer DS, et al. Seven-year outcomes in

ranibizumab-treated patients in ANCHOR, MARINA, and HORIZON: a multicenter cohort study (SEVEN-UP). *Ophthalmology* 2013;**120**:2292-99.

13. Abdelfattah NS, Zhang H, Boyer DS, et al. Progression of macular atrophy in patients with neovascular age-related macular degeneration undergoing antivascular endothelial growth factor therapy. *Retina* 2016;**36**:1843-50.
14. Verteporfin Roundtable Participants. Guidelines for using verteporfin (Visudyne) in photodynamic therapy for choroidal neovascularization due to age-related macular degeneration and other causes: update. *Retina* 2005;**25**:119-34.
15. Yamashiro K, Tomita K, Tsujikawa A, et al. Factors associated with the response of age-related macular degeneration to intravitreal ranibizumab treatment. *Am. J. Ophthalmol.* 2012;**154**:125-36.
16. Cheung CM, Yang E, Lee WK, et al. The natural history of polypoidal choroidal vasculopathy: a multi-center series of untreated Asian patients. *Graefes Arch. Clin. Exp. Ophthalmol.* 2015;**253**:2075-85.
17. Hikichi T. Six-year outcomes of antivascular endothelial growth factor monotherapy for polypoidal choroidal vasculopathy. *Br. J. Ophthalmol.* 2018;**102**:97-101.
18. Kang HM, Koh HJ. Long-term visual outcome and prognostic factors after intravitreal ranibizumab injections for polypoidal choroidal vasculopathy. *Am. J. Ophthalmol.* 2013;**156**:652-60.
19. Rosenfeld PJ, Brown DM, Heier JS, et al. Ranibizumab for neovascular age-related macular degeneration. *N. Engl. J. Med.* 2006;**355**:1419-31.
20. Holz FG, Amoaku W, Donate J, et al. Safety and efficacy of a flexible dosing regimen of ranibizumab in neovascular age-related macular degeneration: the SUSTAIN study. *Ophthalmology* 2011;**118**:663-71.
21. Kang HM, Koh HJ, Lee CS, et al. Combined photodynamic therapy with intravitreal bevacizumab injections for polypoidal choroidal vasculopathy: long-term visual outcome. *Am. J. Ophthalmol.* 2014;**157**:598-606.
22. Martin DF, Maguire MG, Fine SL, et al. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. *Ophthalmology* 2012;**119**:1388-98.
23. Baba T, Kubota-Taniai M, Kitahashi M, et al. Two-year comparison of photodynamic therapy and intravitreal bevacizumab for treatment of myopic choroidal neovascularisation. *Br. J. Ophthalmol.* 2010;**94**:864-70.
24. Schmidt-Erfurth U, Laqua H, Schlotzer-Schrehard U, et al. Histopathological changes following photodynamic therapy in human eyes. *Arch. Ophthalmol.* 2002;**120**:835-44.
25. Tsujikawa A, Ojima Y, Yamashiro K, et al. Association of lesion size and visual

prognosis to polypoidal choroidal vasculopathy. *Am. J. Ophthalmol.* 2011;**151**:961-72.

FIGURE LEGENDS

Figure 1. Representative images showing 5-year changes in macular atrophy after anti-vascular endothelial growth factor treatment with or without photodynamic therapy

Colour fundus photographs(A, B) and SD-OCT images (C, D) acquired at baseline (A, C) and 5 years (B, D) after combination treatment for a 76-year-old woman with PCV (combination group)

Colour fundus photographs (E, F) and SD-OCT images (G, H) acquired at baseline (E, G) and 5 years (F, H) after exclusive treatment with IVR for a 77-year-old man with PCV (IVR group)

While the 5-year colour fundus photographs (B, F) show hypopigmentation and visible choroidal vessels in the macula, the SD-OCT images (D, H) show highly reflective choroidal signals because of retinal thinning and hypopigmentation of the retinal pigment epithelium.

SD-OCT, spectral domain optical coherence tomography; PCV, polypoidal choroidal vasculopathy;.IVR, intravitreal injection of ranibizumab
Combination group: initial treatment with a combination of photodynamic therapy and IVR
IVR group: initially treatment with IVR only

Figure 2. Annual changes in VA (logMAR) and the number of retreatments during a 5-year follow-up period after anti-vascular endothelial growth factor treatment with or without photodynamic therapy for polypoidal choroidal vasculopathy

(A) In the combination group, the 1-year VA is significantly better than the baseline VA (*), whereas VA at 2, 3, 4, and 5 years after treatment is not significantly different from the baseline VA. In the IVR group, VA at 1 and 2 years after treatment is significantly better than the baseline VA ($^{+}$), whereas that at 3, 4, and 5 years is not significantly different from the baseline VA. There is no significant difference in VA between the two groups at any time point.

(B) Findings of subgroup analysis including patients aged ≥70 years
All patients in the combination group were included in this subgroup analysis.
In the IVR group, VA at 1 year after treatment is significantly better than the baseline

VA (+), whereas that at 2, 3, 4, and 5 years is not significantly different from the baseline VA. There is no significant difference in VA between the two groups at any time point.

(C) In the first year, the number of retreatments is higher in the IVR group than in the combination group (*), with no significant differences between groups in the subsequent 4 years.

(D) Findings of subgroup analysis including patients aged ≥70 years
The numbers of retreatments in the first and third years is significantly higher in the IVR group than in the combination group (*), with no significant differences between groups in the second, fourth, and fifth years.

logMAR, logarithm of the minimum angle of resolution; VA, visual acuity; IVR, intravitreal injection of ranibizumab
Combination group: initial treatment with a combination of photodynamic therapy and IVR
IVR group: initially treatment with IVR only

Table 1. Comparison between the combination and IVR groups

		Combination Group	IVR Group	*P*-value
Number of eyes (patients)		20 (20)	41 (41)	
Age, years (range)		77.2±4.4 (70–88)	70.6±7.7 (50–83)	0.001*
Sex (M/F), n		11/9	30/12	0.13#
Axial length, mm		23.09±0.71[a]	23.77±1.46[b]	0.06
LogMAR visual acuity	Baseline	0.41±0.27	0.40±0.46	0.95
	1-year	0.26±0.29	0.29±0.45	0.78
	2-year	0.31±0.32	0.31±0.46	0.97
	3-year	0.33±0.39	0.32±0.46	0.95
	4-year	0.46±0.46	0.36±0.49	0.47
	5-year	0.47±0.40	0.41±0.49	0.63
Central retinal thickness, μm	Baseline	433.1±135.2	363.3±134.1[c]	0.07
	5-year	237.3±114.9	225.1±129.0[d]	0.72
Genotyping, n	*ARMS2* A69S (GG/GT/TT)	4/8/6[e]	10/10/15[f]	0.84##
	CFH I62V (AA/AG/GG)	3/9/6[g]	3/12/20[h]	0.10##
GLD at baseline, μm		3785±1086	3974±2121	0.71
Number of retreatments	Total	5.3±6.4	9.2±10.5	0.14
	Year 1	0.5±0.9	1.7±2.2	0.003*
	Year 2	1.1±1.8	1.6±2.4	0.29
	Year 3	0.8±1.1	2.0±2.8	0.02*
	Year 4	1.5±2.4	2.0±2.7	0.45
	Year 5	1.6±2.3	1.8±2.4	0.70
Additional number of PDT sessions		1.3±1.3	0	-
Macular atrophy including the fovea, n	Baseline	0	4	0.15#
	5-year	9	13	0.31#
	New	9	9	0.06#
Intravitreal gas injection for subretinal haemorrhage, n		1	1	0.55

Data are presented as means ± standard deviations or number of eyes, as applicable.

Combination group: initial treatment with a combination of PDT and IVR

IVR group: initial treatment with IVR only

logMAR, logarithm of the minimal angle of resolution; *ARMS2*, age-related maculopathy susceptibility protein 2; *CFH*, complement factor H; GLD, greatest linear dimension; PDT, photodynamic therapy; IVR, intravitreal injection of ranibizumab

In measurements indicated by [a], [b], [c], [d], [e], [f], [g], and [h], data are missing for one, three, four, one, two, six, two, and six patients, respectively.

[#]chi-square test, [##]chi-square trend test; the remaining: *t*-test

*statistically significant (*P*<0.05)

Table 2. Correlation between the 5-year logMAR VA and other parameters

		Combination Group (n = 20)				IVR Group (n = 41)			
		Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
		***P*-value**	**r**	***P*-value**	**β**	***P*-value**	**r**	***P*-value**	**β**
Age		0.48	-	-	-	< 0.001*	0.53	0.002*	0.37
Sex		0.39	-	-	-	0.44	-	-	-
Axial length		0.38[a]	-	-	-	0.58[b]	-	-	-
LogMAR visual acuity at baseline		0.04*	0.47	0.03*	0.45	< 0.001*	0.58	< 0.001*	0.51
Central retinal thickness	Baseline	0.43	-	-	-	0.051[c]	0.32	0.11	-
	5-Year	0.37	-	-	-	0.73[d]	-	-	-
Genotyping	*ARMS2* A69S	0.66[e]	-	-	-	0.67[f]	-	-	-
	CFH I62V	0.051[g]	−0.47	0.13	-	0.63[h]	-	-	-
GLD at baseline		0.80	-	-	-	0.003*	0.45	0.03*	0.25
Number of retreatments		0.51	-	-	-	0.50	-	-	-
Total number of PDT		0.40	-	-	-	-	-	-	-
Macular atrophy including the fovea	Baseline	0.20	-	-	-	0.13	-	-	-
	5-year	0.02*	0.51	0.03*	0.47	0.23	-	-	-

Combination group: initial treatment with PDT in combination with IVR

IVR group: initial treatment with IVR onlylogMAR, logarithm of the minimum angle of resolution; *ARMS2*, age-related maculopathy susceptibility protein 2; *CFH*, complement factor H; GLD, greatest linear dimension; PDT, photodynamic therapy; IVR, intravitreal injection of ranibizumab

In measurements indicated by [a], [b], [c], [d], [e], [f], [g], and [h], data were missing for 1, 3, 4, 1, 2, 6, 2, and 6 patients, respectively.

In the IVR group, the central retinal thickness at baseline and the 5-year follow-up visit could not be measured because of substantial subretinal haemorrhage in four patients and fibrous scarring in one patient.

Genotyping: 0, non-risk homozygous; 1, heterozygous; 2, risk homozygous

Macular atrophy: 0, absent; 1, present

*statistically significant (*P*<0.05)

Macular atrophy: 0, absent; 1, present

*statistically significant (*P*<0.05).

Table 3. Comparison between patients aged ≥70 years at baseline in the combination and IVR groups

		Combination Group	IVR Group	*P*-value
Number of eyes (patients)		20 (20)	23 (23)	
Age, years (range)		77.2±4.4 (70–88)	76.0±3.5 (70–83)	0.34
Sex (M/F), n		11/9	18/5	0.10[#]
Axial length, mm		23.09±0.71[a]	23.52±1.54[b]	0.28
LogMAR visual acuity	Baseline	0.41±0.27	0.44±0.48	0.81
	1-year	0.26±0.29	0.33±0.40	0.50
	2-year	0.31±0.32	0.38±0.43	0.55
	3-year	0.33±0.39	0.44±0.46	0.40
	4-year	0.46±0.46	0.47±0.47	0.93
	5-year	0.47±0.40	0.53±0.45	0.67
Central retinal thickness, μm	Baseline	433.1±135.2	364.0±150.8[c]	0.13
	5-year	237.3±114.9	210.7±153.0	0.53
Genotyping, n	*ARMS2* A69S (GG/GT/TT)	4/8/6[d]	8/5/4[e]	0.19[##]
	CFH I62V (AA/AG/GG)	3/9/6[f]	1/8/8[g]	0.30[##]
GLD at baseline, μm		3785±1086	4359±1941	0.25
Number of retreatments	Total	5.3±6.4	11.8±11.7	0.04*
	Year 1	0.5±0.9	1.5±1.8	0.02*
	Year 2	1.1±1.8	2.3±2.6	0.08
	Year 3	0.8±1.1	2.9±3.0	0.003*
	Year 4	1.5±2.4	2.6±3.1	0.18
	Year 5	1.6±2.3	2.3±2.8	0.37
Additional number of PDT sessions		1.3±1.3	0	-
Macular atrophy including the fovea, n	Baseline	0	4	0.11[#]
	5-year	9	9	0.76[#]
	New	9	5	0.19[#]
Intravitreal gas injection for subretinal haemorrhage, n		1	1	0.72[#]

Data are presented as means ± standard deviations or number of eyes, as applicable.

Combination group: initial treatment with PDT in combination with IVR

IVR group: initial treatment with IVR only

logMAR, logarithm of the minimum angle of resolution; *ARMS2*, age-related maculopathy susceptibility protein 2; *CFH*, complement factor H; GLD, greatest linear dimension; PDT, photodynamic therapy; IVR, intravitreal injection of ranibizumab

In measurements indicated by [a], [b], [c], [d], [e], [f], and [g], data are missing for one, three, one, two, six, two, and six patients,

respectively.

[#]chi-square test; [##]chi-square trend test; the remaining: *t*-test

*statistically significant (*P*<0.05)

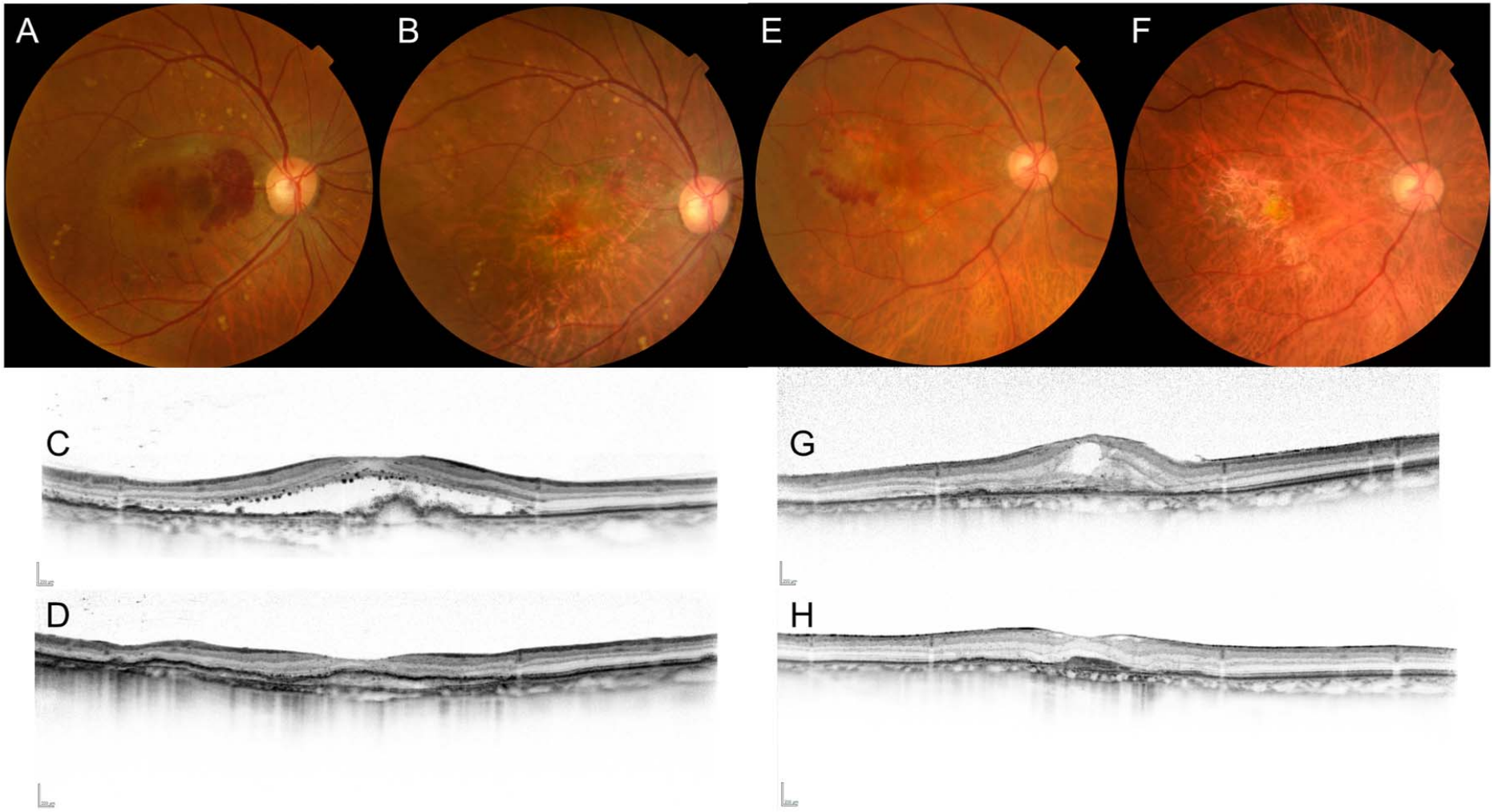

Figure 1

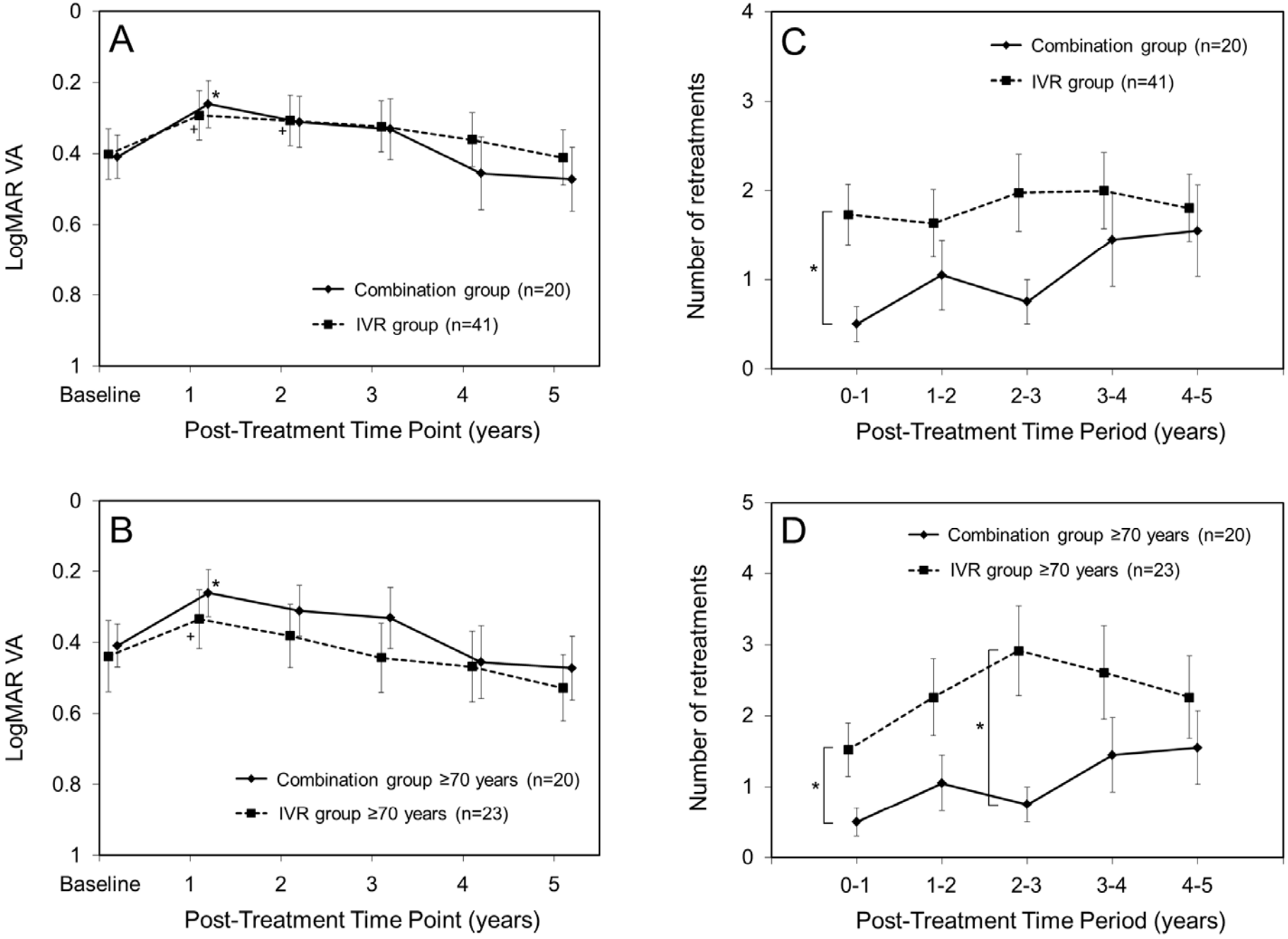
A
LogMAR VA
0
0.2
0.4
0.6
0.8
1
Baseline
1
2
3
4
5
Post-Treatment Time Point (years)
Combination group (n=20)
IVR group (n=41)
*
+
B
LogMAR VA
Combination group ≥70 years (n=20)
IVR group ≥70 years (n=23)
C
Number of retreatments
0
1
2
3
4
0-1
1-2
2-3
3-4
4-5
Post-Treatment Time Period (years)
D
Number of retreatments
0
1
2
3
4
5

Figure 2