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ORIGINAL RESEARCH

Comparison of the 2-Year Results of Photodynamic Therapy with Aflibercept and Aflibercept Monotherapy for Polypoidal Choroidal Vasculopathy

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Purpose: To compare the efficacies of photodynamic therapy (PDT) combined with intravitreal aflibercept (IVA) injections and IVA monotherapy using a treat-and-extend regimen (TAE) for treatment-naïve polypoidal choroidal vasculopathy (PCV).

Patients and Methods: One hundred and nine eyes treated with PDT combined with IVA (PDT+IVA group: 51 eyes) or IVA monotherapy (IVA group: 58 eyes) were assessed for 2 years. The main outcome measures included best-corrected visual acuity (BCVA), central macular thickness (CMT), central choroidal thickness (CCT), number of IVA injections, and macular atrophy (MA). Polypoidal lesions before and after the loading phase were assessed using indocyanine green angiography.

Results: In both groups, BCVA significantly improved after the loading phase and was maintained for 2 years. CMT and CCT were significantly reduced in both groups, without significant differences after 2 years between the groups (P=0.2708). The mean number of IVA injections in the IVA and PDT+IVA groups during the 2 years were 13.2±3.3 and 12.7±1.8, respectively, without a significant difference (P=0.06). The frequencies of MA expansion in the IVA and PDT+IVA groups during the 2 years were 25.9% and 33.4%, respectively, with no significant difference in the incidence (odds ratio: 1.40, P=0.4253). The ratios of polyp regression after the loading phase in the IVA and PDT+IVA groups were 55.2% and 94.1%, respectively, with a significant difference (P<0.0001).

Conclusion: PDT combined with IVA injections using a TAE regimen is effective for anatomical and visual function improvement, without a significant difference as compared to IVA monotherapy. It can facilitate complete regression of polyps with higher odds.

Keywords: polypoidal choroidal vasculopathy, aflibercept, photodynamic therapy, treat-and-extend, macular atrophy

Introduction

Polypoidal choroidal vasculopathy (PCV) is a disease concept proposed by Yannuzzi et al and is characterized by elevated orange-red lesions, branching vascular networks, and dilated polyps at the tip of the lesions on indocyanine green angiography (ICGA).[1] It is classified as a subtype of wet age-related macular degeneration (AMD) and is more prevalent in Asian patients, accounting for approximately half of all wet AMD cases in Japan.[2,3] Recently, the EVEREST II study reported that combination therapy using ranibizumab and photodynamic therapy (PDT) showed more favorable visual outcomes, thinner central macular thickness (CMT), more regression of polypoidal lesions, and required fewer injections than ranibizumab monotherapy.[4]

Conversely, intravitreal aflibercept (IVA), administered as monotherapy for PCV, is effective in improving retinal anatomy and function. Our previous study reported that a treat-and-extend (TAE) regimen comprising IVA for 2 years may be effective for improving best-corrected visual acuity (BCVA) and exudative change in eyes with PCV.[5] In addition, polypoidal lesions regressed completely in 32 patients (55.2%) after the loading phase, and they required

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significantly fewer injections than other patients. As PDT showed a high polyp regression rate in the EVEREST II, we speculated that the combination of PDT with IVA may lead to a high polyp regression rate. Therefore, PDT+IVA may reduce the number of IVA injections.

In the current study, we evaluated the 2-year results of PDT+IVA in a TAE regimen for PCV. We compared the results with those of IVA monotherapy reported by our team.[5]

Materials and Methods

We retrospectively analyzed 51 eyes of 51 patients with previously untreated PCV. This study included patients who received PDT+IVA in a TAE regimen for 2 years at Gunma University Hospital between September 2015 and May 2018. All patients underwent a comprehensive ophthalmic examination, which consisted of slit-lamp biomicroscopy with a noncontact fundus lens (SuperField lens; Volk Optical Inc., Mentor, OH, USA), colour fundus photography, fundus autofluorescence (FAF; Canon CX-1; Canon, Tokyo, Japan), near-infrared reflectance, swept-source optical coherence tomography (OCT) with an axial resolution of 8 μm (DRI OCT-1; Topcon Corp, Tokyo, Japan) or spectral-domain OCT with 5 μm axial resolution (Cirrus OCT; Zeiss Meditec, Inc., Dublin, CA, USA), fluorescein angiography (FA), and ICGA (Spectralis HRA + OCT; Heidelberg Engineering, Heidelberg, Germany). The diagnostic criteria for PCV were elevated orange-red lesions observed on fundus examination and characteristic polypoidal lesions with a branching neovascular network on ICGA.[6]

All eyes were treated with PDT+IVA (2 mg/0.05 mL) injections. PDT with verteporfin (Visudyne; QLT Phototherapeutics Inc., Vancouver, Canada) was administered according to the protocol of the treatment of age-related macular degeneration with a photodynamic therapy study group.[7] Treatment was administered using a 689 nm laser (Carl Zeiss Meditec) that delivered 50 J/cm^2 within 83 seconds. The greatest linear dimension was determined based on the ICGA findings, including polypoidal lesions and blanching vascular networks. An initial IVA was administered 2 days before the application of PDT. Additional IVA was administered each month during the loading phase. The TAE dosing strategy consisted of a loading phase. The interval was prolonged by 2 weeks if a dry macula state was achieved or shortened by 2 weeks if a dry macula was not achieved at the visit. The minimum and maximum dosing intervals were 4 and 12 weeks, respectively. A dry macula was defined as the macula without intraretinal, subretinal, and sub-retinal pigment epithelium (RPE) fluid accompanied by no or diminishing haemorrhage.

At every visit, BCVA, CMT, and central choroidal thickness (CCT) were examined. CMT was defined as the distance between the internal limiting membrane and the bottom of the RPE at the fovea, and CCT was defined as the distance between Bruch's membrane and the margin of the choroid and sclera under the fovea. The CMT and CCT were measured on B-scan OCT images using a computer-based calliper and were recorded independently by two examiners blinded to patient information. FA and ICGA were examined 3 months after the initial treatment. Colour fundus photography, FA, ICGA, FAF, infrared reflectance, and OCT were used to assess macular atrophy (MA) at baseline, 12 months, and 24 months after the initial treatment. The diagnosis of MA was based on previous reports.[8,9] The sharp demarcated hypoautofluorescent areas with the greatest linear dimension over 250 μm in the longest linear dimension in the MA were measured manually using ImageJ software.[10–12] The area of MA was measured on the FAF image at baseline, 12 months, and 24 months after the initial treatment. We compared these results with those of the IVA monotherapy published by Morimoto et al.[5]

The Wilcoxon signed-rank test was used to compare the BCVAs, CMTs, CCTs, and MA at baseline and other time points. The BCVA was converted to a logarithm of the minimal angle of resolution (logMAR) units from decimal values. Unpaired values of the number of IVA injections were compared using the Mann–Whitney *U*-test. One-way analysis of variance was used to assess the associations between the number of polypoidal lesions and the number of injections over 2 years. We analyzed the data using Prism 9. Statistical significance was set at $P < 0.05$.

Results

Table 1 summarizes the baseline characteristics of the included patients. Forty-one men (80.4%) and 10 women (19.6%) were included in the current study. The average age was 74.1±1.0 years (mean±standard error, range: 56–89 years). In 32 eyes (62.7%), exudative changes did not recur after the loading phase, and the IVA injection interval was extended for up to 12 weeks during the maintenance phase. The number of polypoidal lesions observed on ICGA was 2.24±0.16 (mean ±standard error) before treatment.

Table 1 Baseline Characteristics of Patients Treated with Photodynamic Therapy (PDT) Combined with Intravitreal Aflibercept (IVA) Injections (PDT with IVA Group) or IVA Monotherapy (IVA Group) Using a Treat-and-Extend Regimen for Treatment-Naïve Polypoidal Choroidal Vasculopathy

	PDT with IVA (n=51)	IVA (n=58)	P value
Age (years)	74.1±1.0	72.4±1.1	0.3803
Male sex	41(80.4%)	46(78.0%)	0.755
LogMAR BCVA	0.316±0.032	0.268±0.041	0.351
CMT (μm)	295±15	277±13	0.4989
CCT (μm)	237±15	249±15	0.7088
GLD (μm)	2700±155	3167±221	0.2689

Note: Data are presented as mean±SE.
Abbreviations: BCVA, best-corrected visual acuity; IA, indocyanine green angiography; CMT, central macular thickness; CCT, central choroidal thickness; GLD, the greatest linear dimension.

The BCVA was 0.32±0.03 logMAR units (mean±standard error) at baseline, and significantly improved to 0.21±0.03 after 3 months, 0.15±0.03 ($P < 0.01$) after 12 months, and 0.18±0.04 ($P < 0.05$) after 24 months of treatment. CMT was 295±15 μm (mean±standard error) at baseline, and significantly reduced to 157±6 μm ($P < 0.001$) after 3 months, 156±5 ($P < 0.001$) after 12 months, and 162±7 ($P < 0.001$) after 24 months of treatment. CCT was 237±15 μm (mean±standard error) before treatment and significantly reduced to 189±14 μm ($P < 0.05$) after 3 months, 194±14 μm ($P < 0.05$) after 12 months, and 183±13 μm ($P < 0.01$) after 24 months of treatment.

The total number of IVA injections was 7.61±0.16 (average±standard error) in the first year and 5.12±0.16 in the second year. The number of polypoidal lesions before treatment did not correlate with the total number of IVA injections. MA was evaluated in 50 eyes (98.0%). We excluded one patient who developed an RPE tear. MA appeared or expanded in 17 eyes (33.4%) within 2 years. The mean area of atrophy (average±standard error) was 0.083±0.06 mm^2 at baseline, 0.49±0.23 mm^2 after 1 year, and 0.70±0.31 mm^2 after 2 years. Compared with the baseline, the area of MA increased significantly in both the first and second years ($P < 0.001$). In 48 eyes (94.1%), the polypoidal lesions regressed completely in the ICGA after the loading phase. A representative case is shown in Figure 1.

No severe adverse events (including cerebral infarction, myocardial infarction, infectious endophthalmitis, or rhegmatogenous retinal detachment) were observed in the patients.

Discussion

PCV treatment with PDT+IVA in a TAE regimen for 2 years successfully contributed to a significant improvement in BCVA, with the stability of the retinal anatomy throughout the follow-up period. Furthermore, combination therapy facilitated complete regression of the polypoidal lesions in 94.1% of the cases.

We compared these results (PDT with IVA group: 51 eyes) with those of IVA monotherapy (IVA group: 58 eyes) published by Morimoto et al[5] as follows: BCVA was 0.27 ± 0.04 logMAR units (mean ± standard error) at baseline, and significantly improved to 0.18 ± 0.04 ($P < 0.01$) after 3 months, 0.12 ± 0.04 ($P < 0.01$) after 12 months, and 0.15 ± 0.04 ($P < 0.01$) after 24 months of treatment. CMT was 277 ± 12 (mean ± standard error) μm at baseline, and significantly reduced to 147 ± 6 μm ($P < 0.01$), 165 ± 6 μm ($P < 0.01$), and 147 ± 6 μm ($P < 0.01$) after 3, 12, and 24 months of treatment, respectively. The number of polypoidal lesions observed in ICGA was 2.43 ± 0.22 (mean ± standard error) before treatment. In 32 eyes (55.2%), polypoidal lesions regressed completely after the loading phase. CCT was 249 ± 15 μm (mean ± standard error) before the treatment, and significantly reduced to 216 ± 15 μm ($P < 0.01$) after 3 months, 217 ± 13 μm ($P < 0.01$) after 12 months, and 213 ± 13 μm ($P < 0.01$) after 24 months of treatment. The total number of injections (average ± standard error) was 7.71 ± 0.16 in year 1 and 5.45 ± 0.30 in year 2.

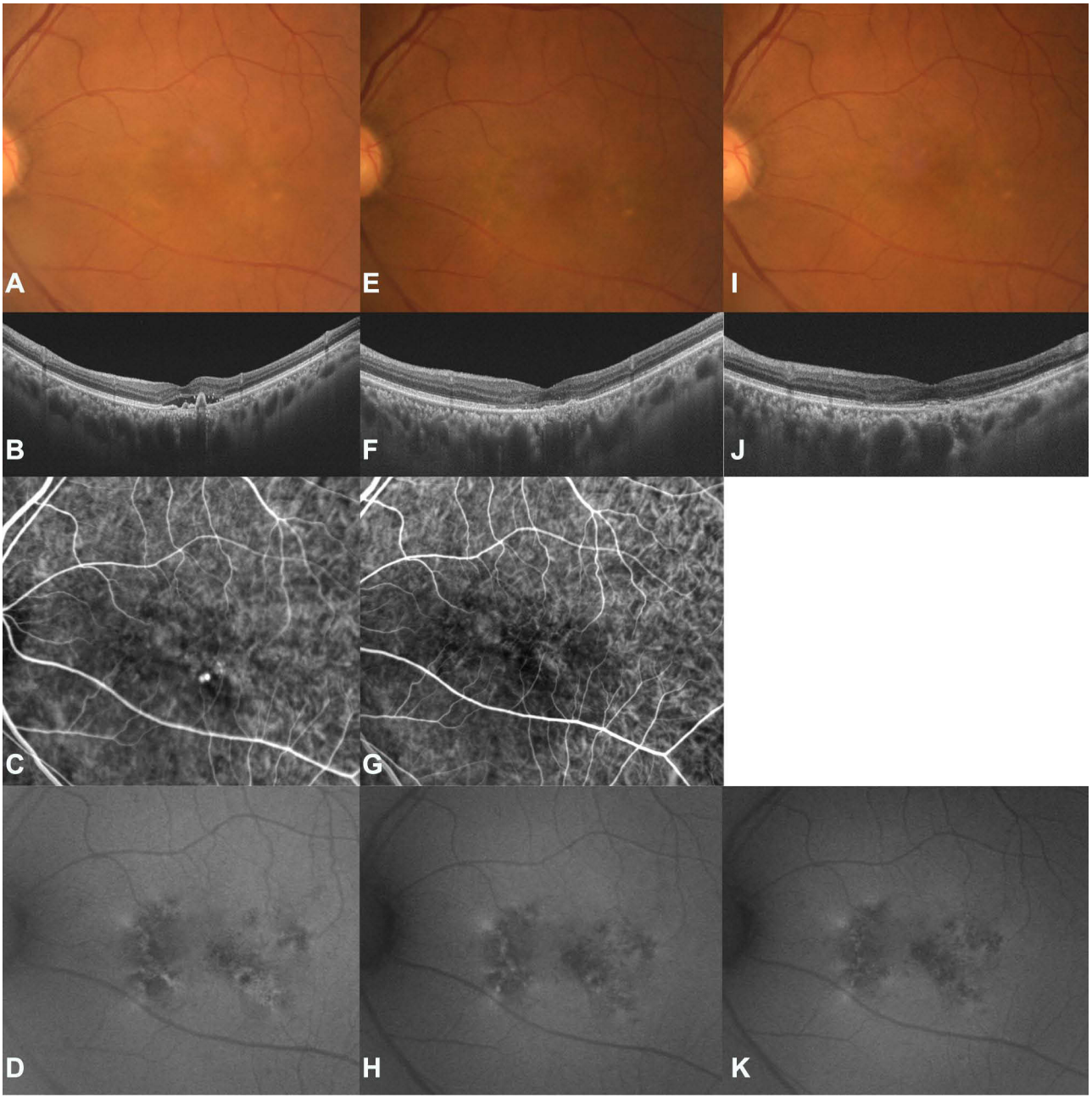

Figure 1 A 75-year-old man with previously untreated polypoidal choroidal vasculopathy (PCV). Best-corrected visual acuity (BCVA) of the right eye was 0.52 logMAR units at baseline. (**A**–**D**) Images were obtained at the baseline. (**A**) A colour fundus photograph showed elevated Orange-red lesion and retinal pigment epithelium (RPE) degeneration at the macula. (**B**) Optical coherence tomography (OCT) B-scan through the fovea showed a protruding pigment epithelial detachment (PED) and double layer sign due to polypoidal lesions with serous retinal detachment (SRD). The CMT and CCT were 242 μm and 546 μm respectively. (**C**) Indocyanine green angiographic (ICGA) image detected branching neovascular networks with two polypoidal lesions. (**D**) Fundus autofluorescence (FAF) revealed a mix of hyperautofluorescence and hypoautofluorescence which corresponded to RPE degeneration. (**E**–**H**) Images were obtained at 3 months after photodynamic therapy combined with intravitreal aflibercept. BCVA of the right eye was 0.52 logMAR units. (**E**) A colour fundus photograph showed diminished Orange-red lesions. (**F**) OCT B-scan through the fovea detected no SRD and polyps regressed. The CMT and CCT were 158 μm and 533 μm respectively. (**G**) ICGA identified no polypoidal lesions but the branching neovascular network remained. (**H**) FAF showed a mix of hyperautofluorescence and hypoautofluorescence and RPE atrophy gradually expanded. (**I**–**K**) Images were obtained 2 years after the initial treatment. BCVA of the right eye was 0.30 logMAR units. (**I**) A colour fundus photograph showed RPE degeneration. (**J**) OCT B-scan through the fovea showed small PEDs but no SRD. The CMT and CCT were 176 μm and 497 μm, respectively. (**K**) FAF revealed enlarged RPE atrophy in the area where polyps had developed.

The BCVA changes during the 2 years in the two groups are shown in Figure 2A. In both groups, BCVA significantly improved after the loading phase and sustained for 2 years. The CMT and CCT changes during the 2 years in the two groups are shown in Figure 2B and C. CMT and CCT reduced significantly in both groups, and there were no significant differences at 2 years between the groups (P=0.2708). The mean number of IVA injections in the IVA and PDT+IVA

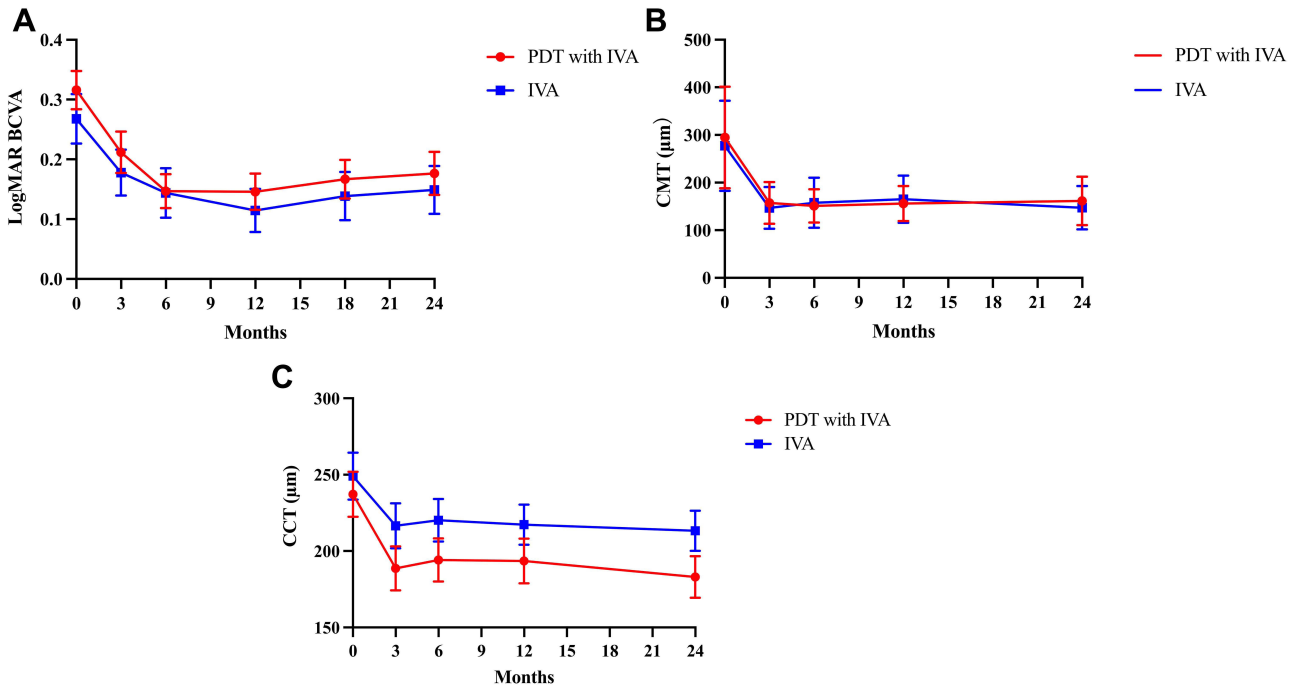

Figure 2 (**A**) Changes in average best-corrected visual acuity (BCVA) in eyes treated for treatment-naïve polypoidal choroidal vasculopathy (PCV). Results were obtained for 51 eyes treated with photodynamic therapy (PDT) with intravitreal aflibercept (IVA; PDT with IVA group) and 58 eyes treated with IVA monotherapy (IVA group). In both groups, BCVA significantly improved after the loading phase and was maintained for 2 years. There was no significant difference between the groups at 2 years. Data are expressed as mean ± standard error. (**B**) Changes in the average central macular thickness (CMT) in eyes treated for treatment-naïve PCV. The results were obtained for 51 eyes treated with PDT with IVA (PDT with IVA group) and 58 eyes treated with IVA monotherapy (IVA group). In both groups, CMT was significantly reduced after 3 months of treatment and was maintained for 2 years. There was no significant difference between the groups at 2 years. Data are expressed as mean ± standard error. (**C**) Changes in the average central choroidal thickness (CCT) in eyes treated for treatment-naïve PCV. The results were obtained for 51 eyes treated with PDT with IVA (PDT with IVA group) and 58 eyes treated with IVA monotherapy (IVA group). In both groups, CCT was significantly reduced after 3 months of treatment and maintained for 2 years. There was no significant difference between the groups at 2 years. Data are expressed as mean ± standard error.

groups during the 2 years were 13.2±3.3 and 12.7±1.8, respectively, without a significant difference (P=0.06). The frequencies of MA expansion in the IVA and PDT+IVA groups during the 2 years were 25.9% and 33.4%, respectively, with no significant difference in the incidence (odds ratio: 1.40, P=0.4253). The proportions of cases of polyp regression after the loading phase in the IVA and PDT+IVA groups were 55.2% and 94.1%, respectively, with a significant difference (P<0.0001).

This study aimed to investigate whether PDT+IVA could reduce the number of IVA injections by increasing the polyp regression rate. In this study, the number of IVA injections for 2 years in the PDT+IVA and IVA groups was 12.7 and 13.2, respectively. There was no significant difference (*P*=0.06); however, the number of IVA injections tended to be lower for the PDT+IVA group than for the IVA group. Hosokawa et al treated 37 patients with IVA using the TAE regimen for 1 year and reported that the average number of treatments was 8.2 for 1 year.[13] Yamamoto et al also treated 67 patients with IVA using the TAE regimen for 1 year and reported that the average number of treatments was 8.3 for 1 year.[14] In this study, the total number of IVA injections was 7.61 in the first year and 5.12 in the second year for the PDT+IVA group and 7.72 in the first year and 4.67 in the second year in the IVA group.

Maruko et al reported that PDT plus ranibizumab combination therapy reduced retinal thickness more than PDT monotherapy, and the changes in the choroidal thickness in both groups were similar.[15] Since the choroid was thinner when treated with IVA than with ranibizumab, we expected that PDT+IVA would result in thinner choroids. In the current study, CCT was significantly reduced in both groups at 2 years. The patients in the PDT+IVA group tended to be thinner than those in the IVA group, but there was no significant difference between the groups.

The frequencies of MA expansion in the IVA and PDT+IVA groups during the 2 years were 25.9% and 33.4%, respectively, with no significant difference in the incidence (odds ratio: 1.40, P=0.4253). Cho et al treated 162 patients with PCV using anti-VEGF injections, and RPE atrophy developed in 17 eyes (10.5%). RPE atrophy occurs at the branching

neovascular network and locations of a polyp or polyp-associated pigment epithelial detachment.[16] They mentioned that subfoveal choroidal thinning at baseline was associated with an increased risk of post-treatment RPE atrophy. Choi et al treated 88 patients with unilateral symptomatic PCV using anti-VEGF injections with or without PDT.[17] They suggested that the incidence of chorioretinal atrophy (CRA) in the anti-VEGF injection plus PDT group (60.2%) was approximately 2 times that in the anti-VEGF injection-only group (31.2%). The absence of subretinal fluid, the presence of intraretinal fluid, and thin choroid were significant risk factors for CRA occurrence for patients with a history of PDT. The incidence of CRA reported by Choi et al was higher than ours because the mean observation period in their study was longer than ours (77.7±31.8 months[17] vs 24 months). Koizumi et al evaluated the development and rate of progression of MA after IVA for AMD over 2 years.[18] They suggested that 14 eyes (16.7%) developed a new MA after 2 years. A poorer BCVA (P=0.01) and the presence of intraretinal fluid (P=0.04) at baseline were independent predictors of MA development.

In our study, the rates of polyp regression after the loading phase in the PDT+IVA and IVA groups were 94.1% and 55.2%, respectively, with a significant difference (P<0.0001). In previous reports, the highest regression rate for polyp lesions was observed after PDT+IVA, followed in order by PDT with ranibizumab combined therapy, IVA monotherapy, and ranibizumab monotherapy.[19–26] The rate of polyp regression in our study was high in the PDT+IVA group. The EVEREST study reported the rates of complete regression of polyps of 77.8% for PDT with ranibizumab, 71.4% for PDT monotherapy, and 28.6% for ranibizumab monotherapy at 6 months.[20] In the current study, polypoidal lesions regressed completely in 48 eyes (94.1%) at 3 months. The regression rate was higher after the PDT+IVA combined therapy. The PLANET study reported a rate of complete regression of polypoidal lesions of 38.9% with IVA monotherapy and 44.8% with IVA plus rescue PDT.[27]

Conclusion

PDT combined with IVA injections using a TAE regimen is effective for anatomical and visual function improvement, without a significant difference as compared to IVA monotherapy. In addition, PDT+IVA can facilitate complete regression of polyps with higher odds.

Consent to Participate

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

Consent to Publish

The authors affirm that human research participants provided informed consent for the publication of the images in Figures (1A–C and 2).

Ethics Approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Gunma university graduate school of medicine (No. HS2020-172).

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Disclosure

The authors report no conflicts of interest in this work.

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