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Comparing Ranibizumab and Aflibercept for Treatment of Polypoidal Choroidal Vasculopathy

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Purpose: To compare the clinical efficacy of intravitreal ranibizumab and aflibercept in treatment-naïve patients with polypoidal choroidal vasculopathy (PCV).

Methods: We retrospectively analyzed the medical records of 82 eyes with treatment-naïve PCV who were treated with ranibizumab or aflibercept and followed for at least six months. Best-corrected visual acuity (BCVA), central foveal thickness (CFT) as measured by optical coherence tomography (OCT), and polyp size in indocyanine green angiography (ICGA) were used for evaluation. The primary endpoint was change at 12 months relative to baseline with respect to BCVA and CFT. Secondary endpoints were anatomical changes in OCT and ICGA findings from baseline.

Results: Data from 46 eyes were considered for the primary endpoint. Twenty-five and 21 eyes received ranibizumab and aflibercept, respectively. Statistically significant improvements in BCVA and CFT compared with baseline were noted in both groups. Of 82 eyes assessed for secondary endpoints, 52 and 30 received ranibizumab and aflibercept, respectively. The subretinal fluid, pigment epithelial detachment, and subfoveal thickness decreased significantly throughout the follow-up in each group. Polyp regression was found in 37.5% and 32.4% of the ranibizumab- and aflibercept-treated groups, respectively. However, there was no significant difference in the treatment results between the drugs.

Conclusions: In a comparison of the clinical efficacy of intravitreal ranibizumab and that of aflibercept in patients with PCV, the treatment groups showed similar clinical results in terms of functional and anatomical outcomes after 12 months.

Keywords: Aflibercept; Polypoidal choroidal vasculopathy; Ranibizumab

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Introduction

Polypoidal choroidal vasculopathy (PCV) is considered a subtype of wet age-related macular degeneration (AMD) characterized by a branching vascular network (BVN) and polypoidal choroidal vascular lesions. These two demonstrable components are seen clearly in indocyanine green angiography (ICGA) [1,2]. PCV incidence differs among ethnic groups; the condition has been reported in 23% to 55% of Asian patients but only in 4.0% to 9.8% of Caucasian patients with neovascular AMD [3-6]. While PCV has a relatively benign course compared with that of typical AMD, vision can still deteriorate significantly due to repeated subretinal hemorrhages, leakage from PCV lesions, and vitreous hemorrhage [5-7].

Photodynamic therapy (PDT) with verteporfin and PDT in combination with anti-vascular endothelial growth factor (VEGF) drugs is safe and effective for treating PCV [8-11]. Conventional anti-VEGF monotherapy has also been reported to improve visual and anatomical outcomes. However, the rate of complete polyp regression is low in comparison with that seen after PDT [12,13]. In the six-month results of a randomized, controlled clinical trial for PCV comparing the efficacy of PDT alone, PDT in combination with ranibizumab (Lucentis; Genentech, South San Francisco, CA, USA), and ranibizumab monotherapy (EVEREST study) [11], treatment with PDT alone and that in combination with ranibizumab yielded a higher rate of complete regression of polyps than did ranibizumab monotherapy.

Aflibercept (Eylea; Bayer HeathCare, Berlin, Germany) is an anti-VEGF agent that is a recombinant soluble decoy fusion protein capable of binding to all VEGF-A and VEGF-B isoforms and placental growth factor [14]. For PCV treatment, intravitreal aflibercept injection shows comparable results to PDT in terms of regression of polyps with stabilization of vision [15,16]. Hosokawa et al. [15] reported that, at six months after aflibercept injection, polyp lesions were completely resolved in 77.7% of patients. These results suggest that aflibercept monotherapy might be a compatible and promising treatment for PCV. To date, only one study has compared intravitreal ranibizumab and aflibercept treatments for PCV [17]. This work showed a significant improvement in visual acuity after 12 months of treatment; however, no difference in acuity was found between the therapeutic agents.

In this study, we compared the 12-month functional and anatomical outcomes following treatment with intravitreal ranibizumab or aflibercept in patients with PCV. In addition to treatment-associated changes in visual acuity, we utilized optical coherence tomography (OCT) and ICGA to characterize anatomical responses such as subfoveal choroidal thickness, polyp and BVN area, and heights of subretinal fluid (SRF) and pigment epithelial detachment (PED).

Materials and Methods

The medical records of patients diagnosed with PCV and treated using anti-VEGF (ranibizumab or aflibercept) intravitreal injections at the Asan Medical Center from August 2009 to July 2016 were retrospectively reviewed. This study was reviewed and approved by the institutional review board (IRB) of the Asan Medical Center (IRB No. 2016-0431) and complied with the guidelines of the Declaration of Helsinki.

Study participants were those diagnosed with treatment-naïve PCV, established on the basis of fundus examination showing orange-red subretinal vascular structures with subretinal hemorrhage and PED and confirmed by findings of typical BVN with polyp-like choroidal vessel dilatation at the periphery in ICGA images using a confocal scanning laser photo ophthalmoscope (HRA2; Heidelberg Engineering Inc., Dossenheim, Germany). The ICGA results of patients who were aged >50 years at diagnosis were reviewed. Subjects who had no treatment before diagnosis and who received intravitreal injections at least three times using only one kind of anti-VEGF agent (ranibizumab or aflibercept) were included. Only patients whose follow-up period was longer than six months were included. The exclusion criteria were the following: concomitant PDT treatment, use of other anti-VEGF agents, presence of active inflammation or infection, uncontrolled intraocular pressure, any ocular condition that may impact vision and/or confound study outcomes, prior treatment with anti-VEGF therapy, verteporfin PDT, other laser and surgical interventions, and/or use of intraocular corticosteroids in the study eye. All included patients were given a loading dose of three intravitreal anti-VEGF (ranibizumab 0.5 mg/0.05 mL or aflibercept 2 mg/0.05 mL) injections within a one-month interval [18]. After the loading injections were administered, most patients were treated via a treat-and-extend strategy or pro re nata (PRN) regimen ac-

cording to the physician's discretion. Criteria for retreatment were new or persistent fluid on OCT, an increase in or persistent PED on OCT, an increase in central retinal thickness of 100 μm or more compared with the lowest previous value, loss of vision from the best previous score in conjunction with recurrent fluid on OCT, new-onset classic neovascularization, or new macular hemorrhage.

Baseline data included patients' medical history, age, sex, and VA and slit-lamp microscopy, dilated fundus examination, OCT (Spectralis OCT; Heidelberg Engineering Inc., Heidelberg, Germany), fluorescein angiography (FA), and ICGA findings. At every visit, all patients underwent measurement of best-corrected visual acuity (BCVA), color fundus photography, and OCT. Additional FA and ICGA inspections were repeated after the initial loading injections. For OCT, central foveal thickness (CFT) was obtained using the automated thickness map of the Heidelberg Eye Explorer (Heidelberg Engineering Inc., Heidelberg, Germany). The SRF, PED heights, and subfoveal choroidal thickness were manually measured using the National Institutes of Health image analysis software (ImageJ 1.48v; National Institutes of Health, Bethesda, MD, USA) by one retinal specialist (A.R.C.). The SRF height was defined as the maximal vertical distance of the hypo-reflective subretinal area from the hyper-reflective line of the retinal pigment epithelium (RPE) to the outermost line of the sensory retina on fovea-centered horizontal images. The PED height was also defined as the

maximal vertical distance of the hypo-reflective sub-RPE area from the hyper-reflective line of Bruch's membrane to the hyper-reflective line of the RPE on fovea-centered horizontal images. Subfoveal choroidal thickness was defined as the subfoveal vertical distance of the hypo-reflective area from the hyper-reflective line of Bruch's membrane to the margin corresponding to the sclero-choroidal interface. The total area of the greatest polyp was measured manually using ImageJ, and the area of the abnormal BVN was also measured on the basis of the ICGA images. The numbers of polyps were counted, and polyp regression was defined as complete disappearance of polyp lesions in ICGA performed after three consecutive monthly injections of each anti-VEGF agent, regardless of the number of polyps present at baseline examination.

The primary endpoint was the change at 12 months from baseline with respect to BCVA and CFT. Secondary endpoints were anatomical change in OCT and ICGA findings from baseline to three and six months, respectively. The secondary endpoints included height of SRF, height of PED, subfoveal choroidal thickness, polyp and BVN size, and polyp regression rate. The differences in BCVA and CFT at baseline and subsequent time points (i.e., one, three, six, nine, and 12 months after the primary injection) were analyzed using repeated-measures analyses of variance (ANOVA). For statistical analysis, the Snellen BCVA was converted to a logarithm of the minimal angle of resolution

Table 1. Baseline characteristics of the two groups (82 eyes total)

	Ranibizumab (n = 52)	Aflibercept (n = 30)	p-value
Age (years)	67.4 $\pm$ 8.7	66.5 $\pm$ 10.7	0.677*
Sex (male:female)	36 : 16	23 : 7	0.611 [†]
Baseline visual acuity (logMAR)	0.56 $\pm$ 0.40	0.55 $\pm$ 0.41	0.956*
Baseline central foveal thickness (μm)	434.9 $\pm$ 155.1	440.0 $\pm$ 138.9	0.854*
Baseline maximal SRF height (μm)	174.61 $\pm$ 176.61	205.72 $\pm$ 158.23	0.445*
Baseline maximal PED height (μm)	301.45 $\pm$ 198.87	264.05 $\pm$ 174.56	0.441*
Baseline subfoveal choroidal thickness (μm)	269.36 $\pm$ 108.17	298.96 $\pm$ 113.39	0.283*
Baseline number of polyps	2.12 $\pm$ 1.29	2.14 $\pm$ 1.35	0.948*
Baseline area of polyp (mm^2)	0.46 $\pm$ 0.52	0.40 $\pm$ 0.33	0.593*
Baseline area of BVN (mm^2)	4.34 $\pm$ 5.40	2.90 $\pm$ 2.49	0.183*

Values are presented as mean $\pm$ standard deviation unless otherwise indicated.

logMAR = logarithm of the minimum angle of resolution; SRF = subretinal fluid; PED = pigment epithelial detachment; BVN = branching vascular network.

*Statistics by repeated-measures analyses of variance (ANOVA); [†]Statistics by repeated-measures Chi-square test.

(logMAR). In addition, the changes in SRF and PED height from baseline at six months were analyzed using repeated-measures ANOVA, and changes in the size of polyps and BVN from baseline to three months were analyzed using Student's *t*-test. For missing data in repeated-measures ANOVA, statistical analysis was performed by carrying forward the last observation. Statistical comparisons between the datasets were performed using SPSS software version 13.0 (IBM Corp., Armonk, NY, USA). *p*-values < 0.05 were considered statistically significant.

Results

A total of 119 eyes (115 patients) were diagnosed with PCV at our institution during the study period. Of these, 37 eyes were excluded because of concomitant PDT treatment or treatment with other anti-VEGF agents. Eighty-two eyes with treatment-naïve PCV were followed for at least six months; the mean age of the included subjects was 66.8 ± 9.2 (range: 51–87) years. Fifty-two and 30 eyes were treated with ranibizumab and aflibercept, respectively. The baseline characteristics and clinical data of the patients are shown in Table 1. There were no significant differences between the

two groups with regard to baseline BCVA, CFT, heights of SRF and PED, numbers of polyps, area of polyps, and BVN (Table 1) at baseline visit. Of the 82 treatment-naïve eyes, 32 were excluded because they either switched to another intravitreal injection agent or were lost to follow-up.

In total, 46 eyes were available for analysis of primary study endpoints; of these, 25 were treated with ranibizumab and 21 were treated with aflibercept. After 12 months, the mean BCVA was significantly improved from baseline in both groups (Fig. 1). Specifically, the mean BCVA (logMAR) for the ranibizumab-treated group improved from 0.59 ± 0.43 to 0.41 ± 0.41 ($p < 0.01$) after one year, while, in the aflibercept-treated group, the BCVA improved from 0.59 ± 0.42 to 0.34 ± 0.30 ($p < 0.01$) after one year. The mean CFT decreased significantly and gradually from baseline throughout the 12-month follow-up in both groups (Fig. 2). In particular, for the ranibizumab-treated patients, the CFT decreased from 414.2 ± 126.7 mm to 270.0 ± 79.9 mm ($p < 0.01$) after one year. In the aflibercept-treated group, the CFT decreased from 449.0 ± 135.1 mm to 253.9 ± 57.5 mm after one year. However, no statistically significant difference was found between the two groups in terms of BCVA or CFT improvement ($p > 0.05$, Table 2). Aflibercept-treated patients showed significantly fewer numbers of injections than did

Figure 1. Changes in mean visual acuity (logMAR) during 12 months of follow-up. Significant visual improvement was achieved at three, six, nine, and 12 months in both groups. However, there was no significant difference between the findings in the two groups (Table 2). BCVA = best-corrected visual acuity; mon = month(s). *Repeated-measures analyses of variance (ANOVA) compared with baseline.

Figure 2. Changes in central foveal thickness during 12 months of follow-up. The mean central foveal thickness decreased significantly at three, six, nine, and 12 months of follow-up in both groups. However, there was no significant difference between the two groups (Table 2). mon = month(s). *Repeated-measures analyses of variance (ANOVA) compared with baseline.

Table 2. Comparisons of clinical outcomes after injection of ranibizumab or aflibercept (46 eyes total)

	Ranibizumab (n = 25)	Aflibercept (n = 21)	p-value
Visual acuity (logMAR) (baseline)	0.59 ± 0.43	0.59 ± 0.42	0.903*
Visual acuity (logMAR) (3 months)	0.48 ± 0.41	0.49 ± 0.45	0.978 [†]
Visual acuity (logMAR) (6 months)	0.44 ± 0.41	0.38 ± 0.35	0.900 [†]
Visual acuity (logMAR) (9 months)	0.43 ± 0.40	0.40 ± 0.39	0.883 [†]
Visual acuity (logMAR) (1 year)	0.41 ± 0.41	0.34 ± 0.30	0.644 [†]
Central foveal thickness (μm) (baseline)	414.2 ± 126.7	449.0 ± 135.1	0.372*
Central foveal thickness (μm) (3 months)	285.8 ± 119.0	248.6 ± 53.3	0.359 [†]
Central foveal thickness (μm) (6 months)	270.9 ± 100.1	252.0 ± 61.3	0.277 [†]
Central foveal thickness (μm) (9 months)	298.6 ± 104.6	243.5 ± 49.9	0.199 [†]
Central foveal thickness (μm) (1 year)	270.0 ± 79.9	253.9 ± 57.5	0.210 [†]
Number of injections (6 months)	4.64 ± 0.91	3.76 ± 0.77	0.001*
Number of injections (1 year)	7.48 ± 2.18	6.76 ± 1.14	0.161*

Values are presented as mean ± standard deviation unless otherwise indicated.

logMAR = logarithm of the minimum angle of resolution.

*Statistics by Student's *t*-test; [†]Statistics by repeated-measures analyses of variance (ANOVA).

Table 3. Six-month clinical outcomes after injection of ranibizumab or aflibercept (82 eyes total)

	Ranibizumab (n = 52)	Aflibercept (n = 30)	p-value*
Maximal SRF height (μm)	34.2 ± 56.1	20.8 ± 48.9	0.296
Mean change from baseline (μm)	-140.4	-184.9	0.298
Maximal PED height (μm)	176.6 ± 123.7	124.6 ± 114.7	0.074
Mean change from baseline (μm)	-124.8	-139.5	0.753
Subfoveal choroidal thickness (μm)	265.2 ± 128.2	274.8 ± 112.0	0.486
Mean change from baseline (μm)	-13.4	-24.2	0.144

Values are presented as mean ± standard deviation unless otherwise indicated.

SRF = subretinal fluid; PED = pigment epithelial detachment.

*Statistics by Student's *t*-test.

Table 4. Three-month clinical and angiographic outcomes after injection of ranibizumab or aflibercept (82 eyes total)

	Ranibizumab (n = 52)	Aflibercept (n = 30)	p-value
Number of polyps	1.32 ± 1.39	1.20 ± 1.35	0.734*
Mean change from baseline	-0.82	-0.84	0.954 [†]
Area of polyp (mm ²)	0.29 ± 0.32	0.16 ± 0.21	0.139*
Mean change from baseline (mm ²)	-0.22	-0.18	0.774 [†]
Polyp regression (%)	37.5	32.4	0.448 [†]
Area of BVN (mm ²)	4.28 ± 4.91	2.57 ± 2.29	0.106*
Mean change from baseline (mm ²)	-0.52	-0.32	0.544 [†]

Values are presented as the mean ± standard deviation unless otherwise indicated.

BVN = branching vascular network.

*Statistics by Student's *t*-test; [†]Statistics by repeated-measures analyses of variance (ANOVA); [‡]Statistics by Chi-square test.

those treated with ranibizumab during the six-month period (4.64 vs. 3.76, $p = 0.001$). However, there was no significant difference at 12 months (7.48 vs. 6.74, $p = 0.161$).

As secondary study endpoints, the parameters related to anatomical changes at six months are shown in Table 3. The mean SRF and PED significantly and gradually decreased throughout the follow-up period in both groups, although there was no significant difference between the drugs. Similarly, the mean subfoveal choroidal thickness decreased throughout the six-month follow-up period in both groups, but no significant difference between the two agents was observed. For the ranibizumab-treated eyes, the polyp area decreased from $0.46 \pm 0.52 \text{ mm}^2$ to $0.29 \pm 0.32 \text{ mm}^2$ and the BVN area decreased from $4.34 \pm 5.40 \text{ mm}^2$ to $4.28 \pm 4.91 \text{ mm}^2$ ($p = 0.067$ and 0.025 , respectively). Changes in polypoidal lesion characteristics are shown in Table 4. For the aflibercept-treated eyes, the polyp area decreased from $0.40 \pm 0.33 \text{ mm}^2$ to $0.16 \pm 0.12 \text{ mm}^2$ and the BVN area decreased from 2.90 ± 2.49 to 2.57 ± 2.29 ($p = 0.01$ and 0.03 , respectively). There were no significant differences between the agents with regard to the area of the polyps or the BVN ($p = 0.136$ and 0.139 , respectively). Complete polyp regression was observed in 11 out of 34 patients in the ranibizumab-treated group (37.5%) and in nine out of 24 patients in the aflibercept-treated group (32.4%) after three months. There was no significant difference in terms of polyp regression between the drugs ($p = 0.448$, Table 4).

Discussion

In the present study, we investigated and compared the 12-month efficacy of intravitreal ranibizumab and aflibercept in terms of anatomical and functional improvement in eyes with newly diagnosed PCV. In the treatment of PCV, several studies report that anti-VEGF therapy improves visual acuity and structural outcomes. Oishi et al. [19] showed that intravitreal ranibizumab therapy was more effective than PDT in the management of PCV. Kokame et al. [20] found that monthly intravitreal ranibizumab administration improved vision and facilitated the resolution of subretinal lesions. However, in terms of polyp regression, other studies have demonstrated that ranibizumab monotherapy is less effective than PDT with or without anti-VEGF therapy in achieving this goal [12,13]. In the study by Kokame et al. [20],

intravitreal ranibizumab showed 33% polyp regression. In contrast, in the EVEREST study [11], PDT combined with ranibizumab or PDT alone was superior to ranibizumab monotherapy in achieving complete polyp regression (77.8% and 71.4% vs. 28.6%, respectively). On the basis of these results, the recommended treatment for PCV has been either PDT monotherapy or a combination of PDT and intravitreal injections.

Recent work investigating the effectiveness of aflibercept treatment in PCV has documented polyp regression rates following intravitreal administration as falling between 67% and 77.7% [15,16,21]. For this reason, aflibercept monotherapy may be considered a comparable treatment option to PDT in patients with PCV. However, our data show that the polyp closure rate after ranibizumab or aflibercept monotherapy is inferior to that of other recent studies that have employed aflibercept. One explanation for this may be that the time point we selected for polyp evaluation was likely different than those chosen in other studies. In this study, ICGA was performed at baseline and after three consecutive injections [15,16]. In other work, regression of the polypoidal lesions was evaluated at the sixth month after at least four rounds of injection. Taking into consideration the early evaluation of polyp closure, the comparable improvement of visual acuity, and the reduction of CFT at the 12th month in the present study, the polyp closure rate may in fact be higher at 12 months.

We can draw comparisons between the results of recent studies to infer the relative efficacies of ranibizumab and aflibercept in the treatment of PCV. Cho et al. [21] reported that intravitreal ranibizumab treatment improved the mean CFT from 338 μm to 286 μm and the mean logMAR BCVA by 0.19 at six months. Additionally, Hosokawa et al. [15] demonstrated that treatment with intravitreal aflibercept for six months improved the mean CFT from 407.2 μm to 229.1 μm and the mean logMAR BCVA from 0.414 to 0.297. In the present study, the mean CFT and logMAR BCVA improvements are similar to those noted in these reports, and we found no significant differences between the two drugs in terms of visual or anatomical improvement. Aflibercept-treated patients showed a larger decrease in mean CFT, but this was not a statistically significant change. In addition, when we analyzed specific anatomical lesions (e.g., SRF, PED), all parameters improved throughout the treatment. Cho et al. [17] showed comparable results following use of

either intravitreal ranibizumab or aflibercept treatment in 98 PCV patients. In their study, BCVA and CFT improved after 12 months of treatment, but the relative improvements did not differ between treatment groups. Aflibercept treatment, however, was associated with a significantly higher rate of polyp regression (39.5% vs. 21.6%). In contrast, in the present study, the polyp regression rate did not differ between ranibizumab and aflibercept therapies. On the basis of this difference across studies, prospective head-to-head randomized trials should be considered to systematically determine the relative efficacies of these therapies in terms of polyp closure rates. Currently, a randomized clinical trial to identify the efficacy of intravitreal aflibercept monotherapy compared with that of aflibercept with adjuvant PDT in PCV patients (PLANET study) and a large-scale phase IV randomized multi-center study using ranibizumab or ranibizumab in combination with PDT (EVEREST II) are ongoing. The results of these large, long-term studies could provide an objective basis for comparing clinical features between these two anti-VEGF agents and for identifying the difference in efficacy between anti-VEGF monotherapy and combination therapy with PDT.

There are several limitations associated with the current study: specifically, the sample size was small with potential selection bias, data were retrospective in nature, treatment groups were not randomized, long-term ICGA analysis was not possible, and the majority of subjects received fewer injections than the number that was scheduled for 12 months because of delayed visits or loss to follow-up. Since this was a short-term study and the follow-up periods for primary and secondary endpoints were different, our data should be evaluated with caution. Nonetheless, this study's results are clinically meaningful with respect to ICGA imaging of the early anatomical responses of PCV lesions to anti-VEGF monotherapy after three initial treatments.

In summary, intravitreal ranibizumab and aflibercept treatments in patients with PCV are effective at 12 months and do not show any significant difference in terms of visual and anatomical improvement.

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