초기에 좋은 시력을 보였던 결절맥락막혈관병증 환자를 대상으로 한 유리체강내 항혈관내피성장인자 치료의 2년 결과

Two-year Outcomes after Intravitreal Anti-vascular Endothelial Growth Factor Therapy for Polypoidal Choroidal Vasculopathy Patients with Good Initial Visual Acuity

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Purpose: To investigate 2-year treatment outcomes of anti-vascular endothelial growth factor (VEGF) therapy in eyes with polypoidal choroidal vasculopathy (PCV) with good baseline visual acuity.

Methods: This retrospective, observational study included 21 eyes (10 eyes with a subfoveal polyp, 11 eyes with an extrafoveal polyp) of 21 subjects diagnosed with PCV. All eyes had a baseline best-corrected visual acuity (BCVA) of 20/25 or better and were administered an initial treatment of three intravitreal anti-VEGF injections at one-month intervals. Additional anti-VEGF treatments were administered as needed for recurring cases. BCVA and central foveal thickness (CFT) obtained 24 months after diagnosis were compared with baseline values.

Results: Mean logarithm of the minimal angle of resolution (logMAR) BCVA was 0.07 ± 0.04 at baseline and 0.19 ± 0.29 approximately 24 months after initial diagnosis, a slight difference that was not statistically significant ($p = 0.560$). Of the 21 eyes included, 17 eyes (80.9%) had stable vision and 4 eyes (19.0%) had a ≥ 0.2 deterioration in logMAR BCVA. Twenty-four-month CFT ($212.9 \pm 76.1 \mu\text{m}$) was significantly lower than baseline CFT ($324.6 \pm 121.2 \mu\text{m}$, $p = 0.015$).

Conclusions: Two-year visual outcomes following anti-VEGF therapy in eyes with PCV and good initial visual acuity were generally favorable. However, logMAR BCVA deteriorated by ≥ 0.2 in 19.0% of treated eyes.

Keywords: Anti-vascular endothelial growth factor; Good visual acuity; Long-term; Polypoidal choroidal vasculopathy

Introduction

Anti-vascular endothelial growth factor (VEGF) therapy is effective for treating exudative age-related macular degeneration (AMD) [1,2] and previous studies have shown rela-

tively favorable long-term outcomes of anti-VEGF therapy in treating exudative AMD [2-6]. Polypoidal choroidal vasculopathy (PCV) is a subtype of exudative AMD and is characterized by the presence of a branching vascular network and polypoidal lesions that are detectable with indocyanine

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green angiography (ICGA). Long-term anti-VEGF therapy outcomes are generally favorable in eyes with PCV [5,7]. However, few studies have examined long-term outcomes of this treatment on eyes with PCV and a good visual acuity at the time of diagnosis [8].

Mori and colleagues [8] investigated treatment outcomes in eyes with PCV and an initial logarithm of the minimum angle of resolution (logMAR) visual acuity of 0.6 (Snellen: 20/80) or better. Visual acuity significantly improved and central retinal thickness significantly decreased after 12 months of treatment. Unfortunately, outcomes beyond 12 months have not been documented.

Here, we investigate the 2-year treatment outcomes of anti-VEGF therapy in eyes with PCV and a good visual acuity (20/25 or better) at the time of diagnosis. Possible mechanisms for marked visual acuity deterioration during the first 2 years of anti-VEGF therapy are also examined.

Materials and Methods

This retrospective, observational case series was performed at a single center. The study was approved by the Kim's Eye Hospital Institutional Review Board and all study conduct adhered to the tenets of the Declaration of Helsinki. The medical records of patients who were newly diagnosed with PCV between January 2010 and December 2012 at our institution were reviewed and considered for inclusion. Eyes with branching vascular networks and/or terminating polypoidal lesions on ICGA were diagnosed with PCV.

All included patients had undergone an initial comprehensive ophthalmologic examination, including best-corrected visual acuity (BCVA) measurement, slit-lamp biomicroscopy (90 D lens), fundus photography, fluorescein angiography, spectral domain optical coherence tomography (OCT; Spectral OCT/SLO[®], OTI Ophthalmic Technologies, Inc., Miami, FL, USA) and indocyanine green angiography (confocal laser-scanning system, HRA-2, Heidelberg Engineering, Dossenheim, Germany). All included patients had been treated with intravitreal anti-VEGF agents and were followed for up to 24 months. Subject were excluded from analyses if they were followed for less than 24 months or had a severe media opacity, history of intraocular surgery (except cataract surgery), evidence of a macroaneurysm, proliferative diabetic retinopathy, a central retinal vascular

occlusion, or other retinal disorders known to affect macular microstructure and function. Eyes that had undergone other treatments for exudative AMD (e.g., photodynamic therapy) were also excluded from analyses. However, eyes that had undergone pneumatic displacement for treatment of a submacular hemorrhage were not excluded. Eyes that underwent cataract surgery or had definite cataract progression during the follow-up period were also excluded.

All eyes underwent an initial series of three consecutive monthly intravitreal ranibizumab injections and were then treated on an as needed basis. Patients were scheduled to visit the hospital for examination every 1-4 months at the treating physician's discretion. All OCT, fluorescein angiography, and ICGA imaging were performed when needed, as determined by the clinician. Re-treatment with intravitreal anti-VEGF (either ranibizumab or bevacizumab) was generally performed when intraretinal/subretinal fluid or retinal/subretinal hemorrhage was accompanied by a central foveal thickness (CFT) that exceeded 300 μm . However, re-treatment was performed if CFT was $<300 \mu\text{m}$ and BCVA had deteriorated. The presence of a pigment epithelial detachment (PED) was not sufficient for re-treatment.

The OCT was used to obtain automated average thickness measurements of the 1 mm diameter central macular area in only some patients. Therefore, manual CFT measurements were used to analyze macular anatomy. The CFT was defined as the distance between the internal limiting membrane and Bruch's membrane at the fovea and was manually measured using the built-in calipers of the OCT system software. The greatest linear dimension of the entire PCV lesion detected by ICGA, including the branching vascular network and polypoidal lesion, was measured using the built-in calipers provided by the ICGA system software. As described in previous reports [9,10], eyes that had multifocal hyperfluorescent areas in the middle and late phases of ICGA were given a diagnosis of choroidal vascular hyperpermeability. The BCVA was converted to the logMAR scale for all data analyses.

Baseline BCVA and CFT measurements were compared with those obtained at 3, 12, and 24 months after initiating treatment. The BCVA and CFT at 24 months were compared between patients with different baseline characteristics, including sex, choroidal hyperpermeability, polyp location (extra- or subfoveal), and the presence/absence of a fovea-involving PED. Additionally, associations between baseline

characteristics (e.g., age, BCVA, CFT, and greatest lesion linear dimension) and BCVA at 24 months and between baseline characteristics and CFT at 24 months were examined. The characteristics of patients who experienced a logMAR BCVA loss of ≥ 0.2 over the 24-month follow-up period were also examined. This was done by dividing subjects into those who had a ≥ 0.2 logMAR BCVA deterioration ($n = 4$ eyes) and those who had stable vision (< 0.2 logMAR BCVA deterioration, $n = 17$ eyes). Baseline characteristics were then compared between the two groups.

Data are presented as mean $\pm$ standard deviation where applicable. Statistical analyses were performed using a commercially available software package (SPSS ver. 12.0 for Windows, SPSS, Inc., Chicago, IL, USA). Differences among values measured at different time points were analyzed using a repeated-measures analysis of variance with Bonferroni's correction. Differences in values between groups were examined using a Mann-Whitney *U*-test or a Fisher's exact test. Correlations between variables were examined using a Pearson's correlation analysis. A $p < 0.05$ was considered statistically significant.

Results

A total of 47 eyes (47 patients) were identified that had newly diagnosed PCV and a BCVA of 20/25 or better at the time of diagnosis. A total of 26 eyes (55.3%) were excluded from analyses because of a follow-up period shorter than 24 months (18 eyes), inadequate OCT imaging (6 eyes), or other reasons (2 eyes). Among the 18 patients lost to follow-up, 6 patients (33.3%) decided to visit another hospital. The exact reason for follow-up loss in the remaining 12 patients (66.7%) was not accurately identified. Ultimately, 21 eyes of 21 patients (44.7%) were included in study analyses (Table 1). Out of the 21 included patients, 14 (66.7%) were men and 7 (33.3%) women. At the time of PCV diagnosis (baseline), subject age was 65.4 ± 7.2 years (range: 54-80 years), BCVA was 0.07 ± 0.04 (20/23, range: 20/25-20/20), and CFT was 324.6 ± 121.2 μm (range: 188-631 μm). The greatest linear dimension of lesions average 2.0 ± 0.9 mm (range: 1.0-4.7 mm) and 9 eyes (42.9%) had choroidal vascular hyperpermeability. Additionally, PCV lesion location at baseline was subfoveal or juxtafoveal in 10 eyes (47.6%) and extrafoveal in 11 eyes (52.4%). A PED that involved the fovea was noted in 7 eyes (33.3%).

Subjects underwent an average of 5.8 ± 2.4 intravitreal injections (range: 3-12 injections) of anti-VEGF agents (ranibizumab: 4.1 ± 1.0 injections, bevacizumab: 1.5 ± 1.9 injections) during the 24-month follow-up period. Subjects with subfoveal/juxtafoveal polyps underwent 5.1 ± 2.4 injections and subjects with extrafoveal polyps underwent 6.1 ± 2.7 injections. Nine eyes (42.9%) were treated with only ranibizumab and the remaining 12 eyes (57.1%) were treated with both ranibizumab and bevacizumab. During the 24-month follow-up period, 2 eyes developed a fovea-involving submacular hemorrhage and patients visited the hospital 9.5 ± 1.7 times (range: 8-13 times) for eye examinations. Additionally, OCT imaging was performed an average of 7.0 ± 1.2 times (range: 6-10 times) in each patient.

The BCVA at baseline and at 3, 12, and 24 months after initial diagnosis was 0.07 ± 0.04 (20/23), 0.05 ± 0.06 (20/22), 0.11 ± 0.17 (20/25) and 0.19 ± 0.29 (20/30), respectively (Fig. 1A). There was no significant difference in BCVA between any of the four time points examined ($p = 0.431$). Additionally, BCVA at baseline was not significantly different from

Table 1. Baseline characteristics of eyes with polypoidal choroidal vasculopathy and a good initial visual acuity ($n = 21$ eyes of 21 patients)

Characteristic	Value
Age (years)	65.4 ± 7.2 (54-80)
Sex (n, %)	
Male	14 (66.7)
Female	7 (33.3)
logMAR BCVA	0.07 ± 0.04 (20/25-20/20)
Central foveal thickness (μm)	324.6 ± 121.2 (188-631)
Greatest linear dimension (mm)	2.0 ± 0.9
Fovea-involving PED (n, %)	7 (33.3)
Choroidal vascular hyperpermeability (n, %)	
Present	9 (42.9)
Absent	12 (57.1)
Location of PCV lesion (n, %)	
Subfoveal	10 (47.6)
Extrafoveal	11 (52.4)

Data are presented as mean $\pm$ standard deviation (range) where applicable.

BCVA = best-corrected visual acuity; logMAR = logarithm of minimal angle of resolution; PCV = polypoidal choroidal vasculopathy; PED = pigment epithelial detachment.

Figure 1. Treatment outcome of polypoidal choroidal vasculopathy. (A) Mean logarithm of the minimal angle of resolution (logMAR) best-corrected visual acuity (BCVA). (B) Central foveal thickness. Statistical analyses were performed using repeated-measures analysis of variance with Bonferroni's correction. Error bars represent one standard deviation. M = months.

BCVA at 3, 12, or 24 months ($p = 1.000$, $p = 1.000$, $p = 1.000$ and $p = 0.560$, respectively). Fig. 2 shows representative images of an eye that had maintained a good BCVA over the 24-month follow-up period.

A total of 4 eyes (19.0%) had a worsening in logMAR BCVA by ≥ 0.2 . However, the remaining 17 eyes (80.9%) had a stable BCVA. Despite treatment, serous subretinal fluid persisted in 1 eye (baseline BCVA = 20/25, 24-month BCVA = 20/40), a subfoveal polypoidal lesion developed in 1 eye (baseline BCVA = 20/25, 24-month BCVA = 20/50), and a fovea-involving submacular hemorrhage developed in 2 eyes during the follow-up period. The two eyes with a submacular hemorrhage were treated with pneumatic displacement (baseline BCVA = 20/20, 24-month BCVA = 20/200) or intravitreal anti-VEGF monotherapy (baseline BCVA = 20/25, 24-month BCVA = 20/200).

Figure 2. A representative case showing treatment outcome of polypoidal choroidal vasculopathy. (A-C) Best-corrected visual acuity (BCVA) at diagnosis (before treatment) was 20/25. (D) Subretinal fluid was no longer present after three consecutive ranibizumab injections. The eye underwent five ranibizumab injections during the 24-month follow-up period. (E) The BCVA was maintained over 2 years and was 20/25 at 24 months. (A) Fundus photography, (B) indocyanine green angiography, (C-E) optical coherence tomography.

Mean CFT at baseline and 3, 12, and 24 months after the initial diagnosis was $324.6 \pm 121.2 \mu\text{m}$, $215.5 \pm 82.4 \mu\text{m}$, $251.4 \pm 118.1 \mu\text{m}$ and $212.9 \pm 76.1 \mu\text{m}$, respectively (Fig. 1B). The CFT was significantly different among the five time points examined ($p = 0.026$) and CFT at baseline was significantly greater than CFT at 3 and 24 months ($p = 0.016$ and 0.015 , respectively). However, the difference from baseline was not significant at 12 months ($p = 0.171$).

The BCVA at 24 months was not significantly different between the two subgroups divided according to baseline subject characteristics (Table 2). In addition, correlations between subject characteristics (age, BCVA, CFT and greatest linear dimension) at baseline and BCVA at 24 months and between subject characteristics at baseline and CFT at 24 months were not significant (Table 3). Additionally, baseline characteristics were not significantly different between patients with stable BCVA over 24 months and those who experienced BCVA loss over 24 months (Table 4).

The mean duration of the follow-up period of the 18 patients lost to follow-up was 11.1 ± 5.4 months (range: 4-21 months). The mean BCVA at diagnosis in these patients was 0.07 ± 0.03 (20/23), which had decreased to 0.12 ± 0.09 (20/26) at the last follow-up visit. The CFT was $318.7 \pm 67.6 \mu\text{m}$ at

Table 2. Comparison of best-corrected visual acuity (BCVA) and central foveal thickness (CFT) at 24 months in groups divided according to baseline characteristics

Characteristic	24-month BCVA	<i>p</i> -value*	24-month CFT	<i>p</i> -value*
Sex				
Male (n = 14 patients)	0.25 ± 0.34	0.220	219.1 ± 83.6	0.370
Female (n = 7 patients)	0.06 ± 0.05		200.4 ± 62.6	
Choroidal vascular hyperpermeability				
Present (n = 9 eyes)	0.19 ± 0.29	0.361	193.4 ± 35.9	0.594
Absent (n = 12 eyes)	0.19 ± 0.30		227.4 ± 95.2	
Location of polyps				
Subfoveal/juxtafoveal (n = 10 eyes)	0.17 ± 0.31	0.262	196.1 ± 26.4	0.888
Extrafoveal (n = 11 eyes)	0.19 ± 0.28		228.1 ± 102.1	
Fovea-involving PED				
Presence	0.23 ± 0.37	0.689	191.6 ± 29.3	0.636
Absence	0.17 ± 0.25		223.5 ± 90.3	

Data are presented as mean ± standard deviation where applicable. Visual acuities were presented as logarithm of minimal angle of resolution scale.

PED = pigment epithelial detachment.

*Indicates statistical analysis performed using a Mann Whitney *U*-test.

Table 3. Correlation of baseline factors with best-corrected visual acuity (BCVA) and central foveal thickness (CFT) at 24 months

Characteristic	<i>p</i> -value* (24-month BCVA)	<i>p</i> -value* (24-month CFT)
Age	0.650	0.180
Baseline BCVA	0.486	0.821
Baseline CFT	0.204	0.759
Greatest linear dimension	0.660	0.756

*Indicates statistical analysis performed using Pearson's correlation analysis.

baseline and 238.1 ± 52.3 µm at the last follow-up visit.

Discussion

In the present study, eyes diagnosed with PCV that had good initial visual acuity maintained acuity up to 24 months after diagnosis. Additionally, CFT at 24 months was significantly lower than baseline value and BCVA remained relatively stable in the majority of eyes during the follow-up period. However, a ≥0.2 logMAR deterioration in BCVA was noted in some eyes, suggesting that a good initial visual acuity

does not guarantee a favorable visual outcome.

Monthly follow-up examinations, including OCT, are generally recommended after initial anti-VEGF treatment for exudative AMD. This approach facilitates early detection and prompt treatment of any recurrent exudation [11,12]. Delaying treatment by even one month can significantly affect visual prognosis [13]. One study that evaluated 12-month treatment outcomes in PCV patients with a good initial visual acuity involved monthly follow-ups and OCT examinations [8]. This allowed for prompt treatment of any recurrence. Unfortunately, a strict monthly follow-up protocol with frequent OCT examinations is not possible in many clinical settings. It has been reported that outcomes following anti-VEGF therapy for exudative AMD are relatively unfavorable in the clinical setting [14,15]. The follow-up schedule and frequency of OCT examinations for the present study were not strictly controlled. During the 24-month follow-up period, the mean number of follow-up visits was only 9.5 and the mean number of OCT examinations was only 7.0. Additionally, the mean number of anti-VEGF injections was 5.8, far less than that reported by previous well-controlled clinical trials [5,11,12]. However, the maintenance or improvement of visual acuity observed in the majority of eyes, despite this study's shortcoming in the follow-up schedule,

Table 4. Comparison of baseline characteristics in eyes with a stable best-corrected visual acuity (BCVA, n = 17 eyes) and eyes with a deteriorated BCVA (n = 4 eyes)

Characteristic	Stable BCVA group	Deteriorated BCVA group	p-value
Age (years)	64.6 ± 6.6	68.8 ± 9.7	0.462*
Sex (n, %)			
Male	10 (58.8)	4 (100)	0.255†
Female	7 (41.2)	0	
logMAR BCVA	0.08 ± 0.04	0.05 ± 0.06	0.484*
Central foveal thickness (μm)	344.4 ± 126.2	240.5 ± 35.9	0.172*
Greatest linear dimension (mm)	1,895.4 ± 808.3	2,566.8 ± 1,492.8	0.362*
Choroidal vascular hyperpermeability (n, %)			
Present	8 (47.1)	1 (25.0)	0.603†
Absent	9 (52.9)	3 (75.5)	
Location of PCV lesion (n, %)			
Subfoveal	8 (47.1)	2 (50)	1.000†
Extrafoveal	9 (52.9)	2 (50)	

Data are presented as mean ± standard deviation where applicable.

logMAR = logarithm of minimal angle of resolution; PCV = polypoidal choroidal vasculopathy.

*Indicates statistical analysis performed using a Mann Whitney U-test; †Indicates statistical analysis performed using a Fisher's exact test.

highlights the favorable outcomes of anti-VEGF therapy in eyes with PCV and a good initial visual acuity.

Here, a deterioration in BCVA of ≥ 0.2 logMAR was noted in 4 eyes. Persistent serous subretinal fluid was noted in one of these eyes, suggesting that chronic subretinal fluid can negatively affect visual prognosis. It has been shown that photodynamic therapy alone or in combination with anti-VEGF therapy can resolve exudate in eyes with fluid that persists after anti-VEGF therapy [16]. These treatment modalities represent useful alternatives in such cases.

Two eyes exhibited signs of submacular hemorrhage, which has been associated with a poor visual prognosis in exudative AMD [17,18]. These two eyes were treated with either pneumatic displacement or intravitreal anti-VEGF monotherapy, both of which have been shown to be effective in treating submacular hemorrhage secondary to exudative AMD [19-24]. However, visual acuity failed to return to baseline values in both patients. This suggests that submacular hemorrhage development has a negative influence on visual prognosis in eyes with PCV. The development of a subfoveal polypoidal lesion was noted in one eye. This was not surprising because new polypoidal lesion development is not unusual in eyes with PCV [25]. What was notable was that the newly developed lesion was a cluster of grape-like

polyps [25-27]. This type of lesion has been associated with a poor prognosis after photodynamic [26] and/or anti-VEGF therapy [27], conversion to typical choroidal neovascularization [26] and the development of submacular hemorrhage [27]. Although our patient did not develop signs of submacular hemorrhage, massive exudate from the newly developed polyps caused a marked deterioration in visual acuity that did not improve with anti-VEGF therapy. This suggests that additional studies are needed to evaluate the efficacy of other treatments not involving anti-VEGF agents on eyes with similar disease.

The results of the present study show that visual prognosis was favorable, even in eyes with subfoveal/juxtafoveal polyps. Because recurrent fluid is associated with a poor visual prognosis in eyes with PCV [28], our result may have reflected the small number eyes with recurrent fluid that required retreatment. In the study by Kang and Koh [28], subjects received an average of 5.39 ± 0.50 injections during the first year of treatment and 3.00 ± 0.53 injections during the second year of treatment. Additionally, the subjects in the study by Lee and Lee [29] received an average of 12.50 ± 2.77 injections over a 2 year treatment period. In the present study, only 5.6 injections were administered during the 24-month follow-up period, with 5.1 injections administered to eyes

with subfoveal/juxtafoveal polyps. Therefore, our subjects had a markedly lower injection frequency than that of previous studies. Second, baseline visual acuity was predictive of long-term visual outcome in eyes with PCV [30,31]. Because our patients had a good baseline visual acuity, regardless of polyp location, this may have influenced our visual outcomes.

In the present study, we attempted to identify factors that were predictive of 24-month visual outcomes. However, none of the variables examined were significantly associated with 24-month visual acuity. Choroidal vascular hyperpermeability is frequently observed on ICGA in eyes with PCV [9,10,32,33] and is associated with greater choroidal thickness [10,32], bilateral neovascular membranes [10] and a poor response to initial ranibizumab treatment [10]. Although a recent study showed that choroidal vascular hyperpermeability is associated with a poor visual prognosis at 12 months [33], the association of this peculiar finding with the treatment outcome beyond this time point is not known. Here, we found that 42.8% of eyes with PCV had choroidal vascular hyperpermeability. The visual acuity at 24 months was not different between eyes with and without choroidal vascular hyperpermeability, suggesting that the presence of choroidal vascular hyperpermeability may not significantly influence long-term visual prognosis in eyes with PCV and a good initial visual acuity. However, considering that only half of our examined patients completed 2 years of follow-up, further studies are needed to confirm our findings. We also found that baseline characteristics were not significantly different between patients who had a marked visual acuity deterioration and patients who maintained stable vision. However, the number of patients ultimately included in the analyses was small, which may have influenced our results. Therefore, further studies on larger populations are needed to confirm our findings.

Our study had some limitations, including its retrospective design and relatively small sample size. The small sample size may have influenced the results of statistical analyses. Additionally, the follow-up examination and treatment schedules were not controlled and only half of eligible patients completed the required 2-year follow-up period. The exact reason for loss of follow-up was also not identified in the majority of lost patients. Therefore, a selection bias towards a favorable outcome may have significantly affected study results. In the present study, no common guidelines

were used to select anti-VEGF agents. Ranibizumab and/or bevacizumab were used in each patient at the discretion of the treating physician. In addition, both ranibizumab and bevacizumab were used in the majority of eyes. Therefore, this study cannot contribute to information on the efficacy of a single anti-VEGF agent. However, both agents have comparable long-term efficacy for treating exudative AMD and the influence of using both anti-VEGF agents may not have significantly influenced study results. Lastly, because ICGA was not routinely performed during the follow-up period, this study does not provide further insight into the influence of anti-VEGF therapy on polypoidal lesion and branching vascular network regression.

In spite of these deficiencies, our study demonstrates that visual acuity is generally maintained over a 2-year follow-up period when anti-VEGF therapy is used to treat PCV in eyes with a good initial visual acuity. However, 19% of the included eyes did have a deterioration in logMAR BCVA of 0.2 or more. This suggests that outcome expectations should be managed by informing patients that their prognosis could be unfavorable even though visual acuity is good at the time of diagnosis. Further studies on consecutive patients are needed to identify predictive factors of long-term (24 months) visual outcomes for this condition.

Conflicts of interest

There are no conflicts of interest.

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