·Clinical Research·

Effects of three consecutive monthly intravitreal injection of ranibizumab for polypoidal choroidal vasculopathy in Korea

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Abstract

• AIM: To evaluate the efficacy and safety of three consecutive monthly injections of intravitreal ranibizumab for the treatment of polypoidal choroidal vasculopathy (PCV) in Korea.

• METHODS: A retrospective chart review of 25 patients (27 eyes) with PCV was conducted. Patients received three initial monthly intravitreal injections (0.5 mg) of ranibizumab and were monitored monthly for 12mo from January 2010 to October 2011. Reinjection of ranibizumab after three initial monthly loading was administered on an as-needed basis, guided by the optical coherence tomography (OCT), fluorescein angiography (FA) and indocyanine green angiography (ICGA). The main outcomes were the changes of the mean best corrected Snellen visual acuity (VA), central macular thickness (CMT) by OCT, the changes of polyps and branching vascular network by FA and ICGA, and total number of injections received by patients during the 12mo.

• RESULTS: The mean best corrected Snellen visual acuities at baseline, 1, 3, 6 and 12mo after primary injection were 0.77±0.59, 0.76±0.53, 0.70±0.47, 0.63±0.43, 0.61±0.43, 0.62±0.42 logMAR, respectively, and showed significant improvement at 3, 6, 12mo (P=0.003, P=0.002, P=0.018, Wilcoxon signed-rank test). The mean CMT at baseline, 1, 2, 3, 6, and 12mo was 312.41±66.38 μm, 244.59±71.47 μm, 232.32±69.41 μm, 226.69±69.03 μm, 228.62±37.07 μm, 227.59±51.01 μm respectively, and showed significant reduction (all P<0.001, Wilcoxon signed-rank test). Polypoidal lesions resolved on ICGA in 3 eyes (11.1%) and a branching vascular network remained in all 24 eyes (88.9%). A total of 106 injections were given in the 12-month period, which equaled to a mean of 3.92 (range, 3-6) times. Sixteen of the 27 treated eyes had additional 1.56±0.91 injections. The others (11 eyes) had just 3 consecutive injections.

• CONCLUSION: An initial loading dose of three monthly ranibizumab injections is a safe and effective method in treating PCV, with visual and anatomical improvement over one year follow-up.

• **KEYWORDS:** ranibizumab; polypoidal choroidal vasculopathy; intravitral injection
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INTRODUCTION

Polypoidal choroidal vasculopathy (PCV) is a choroidal vascular disease characterized by polypoidal and aneurismal dilatations at the terminals of the branching network in the inner choroid [1-3]. It accounts for 23%-54% of neovascular age-related macular degeneration (AMD) in Asian population[4,5]. The natural course of PCV is reported to be more favorable than AMD. However, it results in severe visual loss, secondary to recurrent serosanguinous detachment of retinal pigment epithelium (RPE) or occasional massive submacular hemorrhage.

Nevertheless, there is still no common consent about the most effective and safest treatment of PCV. Photodynamic therapy (PDT) with verteporfin was recently used as a favorable treatment of PCV. However, it has been shown to increase the risk of visual loss in treating PCV; there is a risk of extensive subretinal hemorrhages and massive suprachoroidal hemorrhage[6,7].

Recently, anti-vascular endothelial growth factors (VEGFs), including bevacizumab (Avastin®, Genetech, South San Francisco, California, USA) and ranibizumab (Lucentis®, Genetech, South San Francisco, California, USA), have shown favorable results in AMD[8,9]. The pathogenesis of PCV is yet unknown. However, PCV is very similar to the neovascular membrane of AMD and increased levels of VEGF were found in aqueous humor and tissue samples of PCV patients[10,11].

Nonetheless, only several small group and short-term reports were found in the literature. Recently, a long-term efficacy and safety of intravitreal bevacizumab injection in treating PCV have been reported by Cheng *et al* [12]. They

recommended bevacizumab for treatment of PCV, which has shown a favorable outcome in improving visual acuity and macular exudative changes. It can also improve the partially regressed polypoidal lesion. Ranibizumab is widely known for its smaller molecular mass and higher affinity for VEGF than bevacizumab. Nevertheless, short-term results of ranibizumab were promising in PCV, though no long term studies have been conducted[13].

In this study, we report our 1-year results of using 3 consecutive monthly intravitreal ranibizumab injections for the treatment of PCV by investigating the changes in vision and foveal height on ranibizumab in 27 eyes with PCV during a 12- month follow-up period.

SUBJECTS AND METHODS

We retrospectively reviewed the records of 27 eyes of 25 patients with PCV, who were treated with intravitreal ranibizumab, from January 2010 to October 2011. The study adhered to the tenets of the Declaration of Helsinki and the protocol was approved by the Institutional Review Board of the Yeouido Saint Mary's Hospital. Inclusion criteria included patients who fulfilled all the following items: 1) PCV as defined by the presence of branching vascular network of choroidal vessels with terminating aneurismal polypoidal lesions in indocyanine green angiography (ICGA), 2) recent onset of symptoms and, finally, 3) follow-up of 1y or more. Exclusion criteria included the following: 1) evidence suggesting choroidal neovascularization (CNV) secondary to AMD suggested by the presence of drusen or pathologic myopia, 2) patients with uncontrolled hypertension, a history of thromboembolic events (*e.g.* myocardial infarction or cerebrovascular accident), or a tendency of coagulopathy and 3) previous vitrectomy, 4) previous PDT. All patients signed a comprehensive consent form before intravitreal ranibizumab injection.

At baseline, each patient underwent best corrected Snellen visual acuity (VA), intraocular pressure, slit lamp examination, fundus examination, fluorescein angiography (FA), ICGA using confocal scanning laser ophthalmoscope (Heidelberg Engineering, Heidelberg, Germany), and optical coherent tomography (OCT) (Cirrus HD-OCT, Carl Zeiss, Dublin, CA, USA).

Patients received a monthly injection of 0.05 mL ranibizumab for 3mo and have been followed up monthly. Recording of best corrected VA (BCVA) and measurement of central macular thickness (CMT) by OCT were done on each case in all the monthly follow-up visits. After completion of the initial 3 injections, FA and ICGA were repeated in each case. Additional FA and ICGA were done as and when fundus examination revealed signs of relapse of PCV on subsequent visits.

Injection of intravitreal ranibizumab was performed as an outpatient procedure in an operating room, under an operating microscope, using topical anesthesia and strict aseptic techniques. After topical anesthesia by 0.5% proparacaine (Alcaine®), the ocular surface and the lid were disinfected with povidone iodine. We used a speculum, sterile gloves and a surgical drape. Intravitreal injection of 0.5 mg of ranibizuamb in 0.05 mL was carried out using a 30-gauge needle at 3.5 mm posterior to the limbus. The injection site was compressed by cotton swab to avoid reflux. After this, the fundus was examined to rule out any complications and to check perfusion of central retinal artery. Gatifloxacin (Gatiflo® ophthalmic solution) eye drops were instilled 4 times a day for 7d. In most patients, the main outcome measurements included the changes in BCVA and CMT documented by OCT. The secondary outcome measurements included the changes in polypoidal lesions on ICGA. Data on BCVA changes and OCT features were analyzed at 1-, 3-, 6-, 9-, and 12-month follow-up time points. Additional injections of ranibizumab were offered if any of following changes were observed by the evaluating physician : 1) a VA loss of 0.2 logarithm of the minimum angle of resolution (logMAR) vision or more, 2) a new hemorrhage, 3) any signs indicating the recurrence of PCV leakage (diffuse edema, intraretinal cyst, subretinal fluid by OCT, an area of leakage demonstrated by FA, or an area of hyperfluorescence suggesting an active polyp on ICGA) was seen.

Subsequent injections were given at least 4wk after the previous injection. Changes in the polypoidal lesions were compared on ICGA. The change in polyps on ICGA was classified into four types. "Resolved" was defined as a complete or nearly complete absence of polyps. "Decreased" was defined as a decreased leakage, and "stationary" indicated a similar leakage of the polyps, although, the polyps still existed. Further, "increased" indicated an increased leakage of the polypoidal lesions. Any ocular and systemic adverse events were also recorded.

Statisitcal Analysis Snellen VA were converted to the logMAR scale for analysis. Statistical analysis was performed using SPSS 15.0 (SPSS, Inc., Chicago, IL, USA). A P value of <0.05 was considered to be statistically significant.

RESULTS

Patients´ Demographics From January 2010 to October 2011, a total of 27 eyes from 25 consecutive patients with symptomatic PCV were treated with intravitreal ranibizumab, monthly, for 3mo and were followed for at least 1y in the Yeouido St. Mary's Hospital in Seoul, Korea. The mean age of the patients was 65.1y (range, 50-83). Gender distribution was 21 men (77.8%) and 6 women (22.2%). Bilateral involvements with either active PCV or inactive macular scars indicating previous exudative fibrovascular macular disease in the fellow eye occurred in 4 patients (14.8%) (Table 1).

Visual Outcome Serial changes in the logMAR BCVA during the study are displayed in Figure 1. At baseline, the mean logMAR BCVA was 0.772. The mean logMAR BCVA at post-treatment 1-, 2-, 3-, 6-, and 12-month intervals became 0.756, 0.701, 0.635, 0.611 and 0.620, respectively.

Table 1 Salient features of patients treated by 3 consecutive monthly intravitreal ranibizumab injections

No.	Age	Sex	Eye	laterality	Location of polyp	Ranibizumab injections at 12mo	BCVA (logMAR)		Polyps in ICGA at last visit	OCT outcome at last visit	CMT (μm)	
							0mo	12mo			0mo	12mo
1	59	M	L	U	Juxtafoveal	3	1.40	1.00	Decreased	SRF(-), PED	351	258
2	75	M	L	U	Subfoveal	5	0.40	0.20	Decreased	SRF(-), PED(-)	415	287
3	50	F	L	U	Subfoveal	4	0.40	0.30	Decreased	SRF(-)	235	233
4	62	F	L	U	Subfoveal	4	0.30	0.00	Stationary	SRF(-)	379	259
5	58	M	R	B	Juxtafoveal	4	0.30	0.30	Decreased	PED	267	244
6	58	M	L	B	Juxtafoveal	4	0.20	0.20	Decreased	SRF(-), PED(-)	276	230
7	62	M	L	U	Subfoveal	5	0.20	0.00	Decreased	SRF(-), PED	313	249
8	61	M	R	U	Subfoveal	5	1.70	1.70	Stationary	SRF, PED	421	231
9	67	M	R	B	Juxtafoveal	5	0.10	1.00	Decreased	SRF, PED	391	207
10	67	M	L	B	Juxtafoveal	5	0.90	1.10	Decreased	SRF(-), PED	230	198
11	75	M	R	U	Subfoveal	3	2.30	1.10	Decreased	SRF(-), PED(-)	296	213
12	56	M	L	U	Juxtafoveal	3	0.70	0.60	Stationary	PED(-)	313	249
13	69	M	L	U	Juxtafoveal	3	0.30	0.20	Decreased	SRF(-)	321	249
14	81	F	R	U	Subfoveal	5	1.22	1.00	Decreased	scarring	266	187
15	65	M	R	U	Subfoveal	4	0.80	0.70	Decreased	SRF(-)	248	177
16	62	M	R	U	Juxtafoveal	6	0.70	0.40	Resolved	scarring	380	208
17	76	F	R	U	Juxtafoveal	4	2.00	0.40	Resolved	SRF(-)	294	121
18	66	F	R	U	Juxtafoveal	4	1.00	0.90	Stationary	PED	253	251
19	59	M	R	U	Subfoveal	3	1.40	1.10	Decreased	scarring	284	214
20	61	M	R	U	Subfoveal	5	0.30	0.40	Decreased	SRF	269	235
21	59	M	R	U	Subfoveal	3	0.70	0.40	Stationary	SRF(-), PED(-)	335	244
22	83	M	L	U	Juxtafoveal	3	0.40	0.40	Decreased	PED(-)	224	176
23	69	F	R	U	Juxtafoveal	3	0.30	0.49	Decreased	SRF, PED	264	200
24	56	M	R	U	Subfoveal	4	0.40	0.40	Resolved	SRF(-)	216	161
25	75	M	L	U	Subfoveal	3	1.22	1.22	Decreased	SRF, PED	437	263
26	67	M	L	U	Subfoveal	3	0.90	0.80	Increased	SRF	347	406
27	58	M	R	U	Subfoveal	3	0.30	0.40	Decreased	SRF(-)	410	195

U: Unilateral; B: Bilateral; BCVA: Best-corrected visual acuity; SRF: Subretinal fluid; PED: Pigment epithelial detachment; PED(-): No pigment epithelial detachment was observed; SRF(-): No subretinal fluid was observed.

Although the BCVA changes were not statistically significant at 1, 2mo after intravitreal ranibizumab injection, these were statistically significant at 3, 6, 12mo and were maintained through all 12-mo of follow-up (P=0.376, P=0.109, P= 0.003, P=0.002, P =0.018, Wilcoxon signed-rank test). At 12mo, 21 eyes (77.8%) had the same or better vision and especially, 5 eyes (18.5%) gained 0.3 or more of the logMAR units. In addition, 6 eyes had lost of the BCVA and these were because of massive lipid exudates involving the macular area that developed, even if polyps in ICGA didn't increase. However, new hemorrhage did not occur.

Changes in Optical Coherence Tomography Serial changes in mean CMT are displayed in Figure 2. At baseline, the mean CMT was 312.41±66.38 μm (range, 216-437). The mean CMT reduced significantly to 244.59 ±71.47 μm at 1mo (P<0.001, Wilcoxon signed-rank test) and remained stable throughout the 12-month follow-up period. At the 2, 3, 6 and 12mo follow-up, the mean CMT was 232.32±69.41 μm, 226.62±37.07 μm, 228.62±37.07 μm, and 227.59±51.01 μm, respectively (all P<0.001, Wilcoxon signed-rank test).

Changes in Indocyanine Green Angiography For the detection of the change in polypoidal lesions, ICGA done within 3mo after treatment were compared with ICGA at baseline. There was a great individual variation in the response of polyps to intravitreal ranibizumab injection. After treatment, ICGA revealed features of resolved polyps in 3 eyes (11.1%), decreased polyps in 18 eyes (66.7%), stationary polyps in 5 eyes (18.5%) and increased polyps in 1 eye (3.7%). Also, the reduction or resolution of polyps was not stationary. In patients who had several ICGA taken in the treatment period, the polypoidal complex sometimes showed repeated recurrence and remission, which was usually associated with recurrent macular exudative changes or serous subretinal fluid in OCT examination (Figure 3).

Number of Injections A total of 106 injections were given in the 12-month period, which equaled to a mean of 3.92 (range, 3-6) times. Sixteen of the 27 treated eyes had additional 1.56±0.91 injections. The others (11 eyes) had just 3 consecutive injections. There was a great individual variation in the number of treatments between patients with PCV.

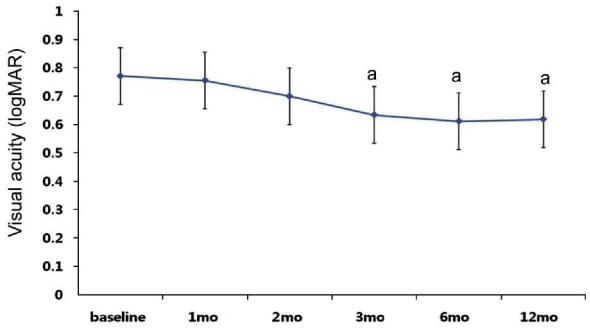

Figure 1 Graph showing changes in the mean logMAR and best –corrected Snellen visual acuity after intravitreal ranibizumab [a]*P* <0.05 when compared with baseline.

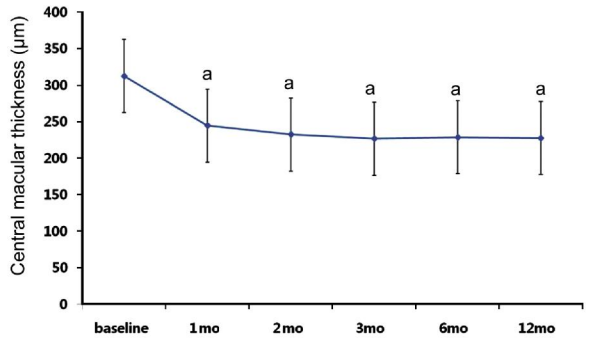

Figure 2 Graph showing changes in OCT and central macular thickness after intravitreal ranibizumab treatment [a]*P* <0.05 when compared with baseline.

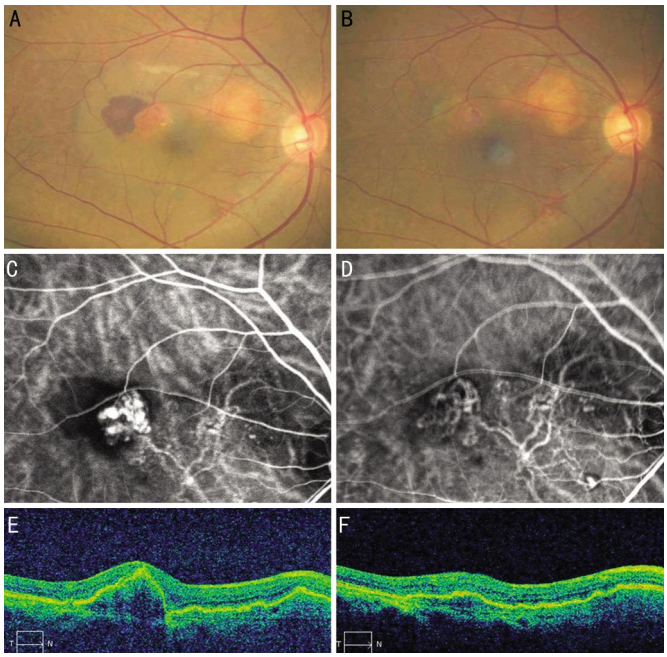

Figure 3 Case 16 A: Baseline fundus photograph showed orange nodular lesion with hemorrhage; B: One year after intravitreal ranibizumab injection, orange nodular lesion resolved with scarring; C: Baseline ICGA showed polypoidal lesions with branch vascular networks (BVN); D: After one year, polyp regressed while BVN remained; E: Baseline horizontal OCT showed pigment epithelial detachment (PED) with macular edema (ME); F: OCT at one year after treatment showed reduction of PED.

Complications None of the patients experienced systemic complications related to intravitreal ranibizumab. Ocular complications, including uveitis, increased intraocular pressure, endophthalmitis, ocular toxicity, and retinal break or detachment, were not observed.

DISCUSSION

The pathogenesis of PCV and the mechanism leading to recurrent hemorrhage and leakage are barely known. Previous known therapeutic modalities included PDT with verteporfin and conventional laser photocoagulation. PDT appears to be superior to conventional laser therapy for reduced retinal damage and ability to treat subfoveal lesions[14,15]. Several studies have reported favorable results in using PDT for the treatment of PCV[6,7]. However, significant adverse effects, such as massive hemorrhage, RPE damage, and fibrous scar formation are still a serious concern that cannot be overlooked [16,17]. The reports of greater expression of VEGF in histopathology and increased VEGF in the aqueous humor have suggested the association of PCV and VEGF [10,11]. Some of the reports present that the anti-VEGF treatment might be a promising treatment to improve PCV [17-20]. Ranibizumab, one of antiangiogenic medications, can block the effects of VEGF. It has been approved and widely used as the primary treatment in CNV, secondary to AMD [21,22]. On the basis of its theoretical and therapeutic effects on CNV, it may also effectively treat PCV [12,23]. In addition to intravitreal anti-VEGF, agents had advantages over PDT because they did not affect the choroidal circulation and were less likely to induce posttreatment hemorrhage[24,25].

In this study, we found that the 3 consecutive monthly intravitreal ranibizumab injections could improve both retinal exudative changes and VA, during a 12mo follow up period. Significant improvements of retinal exudative changes were noted as early as 1mo post-injection and were maintained throughout the 12mo treatment period. There appeared to be a good correlation between the improvement in BCVA and CMT (Figures 1 and 2). The intravitreal ranibizumab treatment also resulted that it did not make the polypoidal lesions worse in 96.3 % of the treated eyes in the 3 monthly consecutive injections in the follow-up periods. However, evidence of complete disappearance of the polypoidal lesions was only found in 3 eyes (11.1%) during the follow-up periods.

Our results suggested that intravitreal ranibizumab injection effectively improved VA and macular exudative changes but had only a limited effect in reducing the choroidal polypoidal abnormalities during the 12mo treatment period. This phenomenon has been noted by several previous reports. Hikichi *et al*[26] reported short term outcomes of the monthly intravitreal ranibizumab injection for 3mo in 50 eyes with PCV. After treatments of one to three injections, most eyes experienced reduced exudative changes, but in 1 eye, the polypoidal lesions worsened. Reche-Frutos *et al*[13] also reported the short term efficacy of intravitreal ranibizumab therapy in 13 eyes with PCV. After the first 3 consecutive monthly 0.05 mL of intravitreal ranibizumab injections,

significant improvement, in both the vision and the foveal thickness, was observed, but persistent polypoidal lesions were still present in 4 eyes (31.2%). Nevertheless, there were still some beneficial effects in the angiography, in which, 6 of the 13 treated eyes had disappeared polyps and all had reduced leakage in FA.

Completely resolved polypoidal lesions were observed in only 3/27 eyes (11.1%) in our study, whereas polypoidal lesions decreased in 4/12 eyes (33%) in the PEARL trial[20] and 13/50 eyes (26%) in Hikichi *et al*'s report[26]. Although, the reason for the difference in the percentage of improved polypoidal lesions is unclear, various response of treatment may be ascribable to the fact that PCV has a variety of clinical manifestations with different natural courses.

Anti-VEGF agents, ranibizumab and bevacizumab, have been widely used in treating CNV [9,27,28]. Furthermore, many recent reports demonstrates the potential effectiveness of these drugs for PCV [17,19,23,26]. There were few published articles on ranibizumab, compared to bevacizumab in treating PCV. However, it would be expected in treating PCV that ranibizumab might be more effective than bevacizumab. This is so since ranibizumab has a smaller molecular weight and is theoretically better able to penetrate the retina and RPE to reach the choroidal vascular lesions of PCV; the drug also has a higher affinity for VEGF, which was previously proposed as the reason for its efficacy in treating PCV. Gomi *et al*[29] reported that 10 eyes with PCV received one to three bevacizumab injection. After 3mo, exudation improved, but bevacizumab was ineffective in diminishing the choroidal vascular change. However, a large study on direct comparison of the two drugs had not been reported yet.

In this study, we treated the patients on the "initial three consecutive monthly injection strategy" as in the PrONTO study basis [30]. Due to the effectiveness of fixed monthly injection strategy and the use of such strategy for several prospective randomized clinical trials of anti-VEGF therapy for neovascular AMD, we treated similarly, like this strategy. As a result, VA and CMT have been relatively maintained after one year and these will ask that compared with "as-needed injection methods". We have previously published regarding the intravitreal ranibizumab injection with or without photodynamic therapy for PCV [31]. In that study, these monotherapy group patients received a pro re nata (PRN; as-needed injection) dosing schedule based on OCT-guided retreatment from the start of the therapy. In these cases, the mean number of injections was 4.46 at 12mo. This could be compared with a mean of 3.92 in three monthly injected cases. It showed that a PRN dosing group seems to need more injections than a loading dose group, but there was no statistically significant difference (P=0.72; Mann-Whitney U test) between a loading dose group and a PRN dosing group. The number of polyps completely resolved were in 2/15 eyes (13.3%) of "as-needed" dosing schedule, decreased or similar in 12/15 eyes (80%), and increased in 1/15 eye (6.7%). The polyp regression rate was

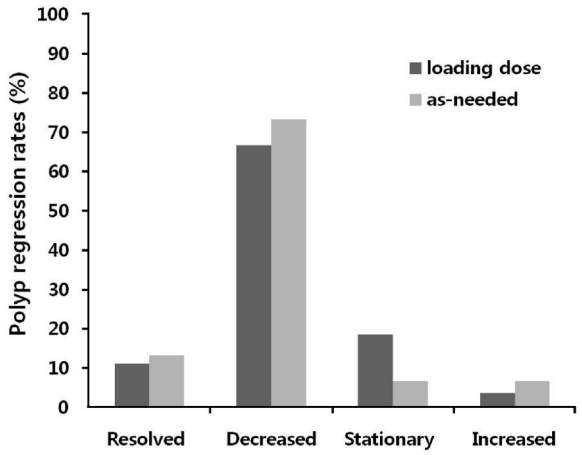

Figure 4 The polyp regression rate was no significant difference between loading dose group and as-needed group (P>0.05, Chi-sqaure test, linear-by linear association).

not significantly different between the two groups (P=0.24; Chi-square test; linear-by-linear association; Figure 4). Although, the patient's characteristics were different and the group sample size were small, the means that our "initial three consecutive monthly injection strategy" lack the potential to reduce the number of reinjections. The randomized Comparison of Age-Related Macular Degeneration Treatments trials (the CATT) [28] was to assess whether a PRN schedule would compromise efficacy, as compared with a loading dose schedule in treating neovacular AMD. It was concluded that ranibizumab given, as needed, was equivalent to ranibizumab given monthly, with a mean difference of 1.7 letters. Yet, these large scale comparative studies has not been performed and the most effective treatment protocols have not been established in treating PCV. Therefore, more effective treatment schedules should be validated in further randomized clinical trials in patient with PCV, because recent studies showed that the intravitreal ranibizumab injection monotherapy itself was effective in the PCV patients [13,31]. According to recently published "EVEREST study", verteporfin PDT combined with ranibizumab was superior to ranibizumab monotherapy (a loading dose schedule) in achieving complete polyp regression (77.8% versus 28.6%; P<0.01)[32]. But all treatments improved mean BCVA and were tolerated over 6mo. Our results are not significantly different from this. But even though polyp regression rate was small, ranibizumab monotherapy (a loading dose schedule) had shown a marked improvement and maintenance in visual acuity and CMT in OCT for over 1y.

In conclusion, our study suggests that a loading dose of three monthly ranibizumab injections is effective in the reduction of macular edema and submacular fluid in PCV, in addition to the improvement in visual acuity for a treatment period of 1y. It can also moderately reduce polypoidal lesions on ICGA.

However, there were limitations in our study. These limitations, such as a retrospective design, lack of a control

group and lack of other injection methods "as-needed base" existed. And the subjects confined to the Korean people only, any ethnic variation and environmental factors did not reflect in our results. Although, intravitreal ranibizumab injection seemed to be not very effective in complete resolution of the polypoidal lesions, the results, sustained effectiveness in reduction of foveal thickness and improvement in vision in our study, was still relatively encouraging.

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Conflicts of Interest: Park YG, None; **Kang S,** None; **Roh YJ,** None.

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