



# Comparison of Intravitreal Ranibizumab and Bevacizumab Treatment for CNV



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## Abstract

**Purpose:** To compare the efficacy of bevacizumab and ranibizumab in the treatment of patients with choroidal neovascularization (CNV).

**Methods:** Patients who received anti-vascular endothelial growth factor (VEGF) agents for CNV. Best-corrected visual acuity (BCVA) and central macular thickness (CMT) were used to compare treatment outcome. BCVA and CMT were by dividing into 3 subgroups; idiopathic CNV, CNV with age-related macular degeneration (AMD), and polypoidal choroidal vasculopathy (PCV).

**Result:** In total CNV patients, both anti-VEGFs showed improvement in BCVA and CMT but they did not show difference in changes of BCVA and CMT. In idiopathic CNV, both anti-VEGFs showed improvement in BCVA and CMT but they did not show difference in changes of BCVA and CMT. In AMD, BCVA and CMT were improved only at 3 months after injection and did not show difference in changes of BCVA and CMT. In PCV, BCVA of patients who received bevacizumab improved through the whole study period, otherwise that of patients who received ranibizumab improved only at 3 months later. CMT of patients with PCV had improved until 3 months after injection in both bevacizumab and ranibizumab group.

**Conclusion:** Intravitreal bevacizumab injection showed similar efficacy and safety as ranibizumab in CNV patients with various pathologic conditions.

**Keywords:** Choroidal neovascularisation; Bevacizumab; Ranibizumab

**Abbreviations:** CNV: Choroidal Neovascularization; VEGF: Vascular Endothelial Growth Factor; BCVA: Best-Corrected Visual Acuity; CMT: Central Macular Thickness; AMD: Age-Related Macular Degeneration; PCV: Polypoidal Choroidal Vasculopathy; PDT: Photodynamic Therapy; OCT: Optical Coherence Tomography

## Introduction

Choroidal neovascularization (CNV) is defined as growth of new blood vessels from the choriocapillaris into the subretinal space or subretinal pigment epithelium [1,2]. CNV causes visual loss by macular exudation, hemorrhage and fibrosis [3]. CNV is a common pathologic condition that occurs in many chorioretinal diseases such as age-related macular degeneration (AMD), pathologic myopia, angioid streak, sarcoidosis, histoplasmosis, choroidal nevus, melanoma, choroidal rupture, polypoidal choroidal vasculopathy (PCV) and idiopathic causes [2,4]. Among these diseases AMD and PCV is very common, in Asia, it represents between 56 and 72 % of all neovascular AMD patients [4]. Various therapeutic options, including photodynamic therapy (PDT) [5-7], anti-vascular endothelial growth factor (VEGF) agents [8-10], have been reported to manage CNV. Recently, pegaptanib, bevacizumab and ranibizumab are used as an anti-VEGF agent [11].

Among these agents, bevacizumab and ranibizumab are commonly used in Korea. Ranibizumab, a high-affinity recombinant

humanized antigen-binding Fob fragment which neutralizes active isoforms of VEGF-A [12]. However, bevacizumab, full-length recombinant humanized antibody binding to all VEGF isoforms, was developed to for treatment of metastatic colorectal cancer and is not approved by Food and Drug Administration for ophthalmic disease [12]. Nevertheless, bevacizumab is used as off-label drug by worldwide ophthalmologist for the treatment of CNV [13,14] because it has been reported that bevacizumab has favorable efficacy and safety profiles and costs lower than ranibizumab [10,14-28]. In this study, the effects of intravitreal bevacizumab injection and ranibizumab injection commonly used in managing CNV were compared and analyzed by dividing into 3 subgroups ; idiopathic CNV, CNV with AMD, and PCV.

## Methods

A retrospective review of patients with CNV was performed. Patients who were treated with bevasizumab or ranibizumab for more than 6 months from January 1, 2008, to June 1, 2011, were

included. From August 1, 2009 in Korea, ranibizumab began to be covered by national health insurance so many patients who had CNV were begun to treated with ranibizumab. Patients were excluded who had any other treatment such as photodynamic therapy (PDT), intravitreal triamcinolone injection or surgery within 6 months. All patients diagnosed by undergoing optical coherence tomography (OCT), fluorescein angiography, indocyanine green angiography. At each follow-up visits best-corrected visual acuity (BCVA) and OCT were performed. BCVA was measured by snellen chart and converted to logarithm of the minimum angle of resolution (log MAR).

OCT was used to quantify central macular thickness (CMT). From January 1, 2008 to August 31, 2009, Stratus OCT (Carl Zeiss Meditec, USA) was used and after then Cirrus OCT (Carl Zeiss Meditec, USA) was used. To minimize the bias from changing of model of OCT during the study period, 50 $\mu$ m was added to CMTs measured by Stratus OCT [29-31]. Both intravitreal bevacizumab and ranibizumab injections were performed with Pro re Nata. Patients received an injection only if the OCT shows a recurrence of fluid or hemorrhage. Intravitreal injections were performed under sterile condition at operating room and before injection the eye was administered topical anesthetics (Alcaine®; Alcon, USA). After then 5% povidone-iodine solution was used to disinfect lids and lashed, and a sterile speculum was placed. The ocular surface was irrigated with 5% povidone-iodine solution and washed out with 5% normal saline. Bevacizumab (1.25mg/0.05ml) or ranibizumab (0.5mg/0.05ml) was injected with 1-mL tuberculin syringe and 30 gauge needle through the pars plana 3.5mm inferotemporally posterior to the limbus. After injection topical anti-biotics (Vigamox®; Alcon, USA) was prescribed to use 4 times a day for a week.

Analyses were performed using SPSS software, version 12.0K (SPSS Inc., Chicago, IL, USA). This study was approved by the Institutional Review Board of Hallym University Medical Center. All subjects signed an informed consent form before participating in the study.

## Results

48 eyes were included in the bevacizumab group and 41 eyes in the ranibizumab group. The mean age of bevacizumab group

was 56 $\pm$ 18 and that of ranibizumab group was 68 $\pm$ 8. Both groups were divided into three subgroups; idiopathic CNV, AMD and PCV. In bevacizumab group, number of idiopathic CNV patients was 24, that of AMD patients were 13 and that of PCV patients were 11. In ranibizumab group, number of idiopathic CNV patients was 15, that of AMD patients were 14 and that of PCV patients were 12 (Table 1). There was no significant difference between the numbers of injection within both groups. ( $p = 0.05$ , independent sample t-test) The number of injections in bevacizumab group was 3.08 $\pm$ 0.74 and that in ranibizumab group was 3.39 $\pm$ 0.74, also showed no significant difference ( $p = 0.372$ , Mann-Whitney U test).

**Table 1:** Demographics of patients.

	Bevacizumab	Ranibizumab
Numbers of Eyes	48	41
Laterality (R* : L†)	21:27	18:23
Sex (M‡ : F§)	27:21:00	26:15:00
Age (Mean $\pm$ SD  )	56 $\pm$ 18	68 $\pm$ 8
Numbers of Idiopathic CNV¶	24	15
Numbers of PCV**	11	12
Numbers of AMD††	13	14

R\*: Right, L†: Left, SD||: Standard Deviation; CNV¶: Choroidal Neovascularization; PCV\*\*: Polypoidal Choroid Vasculopathy; AMD††: Age-related Macular Degeneration

## Total CNV patients group

In bevacizumab group, baseline BCVA was 0.61 $\pm$ 0.45 and 0.70 $\pm$ 0.46 in ranibizumab group. In bevacizumab group, BCVA was improved 1 month, 2 months, 3 months and 6 months later ( $p = 0.001$ ,  $p = 0.001$ ,  $p = 0.001$ ,  $p = 0.001$ , respectively, paired sample t-test). Ranibizumab group also showed improvement of BCVA continuously ( $p = 0.015$ ,  $p = 0.001$ ,  $p = 0.001$ ,  $p = 0.001$ , respectively, paired sample t-test).

CMT in bevacizumab group significantly decreased than baseline at all 4 time points evaluated ( $p = 0.001$ ,  $p = 0.001$ ,  $p = 0.001$ ,  $p = 0.011$ , respectively, paired sample t-test) and same trend appeared in ranibizumab group ( $p = 0.001$ ,  $p = 0.001$ ,  $p = 0.001$ ,  $p = 0.028$ , respectively, paired sample t-test) (Table 2). Changes of BCVA and CMT did not show significant difference (Figure 1).

**Table 2:** Changes in visual acuity and central macular thickness after injection in total CNV patient.

		Bevacizumab	Ranibizumab	p Value
BCVA†	Baseline	0.61 $\pm$ 0.45	0.70 $\pm$ 0.46	0.372
	1 month	0.48 $\pm$ 0.42*	0.64 $\pm$ 0.43*	0.395
(log MAR)	2 months	0.43 $\pm$ 0.41*	0.59 $\pm$ 0.40*	0.853
	3 months	0.42 $\pm$ 0.43*	0.55 $\pm$ 0.40*	0.349
	6 months	0.43 $\pm$ 0.48*	0.53 $\pm$ 0.36*	0.21

CMT‡ (µm)	Baseline	294.51 ± 79.47	269.09 ± 74.20	0.931
	1 month	256.08 ± 53.50*	246.63 ± 52.04*	0.45
	2 months	250.40 ± 57.07*	228.62 ± 54.74*	0.111
	3 months	241.71 ± 46.62*	220.52 ± 60.72*	0.11
	6 months	232.91 ± 65.73*	235.65 ± 58.48*	0.909

\*p-value by paired sample t-test < 0.05 compared with baseline, BCVA†: Best-corrected visual acuity; CMT‡ : Central macular thickness

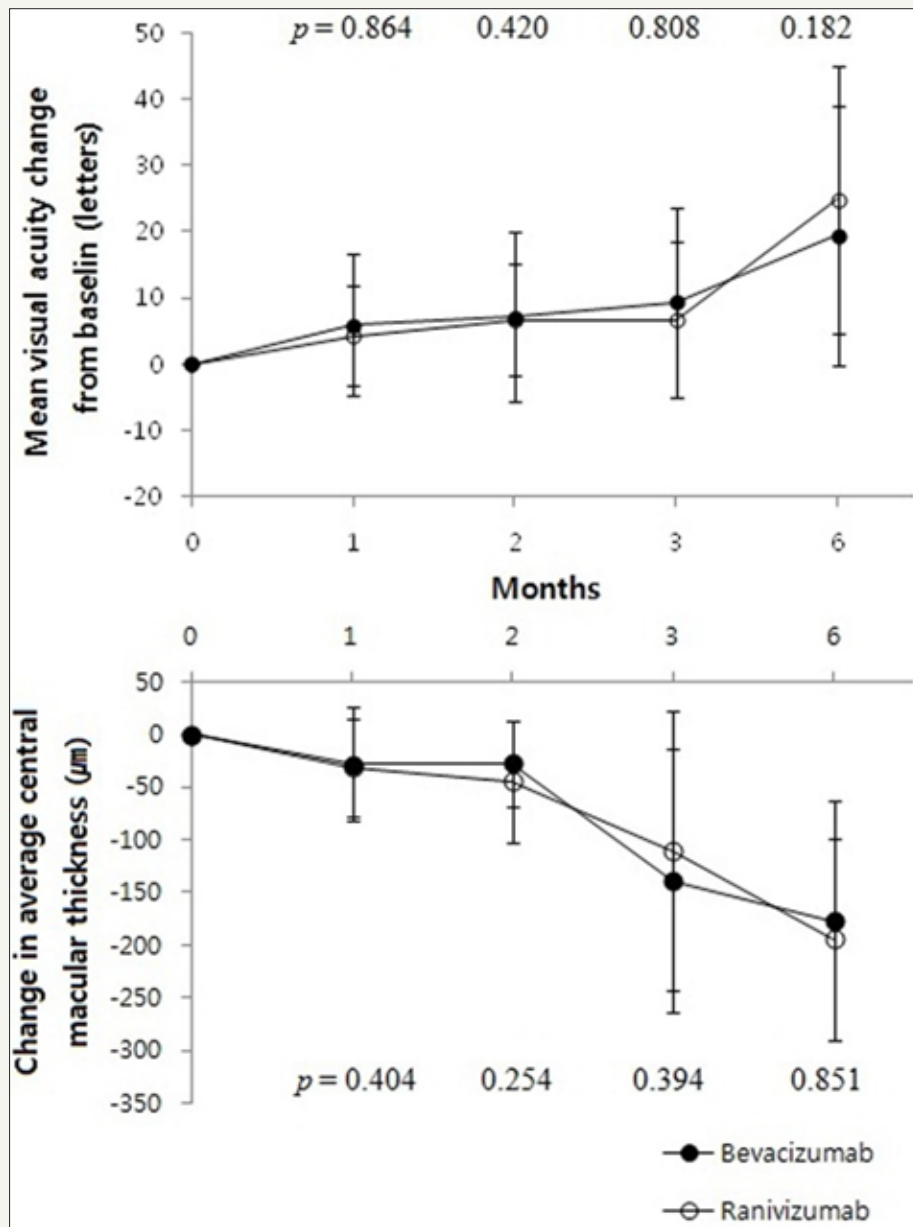


Figure 1: Mean visual acuity and central macular thickness change from baseline in total CNV patients.

**Idiopathic CNV subgroup**

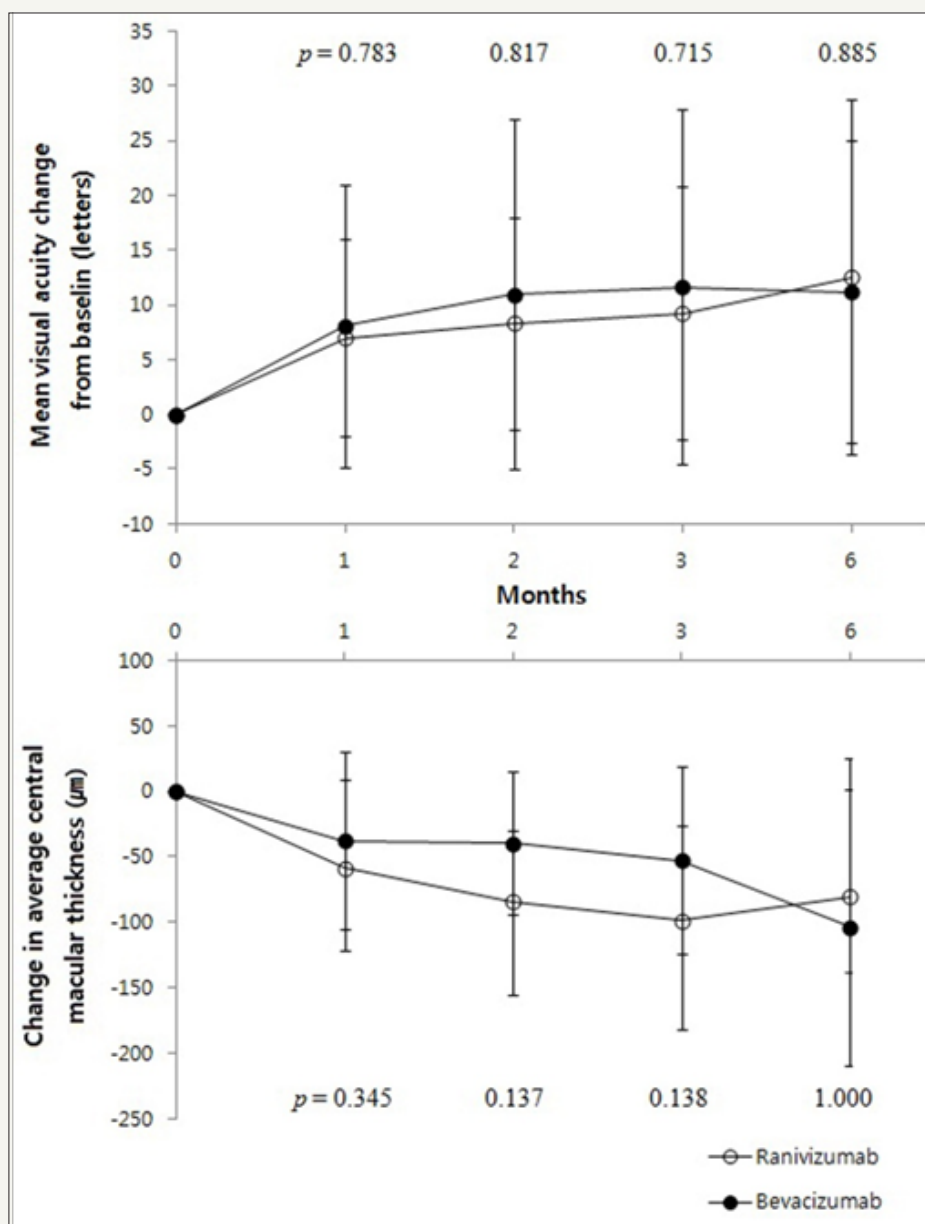
The baseline BCVA was 0.58±0.47 in bevacizumab group and 0.77±0.57 in ranibizumab group. In bevacizumab group, BCVA was improved 1 month, 2 months, 3 months and 6 months later (p = 0.002, p = 0.001, p = 0.001, p = 0.001, respectively, Wilcoxon signed rank test). Ranibizumab group also showed improvement of BCVA continuously (p = 0.015, p = 0.010, p = 0.016, p = 0.009, respectively, Wilcoxon signed rank test).

CMT in bevacizumab group significantly decreased than baseline at all 4 time points evaluated (p = 0.001, p = 0.002, p = 0.002, p = 0.028, respectively, Wilcoxon signed rank test) and same trend appeared in ranibizumab group (p = 0.005, p = 0.004, p = 0.004, p = 0.043, respectively, Wilcoxon signed rank test) (Table 3). Compared with the baseline, the changes in BCVA, as well as the changes in CMT, between bevacizumab group and ranibizumab group did not show any significant difference (Figure 2).

**Table 3:** Changes in visual acuity and central macular thickness after injection in idiopathic CNV subgroup.

		Bevacizumab	Ranibizumab	p Value
BCVA† (log MAR)	Baseline	0.58 ± 0.47	0.77 ± 0.57	0.178
	1 month	0.42 ± 0.45*	0.63 ± 0.51*	0.093
	2 months	0.36 ± 0.45*	0.60 ± 0.49*	0.029
	3 months	0.35 ± 0.46*	0.58 ± 0.50*	0.02
	6 months	0.35 ± 0.49*	0.52 ± 0.40*	0.043
CMT‡ (µm)	Baseline	288.69 ± 91.00	296.77 ± 60.39	0.417
	1 month	250.88 ± 52.97*	238.08 ± 47.08*	0.404
	2 months	250.47 ± 64.27*	215.08 ± 54.86*	0.045
	3 months	237.27 ± 42.75*	204.82 ± 65.28*	0.073
	6 months	225.67 ± 81.17*	211.00 ± 45.01*	0.357

\*p-value by paired sample t-test < 0.05 compared with baseline, BCVA†: Best-Corrected Visual Acuity; CMT‡: Central Macular Thickness

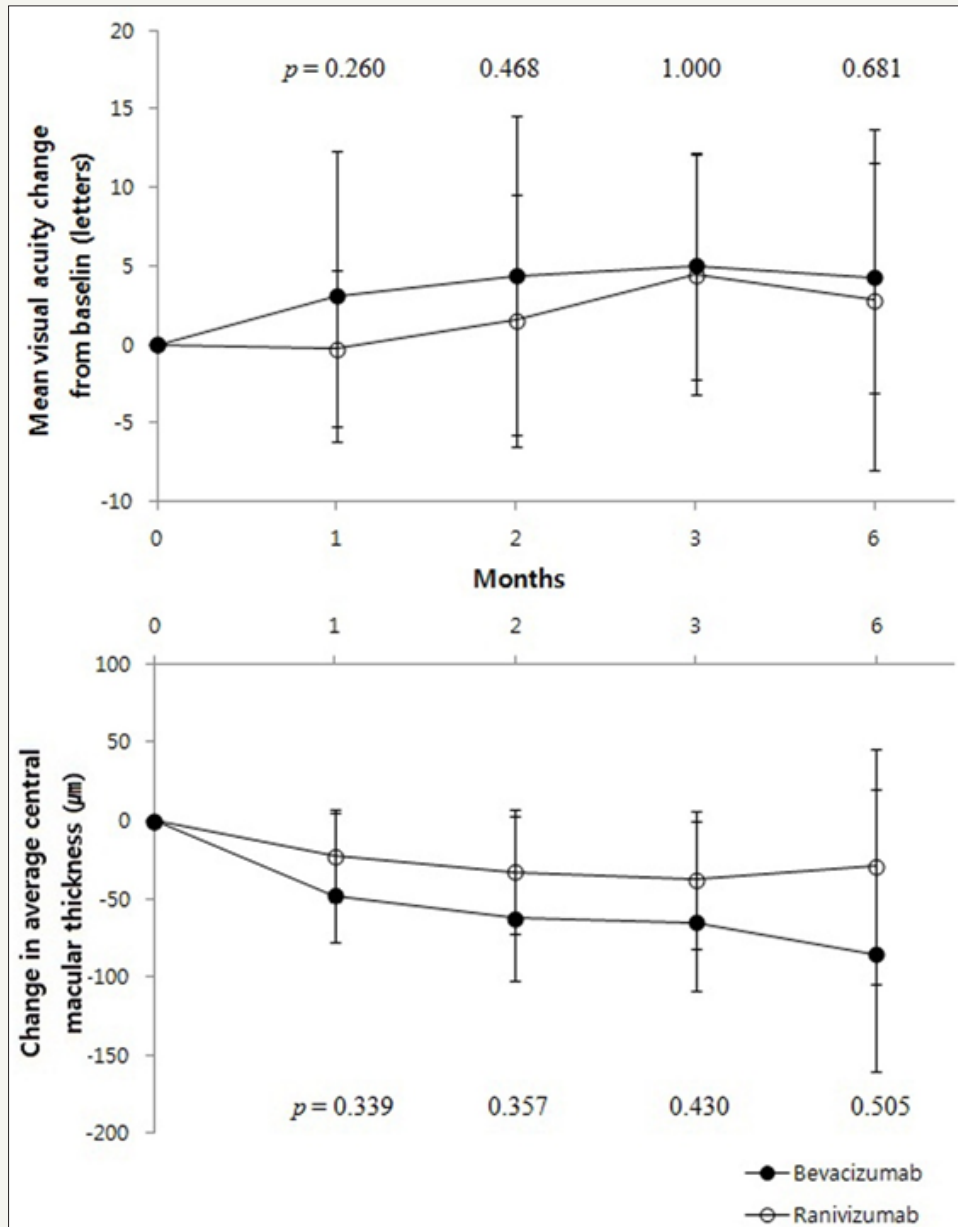


**Figure 2:** Changes in visual acuity and central macular thickness after injection in idiopathic CNV patients.

**AMD subgroup**

In bevacizumab group, baseline BCVA was  $0.59 \pm 0.44$  and  $0.56 \pm 0.43$  in ranibizumab group. The BCVA in bevacizumab group was significantly improved at 3 months later ( $p = 0.030$ , Wilcoxon signed rank test) and did not at 1 month, 2 months and 6 months later ( $p = 0.161$ ,  $p = 0.169$ ,  $p = 0.116$ , respectively, Wilcoxon signed

rank test). In ranibizumab group, BCVA was also significantly improved only at 3 months later ( $p = 0.022$ , Wilcoxon signed rank test) and did not at 1 month, 2 months and 6 months later ( $p = 0.893$ ,  $p = 0.449$ ,  $p = 0.307$ , respectively, Wilcoxon signed rank test) (Table 4). Compared with the baseline, the changes in BCVA, between bevacizumab group and ranibizumab group did not show any significant difference statistically (Figure 3).



**Figure 3:** Changes in visual acuity and central macular thickness after injection in AMD patients.

**Table 4:** Changes in visual acuity and central macular thickness after injection in AMD subgroup.

		Bevacizumab	Ranibizumab	p Value
BCVA† (log MAR)	Baseline	$0.59 \pm 0.44$	$0.56 \pm 0.43$	0.679
	1 month	$0.53 \pm 0.41$	$0.57 \pm 0.42$	0.846
	2 months	$0.49 \pm 0.33$	$0.53 \pm 0.39$	0.857
	3 months	$0.48 \pm 0.38^*$	$0.47 \pm 0.35^*$	0.938
	6 months	$0.61 \pm 0.55$	$0.50 \pm 0.35$	0.891

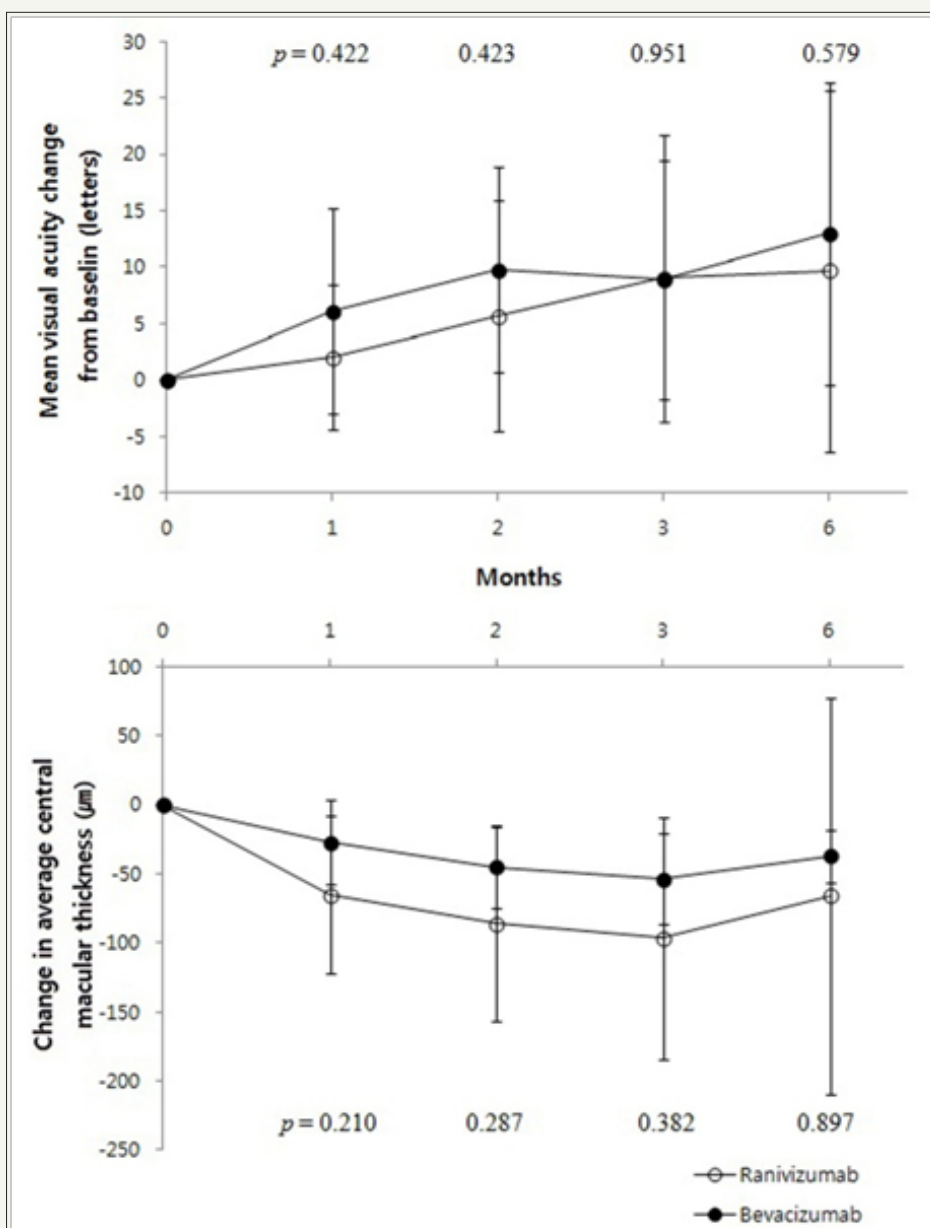
CMT‡ (µm)	Baseline	307.92 ± 77.81	262.73 ± 66.17	0.097
	1 month	260.17 ± 54.18*	240.18 ± 50.01*	0.423
	2 months	257.45 ± 52.59*	229.73 ± 47.70*	0.293
	3 months	254.64 ± 52.53*	224.73 ± 47.28*	0.431
	6 months	242.50 ± 65.76	222.67 ± 35.97	0.739

\*p-value by paired sample t-test < 0.05 compared with baseline, BCVA† : Best-corrected visual acuity, CMT‡ : Central macular thickness

CMT in bevacizumab group significantly decreased than baseline at 1 month, 2 months and 3 months later but not at 6 months later (p = 0.005, p = 0.013, p = 0.008, p = 0.208, respectively, Wilcoxon signed rank test). Same trend appeared in ranibizumab

group (p = 0.008, p = 0.005, p = 0.003, p = 0.345, respectively, Wilcoxon signed rank test) (Table 4). Compared with the baseline, the changes in CMT, between bevacizumab group and ranibizumab group did not show any significant difference (Figure 3).

**PCV subgroup**



**Figure 4:** Changes in visual acuity and central macular thickness after injection in PCV patients.

**Table 5:** Changes in visual acuity and central macular thickness after injection in PCV subgroup.

		Bevacizumab	Ranibizumab	p value
BCVA† (log MAR)	Baseline	0.70 ± 0.46	0.76 ± 0.32	0.494
	1 month	0.58 ± 0.39*	0.72 ± 0.32	0.368
	2 months	0.50 ± 0.39*	0.65 ± 0.31	0.322
	3 months	0.52 ± 0.39*	0.58 ± 0.34*	0.666
	6 months	0.49 ± 0.41*	0.57 ± 0.35	0.551
CMT‡ (µm)	Baseline	287.00 ± 64.55	328.64 ± 87.04	0.171
	1 month	259.89 ± 59.05*	263.18 ± 60.05*	0.97
	2 months	241.67 ± 54.78*	242.27 ± 62.26*	0.648
	3 months	233.33 ± 47.35*	232.00 ± 69.76*	0.494
	6 months	241.00 ± 51.18	269.17 ± 76.63	0.439

\*p-value by paired sample t-test < 0.05 compared with baseline, BCVA†: Best-Corrected Visual Acuity; CMT‡: Central Macular Thickness

In bevacizumab group, baseline BCVA was 0.70±0.46 and 0.76±0.32 in ranibizumab group. The BCVA in bevacizumab group was significantly improved 1 month, 2 months, 3 months and 6 months later ( $p = 0.046$ ,  $p = 0.011$ ,  $p = 0.020$ ,  $p = 0.035$ , respectively, Wilcoxon signed rank test). In ranibizumab group, BCVA was significantly improved only at 3 months later ( $p = 0.037$ , Wilcoxon signed rank test) and did not at 1 month, 2 months and 6 months later ( $p = 0.307$ ,  $p = 0.100$ ,  $p = 0.050$ , respectively, Wilcoxon signed rank test) (Table 5). Compared to the baseline, the changes in BCVA, between bevacizumab group and ranibizumab group did not show any significant difference statistically (Figure 4).

The CMT of bevacizumab group was decreased significantly at 1 month, 2 months and 3 months later after injection but not at 6 months later ( $p = 0.008$ ,  $p = 0.008$ ,  $p = 0.008$ ,  $p = 0.109$ , respectively, Wilcoxon signed rank test). Ranibizumab group showed same trend that decreased until 3 months later but not at 6 months after injection ( $p = 0.010$ ,  $p = 0.004$ ,  $p = 0.003$ ,  $p = 0.249$ , respectively, Wilcoxon signed rank test) (Table 5). Compared with the baseline, the changes in BCVA, between bevacizumab group and ranibizumab group did not show any significant difference statistically (Figure 4).

## Discussion

Intravitreal anti-VEGF injection is one of the most common treatment for CNV patients in the world. It is more effective to prevent decreasing visual acuity by CNV than PDT [29]. Among many anti-VEGF drugs, ranibizumab and bevacizumab are the most commonly used. However, there are not enough prospective and case-control studies about the comparison between them.

As studies about ranibizumab, ANCHOR [30] and MARINA [31] trials has reported and long term follow-up studies are currently in progress. However bevacizumab is also important issue because it is more cost-effective than ranibizumab. Recently, CATT (US), IVAN (UK), VIBERA (German), LUCAS (Norway), GEFAL (France), EQUAL (Netherlands) and MANTA (Austria) are in progress currently to compare the effect between bevacizumab and ranibizumab [32,33-37].

In this study, intravitreal bevacizumab treatment and ranibizumab showed no significant difference in improvement of visual acuity and resolution of increased macular thickness after injection in whole CNV patients group until 6 months. This results for 1 month after injection correlate closely with the findings from previous study that Biswas et al. investigated about the efficacy of bevacizumab and ranibizumab [38]. The result that increases of ETDRS letters in idiopathic CNV are higher than that of CNV with AMD is also similar to previous study [39]. In idiopathic CNV subgroup, both drugs showed improvement of visual acuity and CMT.

In AMD subgroup, both drugs showed improvement of CMT to 3 months but that of visual acuity from 3 months after treatment and after 6 months, visual acuity was decreased to the baseline level. Lastly, in PCV subgroup, the effect of improving BCVA was shown earlier in bevacizumab but effect of reducing CMT was similar and CMT was thickened again after 6 months in both treatment groups. In case of PCV, treatment is not exactly established and it is known that PDT is effective [40-42], therefore it is thought that only anti-VEGFs treatment has limitation.

Although ranibizumab is made for treatment of ophthalmic disease as anti-VEGF, bevacizumab is still used instead of ranibizumab by many clinicians. Recently, a lot of studies have been reported about efficacy of bevacizumab versus ranibizumab [20,23,38,43] but most studies are comparing only in AMD. While the previous studies compared the effects between bevacizumab and ranibizumab in AMD patients, we compared in CNV patients which can occur in not only in AMD but also in PCV and by idiopathic courses.

Subramanian et al reported that the effects of both anti-VEGFs in AMD showed no difference in visual and anatomic outcomes [44]. However the degrees of changes in BCVA and CMT in this study differ from other reports. It is referable to the differences in characteristics of enrolled patient group.

Several adverse events related with intravitreal injection of anti-VEGF, such as elevated intraocular pressure, endophthalmitis,

stroke and myocardial infarction have been reported before [20,32,45]. By the recently reported multicenter, randomized study Comparison of AMD Treatments Trials Ranibizumab-Bevacizumab Trial (CATT), endophthalmitis, uveitis, ocular-vessel occlusion or embolism, retinal detachment and vitreous hemorrhage can develop in less than 1% of patient [32]. In our study, however, such adverse events were not occurred, only several cases of subconjunctival hemorrhage were occurred which improved within a week without any treatment.

Bevacizumab was used under various protocols in previous studied because it was thought to have different effect and efficacy. However this study has the advantage that was conducted in same institute and both anti-VEGFs were injected under the same condition and same protocol.

Our study has limitation that the CMT was measured by two different OCT models, Cirrus HD OCT and Stratus OCT. Because Cirrus HD OCT is reported that measures the same retinal layer about 50µm thicker than Stratus OCT does [46-48], we added 50µm to thickness measured by Stratus OCT and this can make bias of analysis. Furthermore, this study is retrospective and recruited a little number of patients. In the future, Prospective and randomized controlled trials will be needed. However this study is not randomized controlled study, beginning of covering by national health insurance made subjects be divided randomly into bevacizumab and ranibizumab groups.

In spite of small size of subjects and retrospective study, this study shows intravitreal bevacizumab injection has similar efficacy and safety as ranibizumab injection in CNV patients with various pathologies.

### Acknowledgment Disclosure

All authors have no financial interest regarding the subject matter of this manuscript.

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