INTRAVITREAL ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR TREATMENT FOR RETINOPATHY OF PREMATURITY

Comparison Between Ranibizumab and Bevacizumab

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Purpose: To compare the effect and the treatment outcomes of bevacizumab and ranibizumab in the treatment of Type 1 retinopathy of prematurity (ROP).

Methods: This was a bicentered retrospective case series performed at institutional referral centers. Seventy-two eyes of 37 patients who had intravitreal injections of either bevacizumab or ranibizumab as the primary treatment for Type 1 ROP were included. Outcomes' measures included regression and recurrence of ROP, the surgical complications, and refractive errors at a corrected age of 1 year.

Results: All but one eye in the bevacizumab group had retinal neovascularization and plus disease regression after anti-vascular endothelium growth factor treatment. Neither recurrence of ROP nor major ocular complications, including cataract, retinal detachment, and endophthalmitis occurred in any of the treated eyes. There were no significant differences in mean refractive errors between the patients treated with intravitreal injections of bevacizumab or ranibizumab at the corrected age of 1 year. A significantly higher chance of high myopia was noted in the bevacizumab group ($P = 0.03$).

Conclusion: Both bevacizumab and ranibizumab showed similar efficacy in the regression of ROP with minor mean refractive errors at 1 year of corrected age. However, high myopia was more prevalent in the bevacizumab-treated eyes.

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Retinopathy of prematurity (ROP) is one of the major diseases causing blindness in childhood. Laser photocoagulation is the standard treatment for ROP, however, in the Early Treatment For Retinopathy of Prematurity (ETROP) trial,[1] 9.1% of the patients had unfavorable structural outcomes. In addition, a large area of peripheral retina is destroyed in the ablative process and normal vascularization generally cannot be achieved. Another treatment option for ROP is to use intravitreal injections (IVI) of anti-vascular endothelium growth factor (VEGF). The advantages of IVI of anti-VEGF agents include a less time-consuming procedure, fewer risks from general anesthesia in a physically compromised preterm newborn,[2–6] and a potentially lower chance of unfavorable outcomes in Zone 1 ROP.[7–10] For these reasons, the use of IVI of anti-VEGF drugs for the treatment of ROP has gained in popularity.

Bevacizumab (Avastin; Genentech Inc, San Francisco, CA) and ranibizumab (Lucentis; Genentech Inc) are two anti-VEGF agents with different molecular sizes, structures, and half lives, and both have demonstrated efficacy in the treatment of Type 1 ROP.[7–13] Bevacizumab was the first anti-VEGF used for the treatment of ROP.[7–9] Ranibizumab was later used for the treatment of ROP with the aim of being a safer treatment option,[10–13] because less systemic VEGF suppression was found when ranibizumab was used in adult patients with age-related macular degeneration compared with bevacizumab treatment.[14,15]

However, to the best of our knowledge, these two drugs have not been directly compared in the treatment of Type 1 ROP. In this retrospective study, the effect and treatment outcomes on ROP, namely disease regression, recurrence of ROP and the necessity of subsequent ablative procedures, and refractive status at 1 year of corrected age were compared between bevacizumab and ranibizumab.

Methods

This was a bicentered retrospective study of anti-VEGF use in newborns with ROP from April 2011 to December 2013. The two centers were Changhua Christian Hospital, Changhua, Taiwan, and Chang-Gung Memorial Hospital, Taoyuan, Taiwan. The study was approved by the Institutional Review Boards of both hospitals. Informed consent was obtained from the parents for the surgical procedures. All patients had IVI of anti-VEGF agents as the primary treatment for Type 1 ROP. The indications for IVI were the same as those for laser treatment according to the ETROP study,[1] and the patients with salvage anti-VEGF injections after failed laser treatment were excluded from the study. The parents were well informed about the efficacy and possible complications of laser treatment and IVI of anti-VEGF agents, including the risk of general anesthesia, decreased visual field, and high refractive errors with laser treatment; decreased serum VEGF level after anti-VEGF treatment, possible differences in systemic VEGF suppression between these two anti-VEGFs (bevacizumab is more likely to have a greater suppression of systemic VEGF according to previous reports),[14,15] the possible neurodevelopmental impact after systemic VEGF suppression; and the cost needed to pay for these treatments (anti-VEGF agents for ROP are not covered by the National Health Insurance program in Taiwan; cost for bevacizumab and ranibizumab: US $200 and US $1,300, respectively). The parents were ultimately left with the decision whether to treat with laser or anti-VEGF, and if anti-VEGF was selected, whether to use bevacizumab or ranibizumab.

The eyes were prepared in the usual manner for IVI. After topical anesthesia, 5% povidone–iodine disinfection and topical antibiotic instillation, either 0.625 mg/0.025 mL of bevacizumab or 0.25 mg/0.025 mL of ranibizumab was injected intravitreally. The surgical technique was as previously described.[8] The intraocular pressure and central artery perfusion were then checked. Topical antibiotics were given for 7 days postoperatively.

After treatment, the patients were monitored every 1 or 2 weeks until regression of ROP and full vascularization of the retina was observed. Full vascularization was defined as follows: vascularization as far as it would develop without an active component such as hemorrhage or exudation or clinically significant tractional elements.[16] The patients were followed up at clinics until at least 1 year of corrected age. Indirect funduscopy for the evaluation of disease regression and recurrence and peripheral vascularization was performed on each visit. A positive response to treatment included the disappearance of rubeosis iridis (tunica vasculosa lentis), improved pupil dilation, the disappearance of or a decrease in retinal vessel tortuosity and neovascularization, and the presence of vessels that continued to vascularize toward the peripheral retina. The patients who showed a lack of positive response to anti-VEGF treatment or a deterioration in retinal status subsequently received laser treatment.

Measurements of axial length (AXL) and cycloplegic refraction were performed when the patients reached a corrected age of 1 year and at every subsequent follow-up visit. The AXL was measured with an A-scan machine (A-2500; Sonomed, New Hyde Park, NY), and cycloplegic refraction was determined by a portable refractometer (Retinomax K-Plus2; Nikon Corp, Tokyo, Japan) 1 hour after instillation of 2% cyclopentolate hydrochloride twice and 1% tropicamide (10 minutes apart). High myopia was defined as a spherical equivalent (SE) ≤ -5.0 diopters (D),[17] and high astigmatism was defined as minus cylinder ≤ -3.0 D.[18] Numerical variables are presented as mean and 95% confidence interval.

Statistical Analysis

The Mann–Whitney test was used to test the differences between the patients in the two treatment groups (bevacizumab vs. ranibizumab) regarding gestational age, birth weight, and postmenstrual age at IVI, and the corrected age at the measurement of AXL and refractive status. The chi-square test was used to test the differences among the treated eyes in the two groups regarding the stage and zone of disease,

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presence or absence of plus disease and rubeosis iridis. Fisher's exact test was used to test the differences in the prevalence of high myopia and high astigmatism between the two groups. All analyses were performed using SAS version 9.3 (SAS Institute Inc, Cary, NC). A $P < 0.05$ was considered to be statistically significant.

Results

A total of 72 eyes in 37 patients (17 males and 20 females) were included. Two eyes in two patients with Zone 2 Stage 3 disease without plus disease were left untreated and were found to have spontaneous regression during follow-up. The complete data of the patients are shown in Table 1.

Ten eyes of 5 patients had Zone 1 Stage 3 ROP, including rubeosis iridis in 2 eyes, and 62 eyes of 32 patients had Zone 2 Stage 3 disease with plus disease, with rubeosis iridis in 4 eyes. Thirty-one eyes of 16 patients were treated with ranibizumab. Of these eyes, 23 eyes of 12 patients have previously been reported.[13] Forty-one eyes of 21 patients were treated with bevacizumab. All of the eyes received IVI of anti-VEGF agents as the primary treatment. There were no differences in gestational age, birth weight, and postmenstrual age at IVI between these 2 treatment groups (Table 2). There were also no differences in the stage of disease ($P = 0.28$), the presence of plus disease ($P = 0.25$), or rubeosis iridis ($P = 0.72$). However, there was a significant difference in the zone of

Table 1. Demographic Data of the Patients

Case/ Sex	GA, weeks	BW, g	Stage/ Zone	PMA at IVI	RI	PD	Eye	F/U, months	IVI	SE (OD/OS), diopters	Astigmatism (OD/OS), diopters
1/F	30	969	3/II	36	–/–	+/+	OU	12	R	0.125/1.000	–0.750/–1.500
2/F	25	758	3/II	35	–/–	+/+	OU	12	R	0.125/0.250	–0.750/–2.000
3/F	25	770	3/II	35	–/–	+/+	OU	13	R	–2.250/–0.750	–2.000/–3.500
4/F	24	537	3/I	33	–/–	+/+	OU	12	R	–0.750/–0.125	–2.000/–2.250
5/F	26	507	3/I	33	+/+	+/+	OU	12	R	0.500/0.375	–2.500/–0.750
6/F	24	554	3/I	32	–/–	–/+	OU	12	R	–1.125/–2.000	–4.750/–3.000
7/F	30	1,480	3/II	36	–/–	+/+	OU	13	R	–0.500/–0.250	–3.500/–2.000
8/M	27	1,080	3/II	39	–/–	+/–	OD	14	R	1.250	–2.000
9/F	26	521	3/II	38	–/–	+/+	OU	15	R	–0.125/–0.125	–1.250/–2.250
10/M	26	1,133	3/II	34	–/+	+/+	OU	12	R	0.625/0.250	–2.750/–3.000
11/F	25	694	3/I	36	–/–	+/+	OU	12	R	3.250/2.750	–2.500/–4.500
12/M	24	732	3/II	40	–/–	+/+	OU	12	R	–0.250/–1.125	–2.000/–2.750
13/M	28	810	3/II	36	–/–	+/+	OU	13	R	2.125/–0.375	–1.250/–2.250
14/F	25	876	3/II	35	–/–	+/+	OU	13	R	0.875/1.250	–0.750/–0.500
15/M	25	740	3/II	34	–/–	+/+	OU	13	R	–0.250/–0.500	–1.500/–1.000
16/M	29	1,420	3/II	42	–/–	+/+	OU	12	R	–1.125/–0.250	–2.750/–3.000
17/M	30	1,247	3/I	35	–/–	+/+	OU	13	B	0.000/–1.000	–1.500/–0.500
18/M	28	1,039	3/II	46	–/–	+/+	OU	13	B	0.500/–1.000	–5.000/–2.000
19/M	28	1,039	3/II	38	–/–	+/+	OU	13	B	–9.625/–7.500	–1.750/–0.500
20/F	27	878	3/II	40	–/–	+/+	OU	13	B	–0.250/–0.250	–1.000/–1.000
21/M	24	729	3/II	39	–/–	+/+	OU	13	B	2.500/4.500	–0.500/–1.500
22/M	26	724	3/II	35	+/+	+/+	OU	14	B	2.375/2.250	–1.250/–1.000
23/F	24	1,115	3/II	36	–/–	+/+	OU	12	B	1.000/1.500	–0.500/–0.500
24/M	25	736	3/II	40	–/–	+/+	OU	12	B	1.500/0.500	–2.000/–1.500
25/M	26	910	3/II	37	–/–	+/+	OU	12	B	0.880/1.380	–3.250/–2.750
26/M	29	1,003	3/II	41	–/–	+/+	OU	11	B	3.130/4.000	–2.250/–1.500
27/F	29	1,060	3/II	36	–/–	+/+	OU	13	B	0.000/1.380	–3.500/–3.250
28/F	27	954	3/II	42	–/–	+/–	OD	12	B	1.630	–2.750
29/F	25	569	3/II	34	–/–	+/+	OU	14	B	2.000/1.250	–1.000/–1.500
30/M	24	736	3/II	33	–/+	+/+	OU	14	B	0.380/–0.250	–0.250/–0.500
31/F	28	1,120	3/II	33	–/–	+/+	OU	13	B	–5.500/–9.630	–2.500/–3.750
32/F	25	540	3/II	33	–/–	+/+	OU	14	B	1.250/1.500	–2.500/–2.500
33/F	25	710	3/II	34	–/–	+/+	OU	13	B	–13.130/–9.250	–1.250/–1.500
34/M	24	704	3/II	34	–/–	+/+	OU	12	B	0.000/1.380	–1.500/–1.750
35/F	27	597	3/II	38	–/–	+/+	OU	14	B	–2.250/–2.500	–2.000/–4.000
36/M	26	980	2/II	33	–/–	+/+	OU	14	B	6.510/4.770	–1.520/–2.120
37/F	26	860	3/II	36	–/–	+/+	OU	12	B	–0.500/–1.000	–1.000/–2.000

B, bevacizumab; BW, birth weight; F, female; F/U, follow-up duration; GA, gestational age; M, male; OD, right eye; OS, left eye; OU, both eyes; PD, plus disease; PMA, postmenstrual age; R, ranibizumab; RI, rubeosis iridis.

Table 2. Demographics of the ROP Patients With Bevacizumab or Ranibizumab Treatment

	Bevacizumab, Mean (95% CI)	Ranibizumab, Mean (95%CI)	
	N = 21	N = 16	P*
GA, weeks	26.5 (25.6–27.4)	26.2 (25.1–27.3)	0.79
BW, g	869.1 (778.0–960.1)	848.8 (689.1–1,008.6)	0.59
PMA at IVI, weeks	36.8 (35.2–38.4)	36.4 (34.1–38.8)	0.49

*Values were calculated using the Mann–Whitney test.
BW, birth weight; CI, confidence interval; GA, gestational age; PMA, postmenstrual age.

disease, and the ranibizumab group had a higher proportion of Zone 1 disease than the bevacizumab group (26 vs. 5%, respectively; $P = 0.01$). All but 1 eye (Case 37, the right eye) in the bevacizumab group had neovascularization and plus disease regression after IVI anti-VEGF treatment. Laser treatment was performed in this eye 3 weeks after the IVI of bevacizumab because of persistent plus disease and failure of regression of retinal neovascularization. At the end of the study period, all of the study eyes (100%) in both groups had regression of ROP and attached retinas. No recurrence of ROP occurred in either group if the patients initially responded well to the IVI treatment. No major ocular complications, including cataract, tractional or rhegmatogenous retinal detachment, or endophthalmitis occurred in any of the treated eyes. No macular fold or foveal dragging was noted in any of the eyes. Only faint, localized preretinal hemorrhage around the regressed neovascularization occurred in four eyes in the ranibizumab group and three eyes in the bevacizumab group. These hemorrhages were reabsorbed within weeks without any sequelae.

The distributions of SE and astigmatism at the age of 1 year in the ROP patients treated with either ranibizumab or bevacizumab are shown in Figure 1. The mean corrected age at examination, AXL, SE, astigmatism, and the distribution of high myopia and astigmatism are shown in Table 3. There were no differences in corrected age at examination between the two treatment groups ($P = 0.19$). The Mann–Whitney test showed no significant differences in the mean AXL ($P = 0.98$), SE ($P = 0.21$), or astigmatism ($P = 0.12$) between the eyes in the bevacizumab and ranibizumab groups. For the analysis of prevalence of high myopia, there were 6 eyes (14.6%) in the bevacizumab group and none (0%) in the ranibizumab group with a SE ≤ -5.0 D. The bevacizumab group had a significantly higher prevalence of high myopia than the ranibizumab group ($P = 0.03$). For the analysis of prevalence of high astigmatism, 6 eyes (14.6%) in the bevacizumab group and 7 eyes (22.6%) in the ranibizumab group had astigmatism ≤ -3.0 D. No significance difference was noted between these two groups in the prevalence of high astigmatism ($P = 0.54$).

Discussion

In this study, we showed that both bevacizumab and ranibizumab had similar responses in neovascularization and plus disease regression, and none of the eyes had recurrence of ROP after an initial good response. This finding is not surprising as both medications have also been shown to have similar therapeutic effects in wet age-related macular degeneration,[19] retinal venous occlusive diseases,[20–22] and diabetic macular edema.[23,24]

Regarding the refractive outcomes, most patients had only minor refractive errors at 1 year of corrected age in both groups. Comparatively favorable refractive outcomes in bevacizumab-treated eyes versus laser-treated eyes were reported by Harder et al.[25] In their report, the incidence of high myopia was 9% in the bevacizumab treatment group and 42% in the laser treatment group, and the difference was statistically significant. The relatively favorable outcomes in refractive status with anti-VEGF agents[16,25] compared with laser treatment may be due to a relatively better, preserved peripheral retina in anti-VEGF–treated eyes helps the emmetropization process. The peripheral retina was demonstrated to be important in the regulation of emmetropization in an animal model, probably because of its visual feedback.[26] Previous reports have shown that cryotherapy-treated ROP patients are more myopic than laser-treated patients, and that patients with spontaneous regression are least myopic.[27] This implies that the less destruction of the peripheral retina, the better the emmetropization process; in other words, a destroyed peripheral retina may not be able to generate the signals necessary for optimal eye growth and emmetropization.

Although most patients in both groups in this study had minimal refractive errors, the patients in the bevacizumab group had a significantly higher incidence of high myopia (14.6% in the bevacizumab group vs. 0.0% in the ranibizumab group, $P = 0.03$).

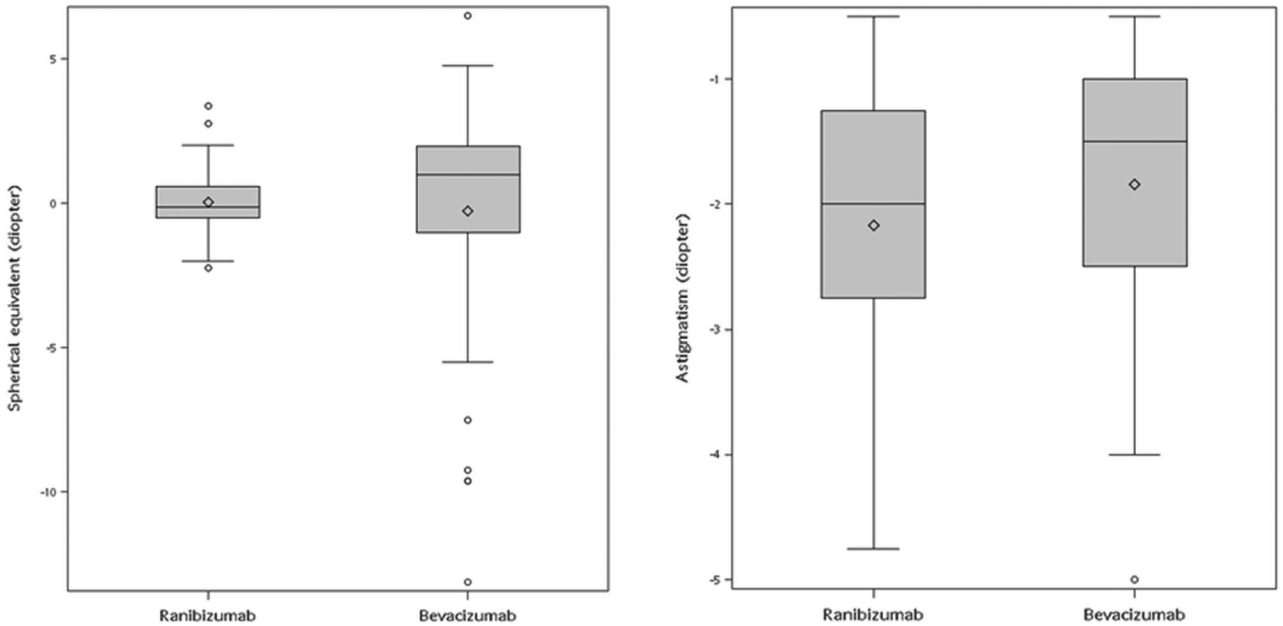

Fig. 1. Box plot showing the distribution of SE and astigmatism at the age of 1 year in the children with ROP and treated with IVIs of either ranibizumab or bevacizumab. There were no significant differences in mean SE ($P = 0.78$) and astigmatism ($P = 0.29$) between the eyes in the bevacizumab and ranibizumab groups.

A possible reason for this difference in the rate of high myopia may be related to the emmetropization process rather than the difference in AXL, because there was no significant difference in AXL between the two groups. Several studies have suggested that refractive errors in patients with threshold ROP are mostly due to anterior segment abnormalities, including a steeper cornea curvature, a shallower anterior chamber depth, and a thicker lens.[18,28,29] The disease severity of ROP may also be attributable to the development of high myopia, however there was no difference in disease severity in the 6 eyes that developed high myopia (all of the patients had Zone 2 Stage 3 ROP). The difference in the prevalence of high myopia in these 2 groups of patients may be due to differences in the regulation of vitreal VEGF between bevacizumab and ranibizumab. In an animal model study of neonatal mice, the loss of inner retinal layer cells including Müller cells, astrocytes, and ganglion cells was noted after inhibition of VEGF Receptors 1 and 2 in the developing avascular retinas.[30] Because bevacizumab has a longer half-life within the vitreous cavity,[31,32] it is reasonable to hypothesize that the sustained inhibition of VEGF by bevacizumab may induce more apoptosis in the peripheral retina, with subsequent dysregulation of emmetropization. However, more evidence is needed to reach a definite conclusion.

Laser therapy remains the gold standard treatment for ROP. The use of IVI of anti-VEGF agents,

Table 3. Refractive Errors and Biometry of the ROP Patients at a Corrected Age of 1 Year After Bevacizumab or Ranibizumab Treatment

	Bevacizumab	Ranibizumab	
	N = 41	N = 31	*P*
Corrected age at examination, mean (95% CI), months	12.5 (11.8 to 13.2)	12.3 (11.5 to 13.1)	0.19*
AXL, mean (95% CI), mm	20.6 (20.3 to 20.9)	20.2 (19.6 to 20.8)	0.98*
SE, mean (95% CI), diopters	−0.3 (−1.6 to 1.1)	+0.1 (−0.4 to 0.5)	0.21*
Astigmatism, mean (95% CI), diopters	−1.8 (−2.2 to −1.5)	−2.2 (−2.6 to −1.8)	0.12*
Presence of high myopia (SE ≤ −5.0 D), %	14.6	0	0.03†
Presence of high astigmatism (minus cylinder ≤ −3.0 D), %	14.6	22.6	0.54†

*Values were calculated using the Mann–Whitney test.
†Values were calculated using Fisher's exact test.
CI, confidence interval.

although showing comparable results in treating ROP compared with laser,[7–13] is controversial. Martínez-Catellano et al[33] reported that after 5 years of follow-up, IVI of bevacizumab for ROP resulted in apparently preserved ocular and systemic development in a small series. However, some authors have expressed concern about the impact on neurodevelopmental development subsequent to anti-VEGF administration in premature babies, and they suggest that such treatment be reserved for only exceptional cases.[34] A decrease in serum or plasma level of VEGF after IVI of anti-VEGF has been demonstrated.[14,15,34–37] In the report of Wu et al,[38] a higher serum level of bevacizumab was detected in newborn rabbits when the IVI was performed at a younger age. Although most ophthalmologists currently use half the dose of anti-VEGF agents used in adult patients with age-related macular degeneration when treating ROP babies, the serum concentration of anti-VEGF agents should be much higher than that in adults because the body weight and plasma volume of newborn babies, and especially low birth weight preterm babies, is less than one twentieth that of adults, the blood retinal barrier may be less mature in newborns,[39] and the clearance function of the kidneys is less efficient in newborn babies.[40] Taken together, IVI of anti-VEGF agents may decrease the serum VEGF more significantly and cause more systemic complications in preterm or newborn babies. Vascular endothelium growth factor plays an important role in neurogenesis in embryos and preterm newborns. In previous reports, blocking VEGF-A expression has been shown to impair brain vascularization[41] and lead to neuron apoptosis in the retina.[30] In addition, hypoxia-induced factors, including VEGF, have been demonstrated to be lower in preterm pups compared with term pups, and this has been proposed to partially explain the neurodevelopmental delay and reduced growth of the cerebral cortex in premature infants.[42] Because neurogenesis may continue in the third trimester,[42] further deprivation of serum VEGF in preterm babies may have long-term effects on the development of the central nervous system. Under such conditions, medications with shorter systemic exposure time and less influence on systemic VEGF may have a lesser impact on the neurodevelopment of newborn infants.

Because of structural differences, a much longer systemic half-life has been noted with bevacizumab than that with ranibizumab in adult patients (20 days vs. 2 hours for bevacizumab and ranibizumab, respectively).[31,32] In addition, the median plasma level of VEGF has been noted to be reduced by 42% in patients with age-related macular degeneration 28 days after receiving the third monthly IVI of bevacizumab, in contrast to no changes in patients treated with ranibizumab.[15] In the "alternative treatments to inhibit VEGF in age-related choroidal neovascularization" (IVAN) study,[14] the serum level of VEGF in patients receiving bevacizumab was suppressed to about one half of that in patients receiving ranibizumab. In addition, the suppression of serum VEGF levels for at least 2 weeks has been reported after IVI of bevacizumab to treat ROP.[35] To date, only 1 case report of the serum level of VEGF in a patient receiving bilateral ranibizumab for ROP has been reported, in whom the serum VEGF level was suppressed for 3 weeks and returned to the original level 4 weeks later.[43] Further studies are needed to investigate whether ranibizumab has less influence than bevacizumab on the serum VEGF level in ROP patients.

In the Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity (BEAT-ROP) study,[7] intravitreal bevacizumab monotherapy showed a significant benefit for Zone I but not Zone II disease in infants with Stage 3+ ROP compared with conventional laser therapy. In this study, most of the cases were Zone II disease. However, the primary ocular outcome in the BEAT-ROP study was recurrence of ROP in one or both eyes requiring retreatment before a postmenstrual age of 54 weeks. The BEAT-ROP study did not compare the results of refractive errors, visual field, visual acuities, foveal contour, choroidal thickness, or neurodevelopment of patients after bevacizumab or laser treatment. This might be one of the reasons why intravitreal bevacizumab showed a significant benefit for Zone I but not Zone II disease compared with laser treatment. Anti-VEGFs for Zone II disease may play a role, because some reports have shown better functional outcomes such as refractive errors compared with laser treatment[25] and no significant systemic complications have been reported to date.[7,10,16,33] Long-term studies are still needed to justify the use of anti-VEGFs for Zone II disease.

In conclusion, this study demonstrated that there were no differences in disease regression and recurrence, SE, or AXL at 1 year of corrected age in ROP patients treated with IVI of ranibizumab or bevacizumab. The mean refractive errors of the ROP patients after either bevacizumab or ranibizumab treatment were mild. The eyes receiving bevacizumab had a higher chance of developing high myopia. The limitations of this study are the short follow-up time, small sample size, and its retrospective nature. In addition, the study is limited by the lack of anterior segment biometry, which may have allowed determination of the cause of myopia. Treatment was given by multiple practitioners, which may have resulted in variability of ROP grading, and Zone II was not

subclassified as anterior or posterior, which would have allowed for a better comparison with the BEAT-ROP study. Future prospective studies with a large sample size are warranted to elucidate whether there are any differences in treatment outcomes between these two medications. Currently, we are actively following these patients and assessing their neurodevelopment.

Key words: bevacizumab, intravitreal injection, ranibizumab, retinopathy of prematurity.

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