EFFICACY OF INTRAVITREAL INJECTION OF ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR AGENTS FOR STAGE 4 RETINOPATHY OF PREMATURITY

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Purpose: To investigate the efficacy of intravitreal injection of anti-vascular endothelial growth factor agents for Stage 4 retinopathy of prematurity.

Methods: Retrospective case series study. The medical records of patients receiving intravitreal injection of anti-vascular endothelial growth factor agents for Stage 4 retinopathy of prematurity from January 2007 to May 2012 in Taipei Veterans General Hospital were reviewed.

Results: A total of 13 eyes of 7 patients (3 boys and 4 girls) with Stage 4 retinopathy of prematurity were included. The mean gestational age and birth weight were 27.6 ± 2.6 weeks (range, 24.5–30.5 weeks) and 893.1 ± 293.2 g (range, 550–1422 g), respectively. The mean age at the time of injection was 38.2 ± 1.9 weeks (range, 36.0–41.5 weeks) postmenstrual age, and the mean follow-up period was 37.8 ± 19.5 months (range, 11.0–67.5 months). The active neovascularization regressed rapidly, and the anatomical outcomes were favorable in all patients. One eye developed recurrent retinal hemorrhage with localized retinal detachment 21 weeks after initial treatment, which resolved after a second injection. There were no ocular or systemic complications in these patients.

Conclusion: Intravitreal injection of anti-vascular endothelial growth factor agents may be effective as monotherapy or as supplement to failed laser treatment for patients with Stage 4 retinopathy of prematurity without additional surgical intervention. Further randomized controlled trials are necessary to compare the clinical efficacy and safety with other conventional interventions.

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Retinopathy of prematurity (ROP) is a multifactorial neovascularizing disease and is a major cause of visual impairment in children around the world. In the United States, the incidence of ROP was reported to be 0.17% overall and 68% among infants with birth body weight <1251 g.[1,2] The Stage 4 ROP was defined as ROP with subtotal retinal detachment (RD), either extrafoveal (Stage 4A) or with foveal involvement (Stage 4B).[3] From the observational study of the natural history of ROP, all Stage 1/2 ROP underwent complete resolution but Stage 3/4 ROP did not, in which cicatricial sequelae subsequently developed in 20.8% to 23.8% of this group.[4,5]

The established treatments for Stage 4 ROP include scleral buckling and vitrectomy, which interrupt the evolution of vitreous traction and have anatomical success rate of 73.2% to 92%.[6–8] However, the adverse events such as endophthalmitis, cataract, delayed-onset intraocular pressure elevation, refractive error, and the need for division (or removal) of the encircling element for the growing eye may evolve.[8–13]

Treatment with intravitreal bevacizumab (IVB) (Avastin; Genentech Inc, South San Francisco, CA), a humanized anti-vascular endothelial growth factor (VEGF) monoclonal antibody, is an emerging modality

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for ROP, with significant treatment effect and better preservation of the peripheral retina compared with conventional laser treatment for Stage 3+ ROP.[14] Significantly elevated vitreous VEGF levels have been identified in vascular-active Stage 4 ROP, and few case series have mentioned IVB for patients with a more advanced stage of ROP.[15–20] Another anti-VEGF agent, ranibizumab (Lucentis; Novartis, Basel, Switzerland), structured with the antibody fragment and having a shorter systemic half-life than bevacizumab, is an alternative for intravitreal anti-VEGF therapy in ROP, as documented in few reports.[21–23] Because both vitrectomy and scleral buckling exposed the infant to the risk of general anesthesia and have their own limitations, intravitreal injection of anti-VEGF agents could be an alternative tool in treating cases of Stage 4 ROP. The purpose of this study is to investigate the efficacy of intravitreal injection of anti-VEGF agents for patients with Stage 4 ROP.

Methods

We conducted a retrospective study of patients who received intravitreal injection of anti-VEGF agents as initial treatment for Stage 4 ROP. All case subjects were Taiwan residents and examined at Taipei Veterans General Hospital from January 2007 to May 2012. The medical records and retinal images of all patients were reviewed. Patients with Stage 4 ROP who received initial treatment other than intravitreal injection of anti-VEGF agents or patients with incomplete contents of chart were excluded. The study protocol complied with the provisions of the Declaration of Helsinki and was approved by the institutional review boards of the hospital. A signed informed consent from each patient's parent or legal guardian was obtained before the administration of IVB or intravitreal injection of ranibizumab (IVR).

The diagnosis of Stage 4 ROP was defined as ROP with extrafoveal (4A) or foveal (4B) partial RD according to the international classification of ROP.[24] The plus disease was diagnosed according to the "standard" photograph.[24]

The surgical technique is described as follows. Topical anesthesia with 0.5% proparacaine hydrochloride (Alcaine; SA Alcon-Couvreur NV, Puurs, Belgium) was applied for all infants. Vital signs were monitored throughout the entire procedure. After pupillary dilatation with 1% tropicamide (Mydriacyl; SA Alcon-Couvreur NV), the eyelids and conjunctiva were cleaned with 5% povidone iodine (sindine; Sinphar Pharmaceutical Co. Ltd, I-Lan, Taiwan). A lid speculum was placed, and intravitreal injection of 0.625 mg/0.025 mL of bevacizumab or 0.15 mg/0.015 mL ranibizumab with a 30-gauge needle 1 mm posterior to the limbus was performed by a vitreoretinal specialist (P.-K.L.). Another doctor held the infant during the whole procedure. Topical antibiotics in the form of 0.25% chloramphenicol (chloramphenicol ophthalmic solution 0.25%; Synpac-Kingdom Pharmaceutical Co. Ltd, Taipei, Taiwan) 4 times a day and 0.3% gentamicin ointment (Oftalmolosa Cusi Gentamicin 0.3%; Alcon Cusi SA, Barcelona, Spain) twice daily were administrated for 5 days postoperatively. The patients were followed up at 1, 2, 3, 5, and 7 days postoperatively and then weekly for 1 month, followed by every 2 weeks until the retina was noted to be fully vascularized.

Gestational age, birth weight, stage and location of ROP, age at injection of anti-VEGF agents, final anatomical outcomes, and duration of follow-up were recorded. Possible complications related to the injection, such as ocular inflammation, cataract, vitreous hemorrhage, and major systemic conditions such as acute cardiopulmonary embarrassment and mortality were also recorded through chart review. Fundus photography was performed with a panoramic fundus camera in some patients (RetCam; Clarity Medical Systems, Pleasanton, CA). Persistence of ROP was defined as the lack of adequate regression after treatment, and the retreatment occurred within 1 month from the previous treatment. Recurrence was defined as arrest of anterior progression of retinal vasculature with new demarcation line, ridge, or RD.[25] In the cases with persistence or recurrence, retreatment with either intravitreal injection of anti-VEGF agents or surgery may be considered.

Results

A total of 13 eyes of 7 patients with Stage 4 ROP were enrolled in this study (3 boys, 4 girls). One patient had Stage 4 ROP in one eye and Stage 3 ROP in the other. The mean gestational age was 27.6 ± 2.6 weeks (range, 24.5–30.5 weeks) with the mean birth weight of 893.1 ± 293.2 g (range, 550–1422 g). All of the patients received intravitreal anti-VEGF agent injection within 3 days of diagnosis. The mean age at the time of injection was 38.2 ± 1.9 weeks (range, 36.0–41.5 weeks) postmenstrual age (PMA). Nine eyes of five patients received IVB, and the other four eyes of two patients received IVR because of the parents' preference. Two eyes of one patient developed RD despite laser treatment at another hospital before being transferred to our hospital. One patient required repeated injections because of the persistence of ROP in the left eye and recurrence of ROP in the right eye. The fibrotic traction of the vitreous resolved, and RD regressed in both eyes after the second injection in this

patient (Figure 1). The active neovascularization (NV) regressed and, the final anatomical outcomes were favorable in all patients with a mean follow-up duration of 37.8 ± 19.5 months (range, 11.0–67.5 months) (Table 1). Three eyes in 3 patients had residual retinal fibrosis at peripheral Zone II or III at the end of follow-up (Figure 2). All eyes attained retinal reattachment and full vascularization without additional vitreoretinal surgery. The macula in all patients was in normal contour without dragging or distortion at the end of follow-up. No apparent ocular or systemic adverse effects related to the injection were noted in these patients.

Case 1

A male infant born at 25.0 gestational weeks was transferred to our hospital because of progressive ROP in both eyes at 40 weeks PMA. Fundoscopy revealed Stage 4B ROP with plus sign in both eyes (Figure 1A). The infant received IVB in both eyes at 40 weeks PMA. The vessel tortuosity and NV decreased significantly 2 days postoperatively. One week after the injection, RD regressed to peripheral Zones II and III (Stage 4A) in both eyes with vessels growing to the previous avascular area. Because of persistent high RD and NV tufts at peripheral Zones II and III in the left eye, the patient received a second IVB in the left eye at 44 weeks PMA. Around 3 weeks after the second injection, RD improved significantly with minor residual RD and vitreous traction at Zone III in both eyes. Eight weeks after the second injection, the retina was well vascularized in both eyes, with residual retinal fibrosis in the right eye and minor RD at the periphery left eye (Figure 1B). However, localized RD at Zone II with vitreous and retinal hemorrhage in the right eye was noted at 61 weeks PMA, and IVB in the right eye was performed (Figure 1C). The RD and hemorrhage in the right eye improved 2 weeks after the injection (Figure 1D). The retina was well attached and fully vascularized in both eyes with mild retinal fibrosis at Zone II in the left eye at the 45.0-month follow-up examination (age, 4.0 years) (Figure 2A).

Case 3

A male infant born at 28.5 gestational weeks was diagnosed as Stage 3 ROP in both eyes and received laser ablation therapy in both eyes at 37 weeks PMA at another hospital. However, ROP still progressed, and he was referred to our hospital at 41.5 weeks PMA. Fundoscopic examination revealed Stage 4A ROP with plus sign in both eyes. The patient received IVB in both eyes at 41.5 weeks PMA. One week after the injection, the height of RD decreased, and the plus sign resolved. Six weeks after the injection, the retina was well attached and fully vascularized in both eyes, with residual vitreous fibrosis in the right eye. The retina remained attached in both eyes with residual vitreous fibrosis superotemporally in the right eye and

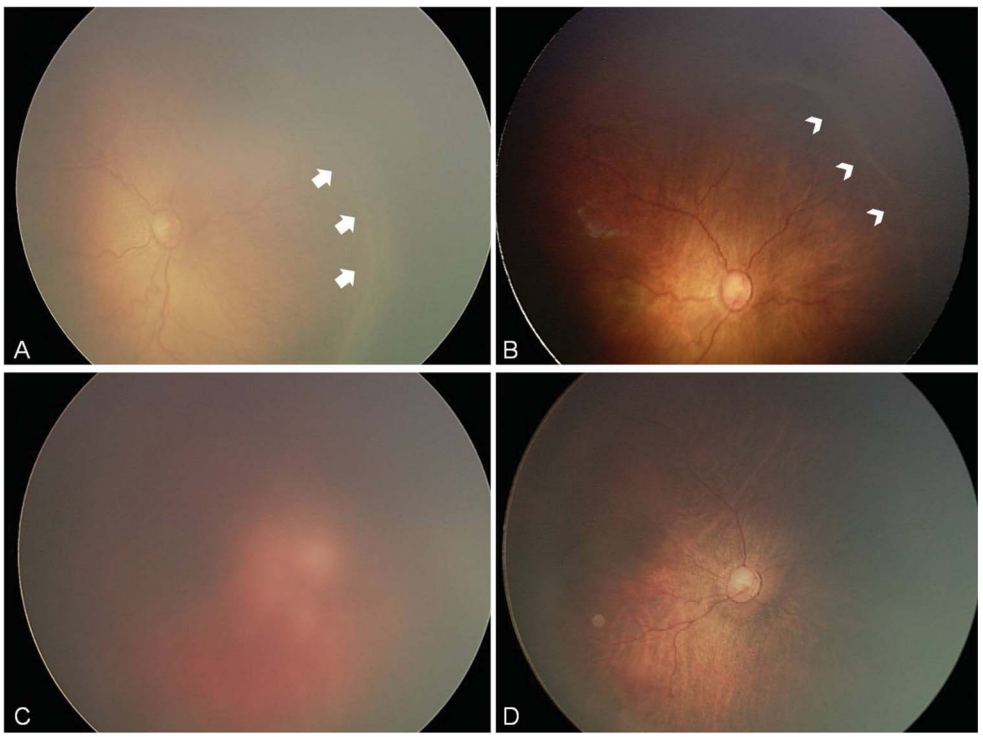

Fig. 1. Case 1: recurrence after initially successful treatment with IVB for Stage 4 ROP improved after a second IVB. **A.** Before IVB, peripheral RD (arrow) extending to the fovea (not shown) in the right eye was seen. **B.** After IVB, the retina was fully attached with residual fibrosis (arrowhead). **C.** Twenty-one weeks after the initial treatment, localized RD at Zone II (not shown) with vitreous and retinal hemorrhage was noted. **D.** After a second IVB, the hemorrhage resolved and the retina reattached during follow-up.

Table 1. Demographic Data, Treatment Sessions, and Anatomical Outcomes of Patients Receiving Intravitreal Injection of Anti-VEGF Agents for Stage 4 ROP

No.	Gender	GA (Weeks)	BW (g)	Eye	Stage	Zone	Plus Disease	Treatment Received Before Anti-VEGF Injection	Age at Injection (Weeks PMA)	Regiment	Repeated Injection (Weeks PMA)	Final Retina Reattachment	Residual Retina Fibrosis	Follow-up (Months)
1	M	25.0	820	OD	4B	I	+	-	40.0	IVB	61.0	+	-	45.0
				OS	4B	I	+	-	40.0	IVB	44.0	+	+	
2	M	29.0	1422	OD	4A	II	+	-	36.5	IVB	-	+	+	67.5
				OS	4A	II	+	-	36.5	IVB	-	+	-	
3	M	28.5	1080	OD	4A	III	+	Laser ablation	41.5	IVB	-	+	-	45.0
				OS	4A	III	+	Laser ablation	41.5	IVB	-	+	+	
4	F	25.5	640	OD	4A*	II	+	-	37.0	IVB	-	+	-	41.5
				OS	4A*	II	+	-	37.0	IVB	-	+	-	
5	F	30.5	950	OD	4A	III	+	-	36.0	IVB	-	+	-	40.5
6	F	30.5	790	OD	4A	II	+	-	38.0	IVR	-	+	-	11.0
				OS	4A	II	+	-	38.5	IVR	-	+	-	
7	F	24.5	550	OD	4A	III	+	-	37.0	IVR	-	+	-	14.0
				OS	4A	III	+	-	37.0	IVR	-	+	-	

*With tunica vasculosa lentis.
BW, birth weight; F, female; GA, gestational age; M, male; OD, right eye; OS, left eye.

a retinal fibrotic band at Zone III in the left eye at the 45.0-month follow-up visit (age, 4.0 years) (Figure 2B). The final best-corrected visual acuity was 6/12 in both eyes.

Case 6

A female infant born at 30.5 gestational weeks was diagnosed as Stage 2 ROP in both eyes at 36 weeks PMA. The ROP progressed to Stage 4A with plus sign in the right eye at 38 weeks PMA. After having the differences between IVB and IVR explained to them, the parents chose IVR, and she received IVR in the right eye at 38 weeks PMA. Two days after the injection, the extent of RD, height of ridges, and NV improved significantly. However, ROP evolved to Stage 4A with plus sign in the left eye, and she received IVR in the left eye at 38.5 weeks PMA. Three weeks after the first injection, ROP regressed to Stage 1 without plus sign in both eyes. The retinas in the left and the right eyes attained full vascularization 3 months and 5 months, respectively, after the injection in the respective eyes. At the end of 11.0 months of follow-up (age, 1.0 years), the retina remained attached and fully vascularized in both eyes.

Discussion

This study demonstrated that intravitreal injection of anti-VEGF agents may be effective either as a monotherapy or as supplement to laser treatment for Stage 4 ROP. All of the eyes showed significant regression of neovascular activity. Retinal detachment also resolved gradually. Even the vitreous fibrotic sheet regressed progressively. One eye with Stage 4B ROP had inadequate response to the first injection and achieved final regression of ROP after the second IVB. Another eye with Stage 4B ROP developed recurrent NV and hemorrhage 21 weeks after the first injection, which resolved after the second IVB. In patients with Stage 4B ROP, repeated intravitreal injection of anti-VEGF agents may be needed to obtain final anatomical success. However, surgery may be still needed in cases with either persistence or recurrence according to the clinical condition.

The established treatments for ROP-related RD include scleral buckling or vitrectomy, which interrupt the evolution of vitreous traction.[6,7] The anatomical success rate of vitrectomy for Stage 4 ROP is ~73.2% to 92.0%, with possible adverse effects of endophthalmitis, iatrogenic retinal break, cataract, and delayed-onset intraocular pressure elevation.[6,10–13] However, the success rate of scleral buckling is ~75%, with possible complications of severe myopia,

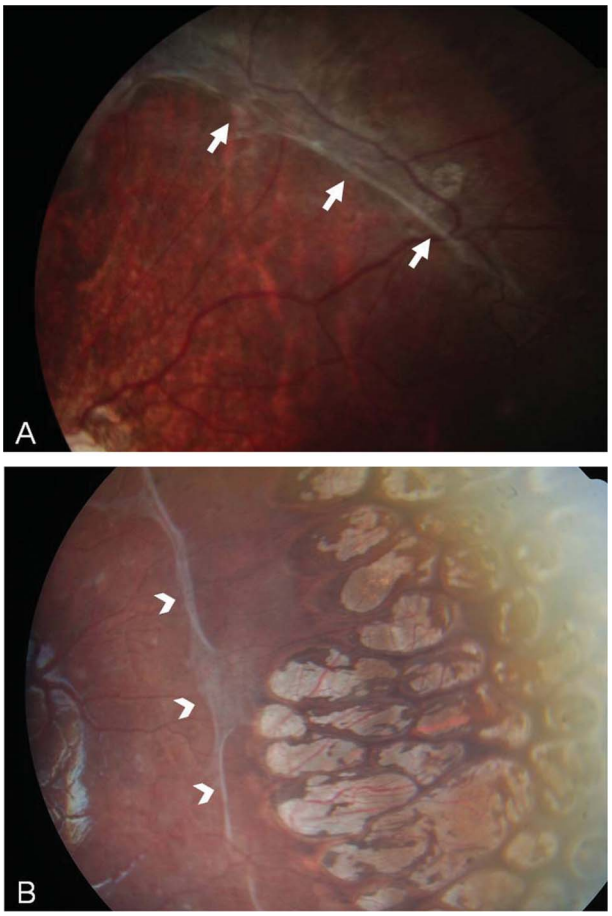

Fig. 2. Residual retinal fibrosis after IVB for Stage 4 ROP. **A.** The retina was well attached with fibrotic band superotemporally in the left eye (arrow) at the end of a 45.0-month follow-up (Case 1). **B.** The retina remained attached with fibrotic band at Zone III in the left eye (arrowhead) at the end of a 45.0-month follow-up (Case 3).

anisometropia, and the need for a secondary procedure for division (or removal) of the encircling element for the growing eye.[8,9] Because both vitrectomy and scleral buckling exposed the infant to the risk of general anesthesia and have their own limitations, intravitreal injection of anti-VEGF agents may provide an effective and more rapid way for the treatment of ROP.

Vascular endothelial growth factor is secreted in response to hypoxic and inflammatory stimuli by a number of different cells, including glial cells, vascular endothelial cells, retinal pigment epithelial cells, and ganglion cells in the retina. Its main role is to orchestrate the development and growth of blood vessels by promoting endothelial cell proliferation, migration, and tube formation.[26] Significantly elevated vitreous VEGF levels have been identified in vascular-active Stage 4 ROP.[15,16] Several case series and large clinical trials have shown promising results with IVB for Stage 3 ROP.[14,19,27] However, few reports mentioned its effect on Stage 4 ROP. Kusaka et al[17] enrolled 23 consecutive eyes (3 eyes of Stage 3, 18 of Stage 4A, and 2 of Stage 4B) of 14 patients with vascular-active ROP and performed IVB as the initial treatment (15 eyes) or at the end of vitrectomy (8 eyes). The neovascular activity significantly decreased after IVB, and two patients receiving IVB as the primary treatment had spontaneous retinal reattachment without vitrectomy. In three eyes, a tractional RD developed or progressed after IVB. Wu et al[19] reported that six eyes of three patients with Stage 4A ROP received a single injection of IVB. Among these patients, 2 eyes (33%) regressed after IVB and 4 eyes (67%) regressed after IVB and subsequent vitrectomy. Kychenthal and Dorta[20] also reported favorable outcomes of vitrectomy after IVB for 11 eyes of 8 children with Stage 4 ROP. Although limited cases with Stage 4 ROP may regress spontaneously, all of the 7 patients with Stage 4 ROP attained final retinal reattachment after IVB or IVR without additional vitreoretinal surgery in our study.[4,5] Intravitreal injection of anti-VEGF agents as a primary or supplementary treatment after failed laser therapy may be effective in patients with vascular-active Stage 4 ROP.

According to the literature, macular dragging, RD, recurrence of vessels, and taut fibrosis had been observed in patients who received IVB as initial treatment for variable stages of ROP.[14,25] Hu et al[25] also observed that reactivation of proliferative ROP after IVB may occur posteriorly at or near the original posterior site of extraretinal fibrovascular proliferation rather than more anterior location. In our study, 1 eye of 1 patient suffered from recurrence with localized RD at Zone II with vitreous and retinal hemorrhage at 61 weeks PMA, which improved after another IVB. Recurrence after treatment of Stage 4 ROP may be presented with RD and hemorrhage but the result was with limited strength because of rarity of the cases.

The use of anti-VEGF agents for patients with ROP requires attention to the risk of acute contraction of the proliferative membrane, thereby inducing or exacerbating RD, like condition in severe proliferative diabetic retinopathy.[28–30] The development or progression of tractional RD is believed to be due to a rapid neovascular involution with accelerated fibrosis and posterior hyaloid contraction, as a response to decreased levels of VEGF.[30] There were two case reports regarding progressive tractional RD after IVB for ROP. The patients were in Stage 3+ and Stage 4+ ROP separately, who suffered from progressive tractional RD 1 day after IVB, with a resultant fibrous ring and RD.[28,29] In this study, no patient had progressive fibrous traction after the injection. One eye that had persistent fibrotic vitreous traction with RD after the initial IVB experienced improvement after the second

injection. Three eyes in three patients had residual retinal fibrosis at peripheral Zone II or III during follow-up, but the retina attained full vascularization and remained attached at the end of follow-up.

Because of rarity of patients with Stage 4 ROP, both patients receiving IVB or IVR were enrolled in this study. Bevacizumab (Avastin; Genentech Inc) is a full-length anti-VEGF antibody, and ranibizumab (Lucentis; Novartis) is an antibody fragment (Fab) that has less molecular weight and better affinity to VEGF than bevacizumab.[31] Studies in animals demonstrated that intravitreally administered full-length IgGs can cross the blood–retinal barrier, which suggests an increased risk for systemic complications with bevacizumab compared with ranibizumab.[31] According to the Comparison of Age-Related Macular Degeneration Treatments Trials (CATT), bevacizumab and ranibizumab had equivalent effects on visual acuity in 1 year. With a limited statistical power, no significant difference in rates of death, arterial thrombotic events, or venous thrombotic events was found.[32] The efficacy of IVB for Stage 3+ ROP had been proven in the bevacizumab eliminates the angiogenic threat of retinopathy of prematurity (BEAT-ROP) study but for few reports regarding the IVR for patients with ROP.[14] Small case series demonstrated that IVB for ROP infants may suppress systemic VEGF levels for at least 7 weeks after the injection.[33] Hoerster et al[34] reported that 1 patient with ROP receiving IVR whose systemic VEGF levels reached a nadir at 2 weeks to 3 weeks returned to normal levels 4 weeks after the injection. Because both bevacizumab and ranibizumab may escape from the vitreous into the systemic circulation and decrease VEGF levels in infants with ROP, systemic side effects cannot be excluded, and continued evaluation of these patients is mandatory.[33,34] In our study, both IVB and IVR improved Stage 4 ROP, but the case numbers were too small to compare the differences. No apparent ocular or systemic adverse effect related to the injection was noted during the periods of follow-up.

The limitations of this study include a small cohort size, retrospective nature, and lack of comparison to a more established treatment comprising of vitreoretinal surgery. The study may lack power to establish the definite role of intravitreal injection of anti-VEGF agent for Stage 4 ROP but provide a possibly alternative treatment for these patients. Additionally, 1 patient had a shorter period of follow-up (11.0 months) in this study. In the BEAT-ROP study, the time to recurrence in the IVB group (mean, 19.2 weeks) is significantly longer than that in the laser group (mean, 6.4 weeks) in Zone I eyes. Hu et al[25] reported late reactivation and progression of ROP after IVB monotherapy in 17 eyes of 9 patients, with a mean time of 14.4 weeks (range, 4–35 weeks) between initial treatment and the treatment-requiring recurrence. They suggested extended follow-up for patients with ROP receiving IVB monotherapy. They also concluded that treatment may only be considered successful with complete vascularization to the ora serrata without active disease. In this study, all patients had follow-up duration of >11 months (mean, 37.8 ± 19.5 months; range, 11.0–67.5 months) and all of them had fully vascularized retina. Although three eyes in three patients had residual retinal fibrosis at the periphery, the retina was well attached and fully vascularized without signs of recurrence at the end of follow-up. The fully vascularized retina was diagnosed by one vitreoretinal specialist (P.-K.L.) through indirect ophthalmoscopy. Blair et al[35] proposed using fluorescein angiography to estimate peripheral retinal nonperfusion in children. We think clinical evaluation with indirect ophthalmoscopy may be appropriate for follow-up of ROP, but fluorescein angiography may be arranged for questionable cases in the future.

In conclusion, this study demonstrated that intravitreal injection of anti-VEGF agents may serve either as a monotherapy or supplement to failed laser treatment for patients with Stage 4 ROP without additional vitreoretinal surgery. Significant and rapid regression of neovascular activity was also observed. Special attention must be paid to the risk of progressive fibrous contraction and late recurrence. Because of the limited case numbers, further randomized, prospective controlled trials are needed to determine the safety, definite efficacy, and to improve our understanding of managing Stage 4 ROP with anti-VEGF agents.

Key words: anti-vascular endothelial growth factor, bevacizumab, ranibizumab, retinopathy of prematurity, Stage 4 retinopathy of prematurity.

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