Case Report

Effects of Low Dose of Intravitreal Bevacizumab in Retinopathy of Prematurity

Yuta SAITO, Isamu ITO, Toshihiko UEDA,
Michiko MATSUBARA and Haruo TAKAHASHI

Abstract : To evaluate the effects of low-dose intravitreal injections of bevacizumab (IVB) in retinopathy of prematurity (ROP). A total of 14 eyes of 7 patients received IVB (0.25 mg/eye) for treatment of ROP from April 2011 to June 2012 at Showa University. This retrospective case series included the patients who were followed up for at least 5 months after IVB. Ten eyes of five patients were included in the analysis. The mean gestational age and birth weight were 24.6 (range : 22–26) weeks and 770 grams (range : 505–1055), respectively. Eight eyes of four patients with stage 3 ROP with plus disease were laser treated, and two eyes of one patient were treated with aggressive posterior ROP (AP-ROP) without laser use. All of the eyes received only a single injection of IVB. The mean injection age and body weight were 37.2 (range : 34–39) weeks of postconceptional age and 2073 grams (range : 1400–2995). Of the eight eyes with stage 3 ROP with plus disease, six eyes (four patients) regressed after IVB treatment. Two eyes (two patients) were treated with vitrectomy after IVB. The AP-ROP regressed after IVB and a subsequent laser treatment. IVB was performed as a salvage therapy, and low-dose IVB was effective for promoting the regression of ROP. However, IVB increased fibrotic traction in some eyes. In the BEAT-ROP study, a dosage of 0.625 mg IVB was used as a monotherapy ; however, intravitreally injected bevacizumab can escape to the systemic circulation. Thus, the use of a lower dosage of IVB for ROP in combination with laser therapy appears to be efficacious until the optimal dosage can be established.

Key words : retinopathy of prematurity, vascular endothelial growth factor (VEGF), bevacizumab, intravitreal injection

Introduction

Retinopathy of prematurity (ROP) remains one of the leading causes of infant blindness. Recently, the Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity (BEAT-ROP) study reported that bevacizumab was effective in the treatment of zone I ROP¹⁾; thus the use of anti-vascular endothelial growth factor (VEGF) antibody therapy for ROP may increase worldwide in the future. However, the use of bevacizumab for the treatment of ROP is an off-label use of this drug, and the possible systemic side effects are not known. A recent

Department of Ophthalmology, Showa University School of Medicine, 1-5-8 Hatanodai, Shinagawa-ku, Tokyo 142-8666, Japan.

review by Micieli *et al*²⁾ discussed the range of bevacizumab dosages used for ROP treatment, ranging from 0.4 to 1.25 mg, with 0.75 mg being the most commonly used dose in nine previous articles. This is consistent with the dosage of 0.625 mg bevacizumab used in the BEAT-ROP study¹⁾, which is half the dosage used for adults. However, no rationale for these dosages was given. In addition, intravitreally injected bevacizumab can escape into the systemic circulation in animal models³⁻⁵⁾ and human infants⁶⁾. The drug also reduced the serum levels of VEGF in infants with ROP⁶⁾; VEGF is an essential factor for normal angiogenesis⁷⁾ and neuronal protection⁸⁾. Based on these possible adverse effects of bevacizumab on VEGF-dependent development, a lower dosage might have the added benefit of decreasing the post-therapy risk of side effects.

In this retrospective study, we further examined the effects of low-dose IVB for treating ROP.

Patients and Methods

This is a retrospective study of bevacizumab use in patients with ROP at Showa University Hospital. The study was approved by the institutional review board of Showa University, and informed consent was obtained from each patient's parents. The data were collected from April 2011 to June 2012, and patients followed up for at least 5 months were included for analysis. IVB was administered for the cases in which conventional laser treatments failed to regress the ROP or in which treatment was difficult because of tunica vasculosa lentis.

The treatment was administered as follows. The pupil was dilated with 0.5% tropicamide and 0.5% phenylephrine (Mydrin-P[®], Santen Pharmaceutical Co., Osaka, Japan) in preparation for the intravitreal injection. In the operating room and after general anesthesia, the eyes were prepared in a standard fashion using a 16-fold dilution of povidone iodine, and 0.25 mg (0.01 ml) of bevacizumab was injected intravitreally via the pars plicata. IVB was simultaneously performed for both eyes in all patients. Paracentesis was not performed. After the injection, the patients received topical tosfloxacin (Tosuflo[®], Nitto Medic Co., Ltd., Toyama, Japan) and betamethasone (Rinderon[®], SHIONOGI & Co., Ltd., Osaka, Japan) for 1 week. The patients were followed up after 1 day, 2 days, and then every week to evaluate the disease progress. Regression of ROP was defined as disappearance of the retinal vessel tortuosity and ridges. Patients who received IVB as a primary therapy subsequently underwent conventional laser treatment after disappearance of the tunica vasculosa lentis. Some patient eyes were photographed using a RetCam II system (Clarity Medical System, Pleasanton, CA) before and after the injection of bevacizumab (Fig. 1, 2).

Results

Fourteen eyes of seven patients were treated with IVB in this study. Two patients were excluded because of a follow-up period shorter than 1 month. In total, 10 eyes of 5 patients (4 males and 1 female) were included in the study analysis. The mean gestational age and birth weight were 24.6 (range: 22-26) weeks and 770 grams (range: 505-1055), respectively. There were 8 eyes of 4 patients with Zone II stage 3 ROP with plus disease treated by conventional

Fig. 1. Case 1: Pre-IVB images of right (A) and left (B) eyes. Right (C) and left (D) eyes at 1 week after IVB, showing regression of the ridges in the temporal retina.

Fig. 2. Case 5: Pre-IVB image of the right eye (A). Due to tunica vasculosa lenticis (C) in the left eye, the fundus could not be observed. One week after IVB, the tunica vasculosa lenticis disappeared (D), and the fundus was clearly observed (B, E). AP-ROP was regressed following the subsequent conventional laser treatment.

laser, and 2 eyes of 1 patient were treated with Zone I aggressive posterior ROP (AP-ROP) without laser treatment (Table 1). Stage 3 ROP with plus disease was laser treated when it met the criteria of the ET-ROP study. All of the eyes received only a single injection of bevacizumab. The mean injection age and body weight were 37.2 (range: 34–39) weeks of postconceptional age and 2073 grams (range: 1400–2995), respectively. No patient experienced complications such as cataract or endophthalmitis. Of 8 eyes with stage 3 ROP with plus disease, 6 eyes (4 patients) regressed after IVB. Two eyes (2 patients) were treated with vitrectomy after the IVB because of progressive tractional retinal detachment, although the retina of one eye failed to reattach. The AP-ROP regressed after IVB and subsequent conventional laser treatment.

Table 1. Patients treated with bevacizumab

Cases	Gender	GA (wks)	BW (g)	Eye	Zone	Stage	Age at Laser (wks)	Age at Injection (wks)	Body Weight at Injection (g)	Age at Vitrectomy (wks)	Final Retinal Attachment	Follow up (months)	Other Diagnosis
1	M	24	618	OD	II	3 +	34, 37, 38	38	2150	—	Yes	1Y9M	RDS, PDA, IVH
				OS	II	3 +	34, 35, 38	38		—	Yes		
2	M	26	1055	OD	II	3 +	37	38	2995	—	Yes	1Y4M	PDA
				OS	II	3 +	37	38		—	Yes		
3	F	25	777	OD	II	3 +	32	37	1799	38, 42*	No	1Y7M	RDS, PDA, IVH, SSSS
				OS	II	3 +	32	37		—	Yes		
4	M	26	896	OD	II	3 +	33, 35, 38	39	2022	40	Yes	11M	RDS, PDA
				OS	II	3 +	34, 35, 38	39		—	Yes		
5	M	22	505	OD	I	APROP	35	34	1400	—	Yes	10M	RDS,
				OS	I	APROP	35	34		—	Yes		congenital CMV infection

M = male ; F = female ; GA = gestational age ; BW = birth weight ; OD = right eye ; OS = left eye, 3 + = stage 3 with plus disease, APROP = aggressive posterior ROP, * Pars Plana Lensectomy + Vitrectomy

RDS = respiratory distress syndrome, PDA = patent ductus arteriosus, IVH = intraventricular hemorrhage, SSSS = staphylococcal scalded skin syndrome, CMV = cytomegalovirus

Discussion

In this study, we investigated the use of a lower dosage of bevacizumab to treat severe ROP based on a number of previous reports²⁾. Intravitreal injection of 0.25 mg bevacizumab caused regression of stage 3 ROP with plus disease for which laser treatment was ineffective in some cases, whereas it caused retinal fibrous proliferation and tractional retinal detachment in other cases. Furthermore, it was effective in regressing AP-ROP when combined with laser therapy. Thus, the optimal dosage of bevacizumab for ROP treatment requires further investigation⁹⁾.

VEGF is an essential factor for normal angiogenesis and neuronal protection^{7, 8)}, as well as normal lung development¹⁰⁾. VEGF is highly expressed during glomerular development in the kidney¹¹⁾, and the inhibition of VEGF may cause bronchopulmonary dysplasia¹²⁾ and glomerular disease¹³⁾. Thus, the report by Sato *et al*⁶⁾ of intravitreally injected bevacizumab leaking from the eye into the systemic circulation and reducing the serum levels of VEGF in infants with ROP is cause for concern due to the potential suppressive effects of IVB on normal development in premature infants. The common adverse effects in adults receiving bevacizumab for cancer are hypertension and proteinuria¹⁴⁾. Although there are no reports on systemic adverse events in infants that received IVB, possible adverse event must be considered^{15, 16)} and the minimum effective dose of bevacizumab should be selected. Additionally, the long-term systemic complications are still unknown, and consideration should be given to the systemic development of organs such as brain, lung, and kidney after IVB.

The limitation of this retrospective study is that there were no control cases. Due to the combination with conventional laser therapy, the lower dosage of bevacizumab used in this study might be sufficient, and thus it remains unclear whether 0.25 mg of bevacizumab is effective in

treating ROP as a monotherapy. The optimal dosage of IVB for ROP requires investigation in prospective randomized trials in the future.

In conclusion, we consider that low-dose bevacizumab should be used as a salvage therapy after failure of conventional laser therapy or as a combined therapy until the optimal dosage of IVB is known. The possible long-term adverse effects after IVB for ROP must be considered.

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[Received November 6, 2013 : Accepted December 13, 2013]