Different Refractive Errors in Triplets With Retinopathy of Prematurity Treated With Bevacizumab

Chien-Chi Tseng, MD; San-Ni Chen, MD; Jiunn-Feng Hwang, MD; Chun-Ju Lin, MD

ABSTRACT

The authors report refractive errors possibly resulting from intravitreal bevacizumab injection. Triplet A presented with stage 3 retinopathy of prematurity, was treated with intravitreal bevacizumab, and high refractive errors were noted. Triplet B presented with stage 2 retinopathy of prematurity in the right eye and stage 3 retinopathy of prematurity in the left eye, which regressed spontaneously. Triplet C presented with stage 2 retinopathy of prematurity in the right eye and stage 3 retinopathy of prematurity in the left eye, which were treated with intravitreal bevacizumab. **[J Pediatr Ophthalmol Strabismus 2012;49:e41-e43.]**

INTRODUCTION

Retinopathy of prematurity (ROP) is a neovascular retinal disorder with highly elevated vascular endothelial growth factor (VEGF) levels in vitreous fluid.[1] It occurs primarily in infants born prematurely before 31 weeks' gestational age with low birth weight (1,250 g or less).[2]

Peripheral retinal ablation with conventional laser therapy or cryotherapy is a proven treatment to destroy the majority of the cells that produce VEGF in the retina, but some destructive complications cannot be averted.[3,4] The current study shows superior efficacy of intravitreal bevacizumab (IVB) injection over peripheral retinal ablation as measured by means of disease recurrence and abnormal structural outcomes.[2] Although IVB injection has shown satisfactory results in treating ROP, the long-term safety remains uncertain.

In the literature, there is no report focusing on the refractive status after IVB injection in ROP. We highlight a case of high refractive errors possibly resulting from IVB injection in triplets with ROP.

CASE REPORTS

Triplet A was a boy of 28 weeks' gestational age weighing 1,039 g at birth. He presented with zone 2, stage 3 plus ROP in both eyes at 38 weeks' postmenstrual age and was treated with IVB injection of 0.625 mg (0.025 mL) via the pars plicata at 2 mm behind the limbus. Disappearance in retinal vessel tortuosity and neovascularization was noted after the treatment, and vascularization toward the peripheral retina with absence of recurrence was noted by 53 weeks' postmenstrual age and until 1 year of follow-up. However, high myopia with axial length elongation in both eyes (23.97 and 22.85 mm) was noted at the age of 1 year and 4 months.

Triplet B was a girl weighing 1,082 g at birth who presented with zone 2, stage 2 ROP in the right eye and stage 3 ROP in the left eye at 45 weeks' postmenstrual age. Full regression of ROP was noted under observation and the peripheral retina was well vascularized at the 1-year follow-up. Both eyes had mild

From the Department of Ophthalmology (C-CT, S-NC, J-FH, C-JL), Changhua Christian Hospital, Changhua; the School of Medicine (S-NC, J-FH, C-JL), Chung Shan Medical University, Taichung; and the Department of Optometry (C-JL), Chung Hwa University of Medical Technology, Tainan, Taiwan.

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Address correspondence to Chun-Ju Lin, MD, Department of Ophthalmology, 135 Nanxiao St., Changhua, Taiwan. E-mail address: doctoraga@gmail.com

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hyperopia with axial length of 20.34 mm in the right eye and 20.38 mm in the left eye, respectively.

Triplet C was a boy weighing 1,039 g at birth who presented with zone 2, stage 2 ROP in the right eye and stage 3 plus ROP in the left eye at 47 weeks' postmenstrual age. He was treated with IVB injection of 0.625 mg (0.025 mL) in the left eye after observation and discussion with the parents. ROP in both eyes regressed at the 1-year follow-up and the cycloplegic refraction showed mild hyperopia similar to triplet B with axial length of 20.94 mm in the right eye and 20.86 mm in the left eye, respectively.

High refractive errors with axial length elongation were noted in both eyes of triplet A after IVB injection. The same situation was not found in the left eye of triplet C. The anterior chamber depth of triplet A was similar to that of the other two triplets and the parents had no history of high myopia. Furthermore, the cycloplegic refractive status of triplets B and C remained stable at the 14-month follow-up visit. The cycloplegic refraction of triplet A progressed from -9.00 to -9.75 diopters in the right eye and from -6.50 to -11.50 diopters in the left eye. The similar results were found after repeated measurements. The axial length also elongated from 22.85 to 23.37 mm in the left eye.

DISCUSSION

IVB injection is an emerging treatment for ROP with promising results as a primary or salvage treatment. It seems to work best in the majority of patients with stage 3 ROP. In advanced ROP with retinal detachment, the treatment benefits of bevacizumab are less evident due to possible inflammation or a tractional force induced by accelerated fibrosis.[6]

IVB can neutralize the VEGF already present in the vitreous cavity but cannot further destroy VEGF expression in the avascular retina as peripheral ablation treatment. Conventional laser therapy results in permanent destruction of the peripheral retina, inevitably causes permanent loss of the peripheral visual field, and often induces clinically significant refractive errors. IVB allows continued normal vessel growth toward the peripheral retina.[6-8] Although numerous potential complications of IVB injection in premature infants should be warranted because the full effect of anti-VEGF on normal developing vessels and organs is unknown, potential systemic side effects have not been documented. The procedure itself has the risk of infection and trauma.

Some ocular complications do occur after the injection, such as transient retinal vessel sheathing and pre-retinal or vitreous hemorrhage.[6] One case of mild anatomical retinal abnormality was reported by Mintz-Hittner et al. after IVB injection.[5] Progressive axial elongation with high refractive errors was noted after single IVB injection in both eyes of triplet A. The same situation was not found in the injected eye of triplet C. Refractions of triplets were not recorded before the IVB injections. The refractive error change might be related to the bevacizumab, but this is not definite due to lack of previous refractive record.

Children with a history of prematurity have a higher incidence of myopia or high myopia at an early age.[9] Multiple studies have been published for the possible refractive elements involved in the development of myopia in ROP, such as increased corneal curvature, increased axial length, decreased anterior chamber depth, and increased lens thickness and power.[10,11] High myopia in ROP appears pathophysiologically different from high myopia in full-term patients. Increased lens thickness accompanied by shallower anterior chamber depth is the major causative factor in high myopia of ROP, irrespective of ROP stage or treatment, with a smaller contribution made by significantly increased keratometry and axial length measurements. For the eyes with high myopia in full-term patients, axial length is the main element accounting for the refractive error.[12]

The high myopia in our triplet A contributed more to axial elongation rather than lenticular-associated high myopia, which is more common in ROP. One of the explanations is that the infants were heterozygous triplets by artificial reproductive technique. They may have different genetic factors driving axial growth. Another possible explanation is that IVB may have some relationship with axial elongation. The concentration of VEGF in the aqueous humor has been proven to be negatively correlated with axial length in adults.[13] However, the cause was thought to be the thinner retina with axial elongation, which might cause relatively increased choroidal perfusion and decreased retinal hypoxia resulting in decreased VEGF production.[14,15] It is interesting that the relation between the cause and effect of the phenomenon would be inverting if IVB in ROP is proven to result in axial elongation in the future. It is difficult to distinguish whether the high myopia is correlated with the treatment under available evi-

dence. IVB injection has advantages compared with ablative treatment, such as ease of the procedure, relatively rapid effect, less destruction of the retina, continued normal retinal vascularization, and tunica vasculosa lentis regression.[2,6] It has been thought to eliminate complications associated with ablative treatments such as refractive errors or visual field loss. However, refractive change in our case might be one of the possible complications related to IVB. It is still uncertain whether bevacizumab may influence the development of myopia in a different manner than in other patients with ROP, but it serves as a warning to clinicians that careful follow-up of refraction is mandatory in infants treated with IVB.

Further randomized, controlled prospective studies with long-term follow-up are urgently needed to clarify the ocular and systemic safety of IVB in ROP.

REFERENCES

1. Alon T, Hemo I, Itin A, et al. Vascular endothelial growth factor acts as a survival factor for newly formed retinal vessels and has implications for retinopathy of prematurity. *Nat Med.* 1995;1:1024-1028.
2. Reynolds JD. Bevacizumab for retinopathy of prematurity. *N Engl J Med.* 2011;364:677-678.
3. Early Treatment for Retinopathy of Prematurity Cooperative Group. Revised indications for the treatment of retinopathy of prematurity: results of the Early Treatment for Retinopathy of Prematurity randomized trial. *Arch Ophthalmol.* 2003;121:1684-1694.
4. Cryotherapy for Retinopathy of Prematurity Cooperative Group. Multicenter trial of cryotherapy for retinopathy of prematurity: preliminary results. *Arch Ophthalmol.* 1988;106:471-479.
5. Mintz-Hittner HA, Kennedy KA, Chuang AZ, et al. Efficacy of intravitreal bevacizumab for stage 3+ retinopathy of prematurity. *N Engl J Med.* 2011;364:603-615.
6. Wu WC, Yeh PT, Chen SN, et al. Effects and complications of bevacizumab use in patients with retinopathy of prematurity: a multicenter study in Taiwan. *Ophthalmology.* 2011;118:176-183.
7. Mintz-Hittner HA, Kuffel RR Jr. Intravitreal injection of bevacizumab (Avastin) for treatment of stage 3 retinopathy of prematurity in zone I or posterior zone II. *Retina.* 2008;28:831-838.
8. Dorta P, Kychenthal A. Treatment of type 1 retinopathy of prematurity with intravitreal bevacizumab (Avastin). *Retina.* 2010;30(suppl):S24-S31.
9. Quinn GE, Dobson V, Repka MX, et al. Development of myopia in infants with birth weights less than 1251 g. The Cryotherapy for ROP Cooperative Group. *Ophthalmology.* 1992;99:329-340.
10. Hibino Y, Takahashi M, Majima A. Studies on ocular functions of cicatricial ROP. Measurements of refractive elements. *Jpn J Clin Ophthalmol.* 1978;32:655-662.
11. Hittner HM, Rhodes LM, McPherson AR. Anterior segment abnormalities in cicatricial ROP. *Ophthalmology.* 1979;86:803-816.
12. Garcia-Valenzuela E, Kaufman LM. High myopia associated with retinopathy of prematurity is primarily lenticular. *J AAPOS.* 2005;9:121-128.
13. Sawada O, Miyake T, Kakinoki M, et al. Negative correlation between aqueous vascular endothelial growth factor levels and axial length. *Jpn J Ophthalmol.* 2011;55:401-404.
14. Lam DS, Leung KS, Mohamed S, et al. Regional variations in the relationship between macular thickness measurements and myopia. *Invest Ophthalmol Vis Sci.* 2007;48:376-382.
15. Blaauwgeers HG, Holtkamp GM, Rutten H, et al. Polarized vascular endothelial growth factor secretion by human retinal pigment epithelium and localization of vascular endothelial growth factor receptors on the inner choriocapillaris: evidence for a trophic paracrine relation. *Am J Pathol.* 1999;155:421-428.