Intravitreal bevacizumab as adjunctive treatment for retinopathy of prematurity

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BACKGROUND While laser photocoagulation remains the standard of care in the treatment of advanced retinopathy of prematurity (ROP), regression is not seen in all cases (especially in aggressive posterior disease) following laser alone. We report the results of the use of the anti-vascular endothelial growth factor monoclonal antibody bevacizumab in eyes with ROP at high risk for progression.

METHODS Records of all infants with ROP treated with bevacizumab were reviewed. Bevacizumab was given when conventional laser therapy was not possible in patients with poor pupillary dilation from iris rubeosis, dense vitreous hemorrhage, or increasing vascular activity and vitreoretinal traction despite completed laser therapy. We recorded birth weight, gestational age at birth, severity of ROP, anatomic result, any additional ophthalmic interventions, and early or late adverse systemic effects.

RESULTS Thirteen eyes of 7 infants (median gestational age, 25 weeks; median birth weight, 700 g; follow-up, 9 months [range, 2-17]) were treated with an intravitreal injection of 0.75 mg bevacizumab under sterile conditions by 1 surgeon following detailed discussion with family and attending neonatologists. Injection was not used as monotherapy in any case. Definitive treatment (laser or vitrectomy) was completed successfully within 72 hours of injection. No systemic complication attributable to bevacizumab treatment has been recorded within 2 to 17 months of follow-up.

CONCLUSIONS Treatment with bevacizumab may be used to improve visualization for more definitive laser or surgical treatment and may facilitate disease regression without obvious systemic toxicity. Optimization of dosing, timing, and indications will require additional study. (J AAPOS 2010;14:6-10)

Introduction

Retinopathy of prematurity (ROP), associated with early gestational age and low birth weight, is a major cause of irreversible visual impairment in developed countries.[1] The suggested biphasic process of ROP leads to avascular zones of the retina with increased production of cytokines and growth factors—notably, vascular endothelial growth factor (VEGF)—resulting in neovascularization. If untreated, these new vessels may ultimately lead to irreversible vision loss from retinal detachment.

See editorial on page 2.

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The therapeutic efficacy of peripheral retinal ablation at defined stages of ROP was established in the late 1980s with the Cryotherapy for Retinopathy of Prematurity Study and confirmed with the Early Treatment of ROP Study.[1,2] Despite appropriate laser treatment, however, progression to tractional retinal detachment was seen in 10% to 15% of cases of threshold ROP and in up to 50% in a subset of infants with particularly aggressive ROP. The concept of a more severe form of ROP, aggressive, posterior ROP (AP-ROP), was introduced in the revised ROP classification[3] and is frequently associated with congestion of iris vessels, prominence of tunica vasculosa lentis, poor pupillary dilation, and vitreous haze, all of which can compromise the integrity of the examination and completeness of laser treatment.

The incidence of persistent neovascularization and possibility of unfavorable outcome, especially among cases of AP-ROP, has spurred the quest for alternative treatments. Pharmacologic inhibition of VEGF in ROP has both biological plausibility and empiric clinical success in various retinal vascular proliferative diseases.[4-6] Elevated levels of VEGF have been found in serum of patients with threshold disease (Brady-McCreery KM, et al. Annual Meeting of the American Academy of Ophthalmology 2001;3:113

[abstract]), subretinal fluid,[7] and vitreous fluid[8] of eyes with vascularly active stage 4 ROP.

We report the results of the use of the anti-VEGF monoclonal antibody bevacizumab (Avastin; Genentech, Inc, South San Francisco, CA) in a consecutive series of eyes with ROP at high risk for progression to retinal detachment.

Materials and Methods

This study was approved by the Vanderbilt University Institutional Review Board and conformed to the requirements of the U.S. Health Insurance Portability and Accountability Act. A retrospective review of all records of all infants with ROP treated with bevacizumab at our institution was performed. Bevacizumab was used either as an adjuvant to conventional laser therapy when laser was not initially possible due to iris rubeosis and poor pupillary dilation, dense vitreous hemorrhage, or in cases of increasing vascular activity and vitreoretinal traction despite complete retinal laser. The following data were recorded: birth weight, gestational age at birth, severity of ROP, anatomic result, any additional ophthalmic interventions, and early or late adverse systemic effects.

Prior to the procedure, a detailed conversation with the parents or legal guardian was documented and informed consent regarding the off-label use of bevacizumab was obtained. The injections were done at the bedside in the neonatal intensive care unit utilizing a continuous cardiorespiratory monitor and with a pediatric critical care physician administering intravenous, conscious sedation.

Bevacizumab was obtained from the hospital pharmacy, supplied in sterile unit doses of 0.75 mg (0.03 mL) in single-use 1 mL syringes with a half-inch 32-gauge needle (TSK Steriject; Air-Tite Products Co, Inc, Virginia Beach, VA) for intravitreal use.

One drop of proparacaine hydrochloride (0.5%) ophthalmic solution was instilled in the eye, and a sterile Alfonso eyelid speculum was placed between the lids. One drop of povidone-iodine (5%) was then instilled. After waiting 1 minute, a pledget soaked in proparacaine was placed on the bulbar conjunctiva over the site of injection. The eye did not need to be immobilized because the patient was sedated. Bevacizumab (0.03 mL [0.75 mg]) was injected either nasally or temporally 1 mm behind the limbus through the pars plicata into the central vitreous cavity, with the surgeon taking care to avoid the crystalline lens. Following the injection, a second drop of povidone-iodine (5%) was instilled and the lid speculum was removed. Palpation of the eye over closed lids was performed to gauge tactile intraocular pressure. All patients were prescribed an ophthalmic antibiotic drop (moxifloxacin [0.5%] ophthalmic solution) to be given every 6 hours for 4 days and reexamined daily for sign of infection.

Results

A total of 13 eyes of 7 infants (median gestational age, 25 weeks; birth weight, 700 g; follow-up, 9 months [range, 2-17]) were treated between October 2007 and November 2008. All infants were treated by a single surgeon (FMR) following referral from either a pediatric ophthalmologist (2 infants) or another retinal specialist (5 infants). A total of 14 injections were given (12 eyes received 1 injection only and 1 eye received 2 injections). Prior to initial injection, 8 eyes were treatment-naive, and 5 eyes had received partial or complete laser retinopexy. Injection was not used as monotherapy in any case.

Indications for initial bevacizumab treatment included iris rubeosis and poor pupillary dilation precluding complete laser treatment (6 treatment-naive eyes and 1 eye treated with incomplete laser), dense vitreous hemorrhage precluding treatment (2 treatment-naive eyes), and increasing vascular activity and vitreoretinal traction despite complete retinal laser (4 eyes). A second injection was given to 1 eye (Patient 3; left eye) because of new vitreous hemorrhage and tractional retinal detachment (e-Supplement 1, available at jaapos.org).

In the 7 untreated/partially treated eyes of 4 patients (all with aggressive posterior ROP), definitive treatment with diode laser photocoagulation was planned and performed within 72 hours of injection. In 1 patient (Patient 7) laser treatment could not be administered until 5 days later due to a need for closure of a patent ductus arteriosus. In all eyes, marked regression of anterior segment vascular activity and increased pupil dilation were seen within 48 hours (Figure 1), facilitating retinal visualization and laser treatment. In 7 of these eyes, complete regression of ROP was seen within 1 month of laser, with no subsequent retinal detachment. In 1 eye there was initial response with localized 4-A tractional retinal detachment developing 2 months later (Patient 7, left eye). Progression to a localized tractional detachment requiring surgery occurred in 1 eye (Patient 7, right eye).

Two eyes with dense vitreous hemorrhage underwent lensectomy and vitrectomy following treatment with bevacizumab. Three months postoperatively, retinal reattachment was seen in 1 eye, and open-funnel retinal detachment was seen in 1 eye.

In the 4 eyes previously treated with laser but with persistent vascular activity and progressive vitreoretinal traction, complete regression was seen in 2 eyes (1 infant) within 1 month of bevacizumab injection. Progression to retinal detachment occurred in 2 eyes (2 infants). One eye underwent lens-sparing vitrectomy for tractional retinal detachment 3 months after injection, and 1 eye underwent lens-sparing vitrectomy for a combined traction-rhegmatogenous retinal detachment that developed 2 weeks after injection.

There were no cases of trauma to ocular structures or evidence of endophthalmitis. No early or late systemic complication attributable to bevacizumab treatment has been recorded within 2 to 17 months of follow-up. The neonatology team closely monitored vital signs for each patient immediately after injection and there were no reports of changes unrelated to the patients' preexisting complicated systemic conditions. Subsequent follow-ups beyond the first 4 weeks after injection revealed no unexpected untoward events such as cardiopulmonary distress, stroke, or renal insufficiency as reported from the neonatologist.

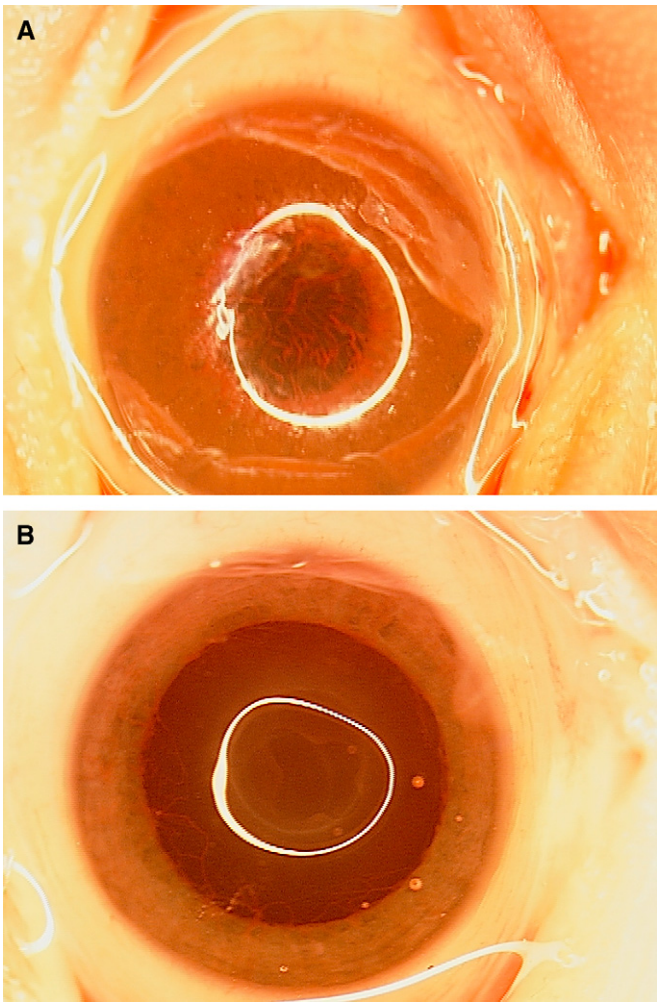

FIG 1. Patient 1. A, Left eye anterior segment vascularization and poor pupillary dilation prior to intravitreal bevacizumab. B, Improvement of left eye anterior segment vascularization and improved pupillary dilation 48 hours after intravitreal bevacizumab.

However, 2 patients died from complications of their previous systemic conditions. One patient (Patient 2) died 16 weeks post-bevacizumab, after medical and surgical treatments for multisystem organ failure. Patient 7 died (38 weeks post-bevacizumab) from cardiac arrest secondary to severe bronchopulmonary dysplasia complicated by pulmonary hypertension. Postmortem eyes were not obtained since both patients were out of care at the time of death.

Discussion

Peripheral laser retinal ablation, which prevents unfavorable structural and visual outcome in the majority of cases, has become the standard of care for advanced ROP. Nevertheless, there are cases in which ROP progresses despite full treatment and cases in which complete treatment may not be possible because of poor retinal visualization. We describe in this article the potential benefit of adjunctive bevacizumab in such cases. We have used bevacizumab in cases of advanced AP-ROP with a high chance for progression using laser alone and cases of documented progression despite full laser treatment. We have not used it as monotherapy because of the proven long-term benefit of laser photocoagulation and the unknown duration of effect of bevacizumab.

Previous uses of intravitreal bevacizumab for diverse scenarios of ROP have recently been reported (Table 1).[9-16] Overall, results have generally been promising, showing regression or stabilization of varying stages of ROP. Our findings are grossly consistent with prior reports, showing complete regression in a majority of cases with AP-ROP. Comparison among studies is difficult because of variability of inclusion criteria, indications, and outcome measures. Intravitreal bevacizumab has been demonstrated as a possible adjunct to laser or surgery and as a possible monotherapy. Three studies, however, have demonstrated the possible adverse effect of bevacizumab on fibrovascular membrane contraction.[14-16] In 1 patient, 1 eye was treated with intravitreal bevacizumab after failed laser for posterior ROP.[15] Within 7 days of the injection, the vascular activity resolved but acute membrane contraction resulted in a funnel-shaped retinal detachment. The authors attribute the tractional detachment to the rapid fibrosis and contraction of the posterior hyaloid from acute regression of neovascularization. In our study, 4 eyes progressed to tractional retinal detachments following intravitreal injections; 1 also developed a small posterior retinal break suspected to have resulted from posterior hyaloidal contraction and less likely as a result of a jet stream from the injection. We recommend caution in treatment of eyes with active fibrovascular proliferation or prompt treatment with vitreous surgery to prevent rapid progression to tractional or rhegmatogenous retinal detachment.

Concerns about potential ocular and systemic adverse effects following VEGF blockade remain, especially in a growing infant in whom VEGF is required for normal vasculogenesis and organ development. While there are no systemic safety data on preterm infants receiving intravenous bevacizumab, there have been reports on pediatric patients as young as 1 year of age. The Children's Oncology Group recently completed a phase I dose escalation study on the use of intravenous bevacizumab in 20 children with refractory solid tumors. Their aims were to estimate the maximum tolerated dose and to determine dose-limiting toxicities. Femur and tibia radiographs were required at baseline and every 2 months while on therapy with bevacizumab. No one with open epiphyses had physeal abnormalities noted. The study concluded that doses of bevacizumab up to 15 mg/kg intravenously every 2 weeks are well tolerated in children.[17]

We found no observable systemic adverse reactions directly attributable to intravitreal bevacizumab in early or late follow-up, such as hypertension, cardiopulmonary distress, or renal insufficiency. One child (4 months after bevacizumab treatment) in the present series expired due to multiorgan system failure. Another (9 months after

Table 1. Clinical features of previously reported uses of intravitreal bevacizumab in patients with retinopathy of prematurity

Study and follow-up	Eyes	Zone	Stage	Dose	Prior ROP Rx	Therapy	Adjunctive surgery/laser	Regressed or stable	Progressed
Present study (1-17 mo)	13			0.75 mg	5		11	9	4
		I	3-AP-ROP (2)		2	Rescue (2)	Yes (2)	1	TRD 4-A (1)
		II	3 (2)		2	Rescue (2)	No (2)	2	
			2-AP-ROP (2)		0	Rescue (2)	Yes (2)	2	
			3-AP-ROP (6)		0	Rescue (6)	Yes (6)	4	TRD 4-A (1), TRD 4-B (1)
			4-A (1)		1	Rescue (1)	Yes (1)		TRD-RRD 4-B (1)
Kusaka et al[14] (3-15 mo)	23			0.5 mg	23		20	20	3
		I	3 (1)		1	Rescue (1)	Yes (1)	1	TRD 4-A (1)
			4-A (11)		11	Rescue (11)	Yes (10)	10	
			4-B (2)		2	Rescue (2)	Yes (2)	2	
		II	3 (2)		2	Rescue (2)	Yes (1)	1	TRD 4-A (1)
			4-A (7)		7	Rescue (7)	Yes (6)	6	TRD 4-B (1)
Honda et al[15] (6 mo)	1			0.4 mg				0	1
		NR	4-A		1	Rescue (1)	No (1)		Funnel TRD
Mintz-Hittner and Kuffel[13] (3-20 mo)	22			0.625 mg	0		0	22	0
		I	AP-ROP (2)		0	Mono (2)	No (2)		
			sev 3 (4)		0	Mono (4)	No (4)		
			mod 3 (2)		0	Mono (2)	No (2)		
		II	mod 3 (+ 14)		0	Mono (14)	No (14)		
Lalwani et al[16] (1-2.5 mo)	5			0.63-1.25 mg	3		5	4	1
		I (+)	NR	0.63 mg (1)	1	Rescue (1)	Yes (1)	1	
		NR	Threshold	0.63 mg (2)	2	Rescue (2)	Yes (2)	1	1
		NR	Threshold	1.25 mg (2)	0	Rescue (2)	Yes (2)	2	
Quiroz-Mercado et al[12] (6 mo)	18			1.25 mg	4		2	16	2
		NR	Threshold poor view (5)		0	Mono (5)	No (5)	5	
		NR	3 (+) pre/ threshold (9)		0	Mono (9)	No (9)	9	
		NR	4-A (3)		3	Rescue (3)	Yes (1)	2	TRD 4-A (1)
		NR	4-B (1)		1	Rescue (1)	Yes (1)	0	TRD 4-B (1)
Chung et al[11] (3 mo)	2			0.75 mg			0	1	0
		I	3-AP-ROP (2)		0	Combo (2)	No (2)	2	
Travassos et al[10] (10 mo)	3			0.75 mg			0	3	0
		NR	AP-ROP (3)		0	Mono (2)	No (2)		
					1	Rescue (1)	No (1)		
Shah et al[9] (10 mo)	2			0.75 mg			0	1	0
		NR	AP-ROP (1)		1	Rescue for NVI (1)	No (1)	1	
Total	89						38	74	11

AP-ROP, aggressive posterior retinopathy of prematurity; *NVI*, neovascularization of the iris; *TRD*, tractional retinal detachment; *TRD-RRD*, tractional rhegmatogenous retinal detachment; *Rescue*, intravitreal bevacizumab used when other treatments have failed or are expected to fail; *Mono*, intravitreal bevacizumab used as only treatment; *Combo*, intravitreal bevacizumab used at the same time as a planned laser or vitrectomy; *Sev*, severe; *Mod*, moderate; *NR*, not reported, (+), plus disease.

bevacizumab treatment and surgery) had cardiac arrest secondary to bronchopulmonary dysplasia. It is unknown whether this is directly related to bevacizumab injection or to the general high systemic morbidities among patients with AP-ROP. A review of our cases with AP-ROP treated with laser alone as well as babies without AP-ROP treated with laser only revealed a similar mortality rate. We are currently examining more closely these cohorts to identify any systemic adverse events that may be associated with bevacizumab injection. The minimum safe concentration of intravitreal bevacizumab has not been determined. In previous reports of bevacizumab use in ROP, doses ranged

from 0.4 mg to 1.25 mg, the widely accepted adult dose. The preterm eye is 50% smaller and the vitreous content more viscous compared with the more liquefied vitreous of adults. This could result in greater exposure of bevacizumab in the preterm infant. In a rabbit pharmacokinetic study, Bakri and colleagues[18] found the maximum serum concentration was 0.8% of the maximum vitreous concentration and was reached after 8 days. The total exposure of the aqueous to bevacizumab was 8.9% of that of the vitreous. Since the rabbit eye is smaller and the serum compartment of the rabbit is less than the adult human, it may be a comparable model for a preterm infant.

Al-Dhibi and Khan[19] demonstrate the bilateral benefit of bevacizumab in an 8-year-old girl who was treated for cystoid macular edema secondary to intermediate uveitis. Their conclusions were that smaller body mass and increased ocular permeability from uveitis may have led to the contralateral absorption of bevacizumab. Perhaps additionally, it is the increased permeability of the injected eye that led to the increased systemic absorption. Since 6 patients in our series had bilateral injections, we were unable to observe any contralateral effects. The only patient who received unilateral treatment (Patient 5) had already demonstrated regression of ROP in the contralateral eye after the initial laser treatment and a contralateral effect would be difficult to assess. It is possible that eyes with threshold retinopathy may have increased breakdown of the blood-retinal barrier and be more susceptible than others for systemic absorption. A recent editorial by Avery[20] highlights the importance of proper vigilance for possible systemic side effects of using intravitreal bevacizumab. The authors agree that the use of an anti-VEGF agent in a developing neonate requires careful deliberation and monitoring. Intravitreal injection of bevacizumab has a rapid and profound effect on plus disease, iris vascular engorgement, and tunica vasculosa lentis. Infants with pupils too rigid to be fully dilated or with media too opaque for adequate visualization for laser therapy may be pretreated with intravitreal injections of anti-VEGF agents to improve visualization for more definitive laser or surgical treatment. Progression to retinal detachment may still occur following injection, possibly as a result of accelerated fibrovascular involution and contraction, as has been seen in proliferative diabetic retinopathy.[21] Randomized, prospective, clinical trials designed to evaluate the safety of intravitreal bevacizumab in ROP will guide us further on this treatment modality.

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