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A Dosing Study of Bevacizumab for ROP: Late Recurrences and Additional Treatments

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Abstract

Purpose: Intravitreal bevacizumab is increasingly used to treat severe ROP, but it enters the bloodstream, and there is concern that it may alter development of other organs. Previously we reported short-term outcomes of 61 infants enrolled in a dose de-escalation study, and herein report late recurrences and additional treatments.

Design: Masked, multicenter, dose de-escalation study

Participants: 61 premature infants with type 1 ROP

Methods: If type 1 ROP was bilateral at enrollment, then the study eye was randomly selected. In the study eye, bevacizumab intravitreal injections were given at de-escalating doses of 0.25mg, 0.125mg, 0.063mg, or 0.031mg; if needed, fellow eyes received one dose level higher: 0.625 mg, 0.25 mg, 0.125 mg, or 0.063 mg, respectively. After 4 weeks, additional treatment was at investigator discretion.

Main Outcome Measures: Early and late ROP recurrences, additional treatments, and structural outcomes after 6 months

Results: Of 61 study eyes, 25 (41%; 95% CI=29% to 54%) received additional treatment: 3 (5%; 95% CI=1% to 14%) for early failure (within 4 weeks), 11 (18%; 95% CI=9% to 30%) for late

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recurrence of ROP (after 4 weeks), and 11 (18%; 95% CI=9% to 30%) for persistent avascular retina. Re-treatment for early failure or late recurrence occurred in 2 of 11 eyes (18%; 95% CI=2% to 52%) treated with 0.25 mg, 4 of 16 eyes (25%; 95% CI=7% to 52%) treated with 0.125 mg, 8 of 24 eyes (33%; 95% CI=16% to 55%) treated with 0.063 mg, and 0 (0%; 95% CI=0% to 31%) of 10 eyes treated with 0.031 mg. By 6 months corrected age, 55 of 61 study eyes had regression of ROP with normal posterior poles, one study eye had developed a Stage 5 retinal detachment, and 6 infants had died from preexisting medical conditions.

Conclusion: Retinal structural outcomes are very good after low-dose bevacizumab treatment for ROP, although many eyes received additional treatment.

Introduction

Retinopathy of prematurity (ROP) is a leading cause of childhood blindness.¹ Treatments for severe ROP include retinal ablative laser therapy, cryotherapy, and intravitreal injections of drugs that block the effects of endogenous vascular endothelial growth factor (VEGF).^{2,3} Successful treatment of ROP has been reported with several anti-VEGF drugs.⁴⁻⁹ Of these, bevacizumab is the most commonly used worldwide because it is widely available and inexpensive. In the BEAT-ROP study, the dose of bevacizumab used was 0.625 mg, which is one-half the adult dosage used to treat the neovascular form of age-related macular degeneration in adults. However, it has been estimated that the standard 0.625 mg dose of intravitreal bevacizumab for ROP may be 10,000 times the dose necessary to neutralize intraocular VEGF.¹⁰ In addition, there is mounting evidence that lower doses may be equally effective for ROP.^{11,12} It may be desirable to reduce the dosage as much as possible while maintaining efficacy, because bevacizumab enters the bloodstream after intravitreal injection and there is speculation that it may alter development of other organs.¹³⁻¹⁵

We enrolled 61 infants into a masked, multicenter, dose de-escalation study in which one eye (selected by randomization when bilateral) received 0.25 mg, 0.125 mg, 0.063 mg, or 0.031 mg of intravitreal bevacizumab. We found that the lowest dosage of 0.031 mg (5% of the BEAT-ROP dosage) was effective after 4 weeks in 9 of 9 infants.¹² Although these results were promising, it is possible that very low doses will have a higher recurrence rate, require more re-treatments, and/or have worse outcomes. Herein we report ROP recurrences, additional treatments and retinal structural outcomes for infants receiving very low doses of bevacizumab.

Methods

Institutional review board approval was obtained from all participating institutions and parents provided written informed consent. Details of drug dilution and injection, and 4-week outcomes, were reported previously.¹² A 300- μ L syringe was used to allow delivery of 10- μ L as accurately as possible. One eye (subsequently referred to as the “study eye”) in each of 61 infants (mean birthweight = 709 g; mean gestational age = 24.9 weeks) received the study-specified dose of bevacizumab: 11 received 0.250 mg, 16 received 0.125 mg, 24 received 0.0625 mg, and 10 received 0.031 mg. If type 1 ROP was bilateral at enrollment, then the study eye was randomly selected. If type 1 ROP was unilateral at enrollment, then that eye was the study eye. Fifty-seven fellow eyes also had bevacizumab injections,

receiving a dose that was one level higher than the study eye (i.e., the last previous dose found to be effective at each stage of the study of progressively decreasing doses).

“Early failure” was defined as no improvement (for example, persistent plus disease) 3 to 5 days after injection, or recurrence of type 1 ROP or severe neovascularization requiring additional treatment within 4 weeks. Beginning 4 weeks after the initial bevacizumab injection, any additional treatment was at investigator discretion. After 6 months corrected age, medical records were reviewed to collect data on ROP recurrences, additional treatments, timing and indications for treatment, and retinal structural outcomes. “Late recurrence” was defined as recurrence of plus disease or neovascularization that prompted investigators to give additional treatment after 4 weeks. Laser treatment for “persistent avascular retina” was given as prophylaxis by some investigators several weeks or months after bevacizumab, in the absence of recurrent severe ROP. Adverse events, including retinal detachment or vitreous hemorrhage, were monitored and recorded when they occurred. Log-binomial regression was used to evaluate the association between re-treatment for early failure or late recurrence of type 1 ROP and 1) initial study-eye dose received at baseline and 2) category of type 1 ROP at enrollment. The logarithm (base 2) of the initial dose of bevacizumab received at baseline was used to test the association with re-treatment for early failure or late recurrence. Relative risks were calculated for each dose level.

Results

Treatments after Initial Bevacizumab Injections

Twenty-five (41%; 95% confidence interval (CI)=29% to 54%) of 61 study eyes received additional ROP treatment (Table 1); 3 (5%; 95% CI=1% to 14%) were re-treated for early failure (within 4 weeks), 11 (18%; 95% CI=9% to 30%) had late recurrence of ROP, and 11 (18%; 95% CI=9% to 30%) were re-treated for persistent avascular retina. Results for fellow eyes were similar (Table 1). Following the initial injection, 19 study eyes were re-treated once, 5 were re-treated twice, and one received 3 additional treatments. The first or only additional treatment was laser for 18 eyes and repeat intravitreal bevacizumab for 7 eyes (0.625 mg for 4 eyes, 0.500 mg for 2 eyes, and 0.125 mg for one eye). Among the 11 study eyes that received additional treatment for late ROP recurrence, 7 had laser at a mean postmenstrual age (PMA) of 46 weeks, and 4 received an injection of bevacizumab at a mean PMA of 42 weeks. Eleven infants received laser for persistent avascular retina, at a mean PMA of 64 weeks. Characteristics of study eyes and details of their treatment(s) are reported in Table S1 (available at www.aaojournal.org).

Re-treatment for early failure or late recurrence in study eyes was not associated with initial dose ($p=0.64$) or category of type 1 ROP at baseline ($p=0.61$). Re-treatment for early failure or late recurrence occurred in 2 (18%) of 11 eyes treated with 0.25 mg at baseline, 4 (25%) of 16 eyes treated with 0.125 mg, 8 (33%) of 24 eyes treated with 0.063 mg, and 0 (0%) of 10 eyes treated with 0.031 mg (Tables 1, 2). Re-treatment for early failure or late recurrence occurred in 4 (21%) of 19 eyes with ROP in zone I with plus disease, 3 (38%) of 8 eyes with stage 3 in zone I without plus disease, and 7 (21%) of 34 eyes with stage 2 or 3 in zone II with plus disease (Tables 2, 3). The relative risks for retreatment at each decreasing dose and

for each category of type 1 ROP had very wide 95% CIs (Table 2), which limited our ability to draw definitive conclusions.

Of 61 infants, 55 (90%) were enrolled with bilateral type 1 ROP, and 6 (10%) had type 1 ROP in only one eye at enrollment. All 55 infants with bilateral type 1 ROP received bevacizumab treatment in the fellow eye at the previously effective higher dose. Four of 6 enrolled with unilateral ROP eventually received treatment in the fellow eye; 2 received a bevacizumab injection at 1 week (1 eye) or 3 weeks (1 eye) after injection of the study eye, while 2 received laser at 11 weeks (for type 1 ROP) and 31 weeks (for persistent avascular retina) after study eye injection. Two received no treatment in the fellow eye.

Among infants receiving bilateral injections, 25 (44%; 95% CI=31% to 58%) of 57 fellow eyes were eventually re-treated (Table 1): 3 (5%; 95% CI=1% to 15%) were re-treated for early failure, 11 (19%; 95% CI=10% to 32%) experienced late recurrence of ROP, and 11 (19%; 95% CI=10% to 32%) were re-treated for persistent avascular retina without recurrent severe ROP. Following initial injection, 21 were re-treated once, 3 re-treated twice, and one re-treated 3 times. The first or only additional treatment was laser for 18 eyes and bevacizumab for 7 eyes, 0.625 mg for 5 eyes and 0.500 mg for 2 eyes.

Structural Outcomes

Of 112 treated eyes of 57 infants surviving to at least 6 months, 108 had regression of ROP with no retinal detachment and normal macular structure by indirect ophthalmoscopy, one eye developed stage 4A, one eye had stage 4B, and 2 eyes (2 different infants) had stage 5. All 4 eyes that developed retinal detachments had zone I ROP when initially treated. One infant had a stage 4A retinal detachment in the study eye (initially treated with 0.063 mg bevacizumab) that resolved after vitrectomy, and a stage 4B retinal detachment in the fellow eye (initially treated with 0.125 mg bevacizumab) that persisted after vitrectomy. One infant developed a stage 5 retinal detachment in the study eye (initially treated with 0.25 mg bevacizumab) and had regression of ROP in the fellow eye (initially treated with 0.625 mg bevacizumab). Another infant had asymmetric ROP and developed a stage 5 retinal detachment in the fellow eye only. The study eye received 0.25 mg bevacizumab at enrollment and had regression of ROP. The fellow eye did not develop type 1 ROP until several weeks later. Despite treatment with laser, vitreous hemorrhage and stage 5 developed and the infant's mother declined additional treatment.

Adverse Events

Six infants died from preexisting medical conditions associated with preterm delivery; 2 with chronic lung disease, and one each with acute respiratory failure, liver failure, necrotizing enterocolitis, and cardiac arrest (the cardiac arrest occurred 57 weeks after bevacizumab injection). One infant had a mild vitreous hemorrhage in both eyes noted after injection that resolved by 7 weeks. One infant was noted to have a posterior, superior-nasal cataract that was first noted 3 weeks after an injection that was given inferior-temporal. It was visually significant and required removal at 13 weeks post-injection. Another infant was noted on intravenous fluorescein angiography done 8 weeks after bevacizumab injection to

have a large and dilated retinal vein that appeared occluded, and a smaller area of delayed filling in the other eye, without neovascularization in either eye.

Discussion

In this dose de-escalation study, we found that 11 of 61 study eyes (18%) received additional treatment for recurrent ROP after the 4-week primary outcome. We did not observe a relationship between lower dose levels and need for additional treatment; however, the sample size is too small for a definitive conclusion. Retinal structural outcomes were very good, with only one of 57 study eyes of surviving infants (2%) developing a retinal detachment involving the macula.

There are several potential advantages of treating severe ROP with anti-VEGF drugs. They are particularly useful in zone I disease, which has a higher rate of unfavorable outcome after retinal ablation than zone II,^{2,16} and there is concern for macular damage from the very posterior laser needed in some eyes. In these cases, initial treatment with an anti-VEGF drug typically allows retinal vascular growth toward the periphery. It is hypothesized, but unproven, that this vascular growth may preserve better peripheral vision.³ Other potential advantages of anti-VEGF treatment are less myopia¹⁷ and ease of administration relative to laser. Although the initial treatment may be less stressful to infants, many more outpatient follow-up exams are typically needed after anti-VEGF compared with laser.¹⁸

Despite its advantages, there are concerns about using anti-VEGF drugs in extremely low birthweight infants. Previous studies have shown a reduction in circulating VEGF after intravitreal injection,^{13–15} and VEGF is required for normal development of many tissues in premature infants,¹⁹ including brain, lungs, bones, kidneys and retina. One study found that motor development was delayed in infants receiving bevacizumab versus laser, although the authors acknowledge that their observational study results may be confounded because sicker infants and those with more severe ROP were more likely to receive bevacizumab.²⁰ Because of the risk of late recurrence,^{21,22} careful monitoring up to at least 65–70 weeks PMA (or about 6 months corrected age) has been recommended unless full vascularization occurs or laser treatment is done. Some physicians choose to treat with laser several weeks or months after anti-VEGF injection to prevent late recurrence, particularly if there appears to be cessation of vascular growth and/or the infant is at risk for poor outpatient follow-up, although it is unknown whether this improves outcomes. Our study investigators reported that 11 of 61 study eyes (18%) received late laser treatment (at a mean PMA of 64 weeks) for persistent avascular retina. Another concern with anti-VEGF treatment is a possible adverse effect on retinal blood vessel development, including macular development. One study found retinal vascular abnormalities in bevacizumab-treated eyes that were not typically observed in laser-treated eyes.²³ In the rat model, antibody-based anti-VEGF treatment disrupts normal vascularization of inner and deeper retinal capillary beds and leads to recurrent intravitreal neovascularization, potentially by activation of hypoxia-related factors and/or activated pathways.^{24,25}

We chose to test lower doses of bevacizumab because it is the most commonly used anti-VEGF drug for ROP worldwide. It is possible that ranibizumab has fewer systemic effects

than bevacizumab, because it is an antibody fragment with a shorter half-life in the bloodstream. One study found that, after intravitreal injection of ranibizumab, plasma VEGF levels were reduced the next day but returned to normal one week later.²⁶ In another study, plasma VEGF levels were not altered in 9 infants receiving 0.12 mg or in 7 infants receiving 0.20 mg of ranibizumab.²⁷ However, it is possible that the rate of recurrence after initial injection may be higher in eyes treated with ranibizumab because of its more rapid clearance from the eye; one large study found that 127 of 283 eyes (45%) had reactivation of ROP after intravitreal ranibizumab.²⁸

A limitation of this study is that our sample size was too small to be able to make conclusions regarding relationships between variables such as dose and recurrence rate. For example, there were no recurrences observed in 9 eyes in the lowest dosage group, but this finding may have been due to chance. Also, the treatment response in study eyes, and the incidence of recurrence, were likely influenced by crossover effect from the higher dose in the fellow eye. We designed the study in this way to avoid giving a dose that was potentially too low in both eyes, although we tried to minimize this crossover effect by reducing the fellow eye dose as the study eye dose decreased.

In conclusion, we found that retinal structural outcomes are very good after bevacizumab doses as low as 0.031 mg, although some eyes received additional treatment. Future studies are underway to test lower doses of bevacizumab, which may possibly enhance normal retinal vascularization while posing less systemic risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Re-treatment* by Initial Dose of Intravitreal Bevacizumab

	0.625 mg	0.250 mg	0.125 mg	0.063 mg	0.031 mg	All Eyes
Study Eyes						
Enrolled & Treated	N/A	11	16	24	10	61
Re-treated for early failure (4 weeks)	N/A	0 (0%)	0 (0%)	3 (13%)	0 (0%)	3 (5%)
Re-treated for late recurrence of ROP	N/A	2 (18%)	4 (25%)	5 (21%)	0 (0%)	11 (18%)
Re-treated for persistent avascular retina	N/A	3 (27%)	2 (13%)	3 (13%)	3 (30%)	11 (18%)
No additional treatment	N/A	6 (55%)	10 (63%)	13 (54%)	7 (70%)	36 (59%)
Fellow Eyes						
Treated at enrollment	10	16	23	8	N/A	57
Re-treated for early failure (4 weeks)	0 (0%)	0 (0%)	3 (13%)	0 (0%)	N/A	3 (5%)
Re-treated for late recurrence of ROP	2 (20%)	4 (25%)	5 (22%)	0 (0%)	N/A	11 (19%)
Re-treated for persistent avascular retina	3 (30%)	2 (13%)	3 (13%)	3 (38%)	N/A	11 (19%)
No additional treatment	5 (50%)	10 (63%)	12 (52%)	5 (63%)	N/A	32 (56%)

* Re-treatment included photoablative therapy or intravitreal bevacizumab at investigator discretion.

Table 2.

Re-treatment for Early Failure or Late Recurrence of Type 1 ROP

	N	Number (%) Retreated for Early Failure or Late Recurrence (95% CI)	Relative Risk (95% CI)
Dose of Bevacizumab			
0.250 mg	11	2 (18%) 2% to 52%	ref ^a
0.125 mg	16	4 (25%) 7% to 52%	1.4 (0.3 to 6.2)
0.063 mg	24	8 (33%) 16% to 55%	1.8 (0.5 to 7.3)
0.031 mg	10	0 (0%) 0% to 31%	-
Category of Type 1 ROP at Enrollment			
Zone I, any Stage with Plus Disease	19	4 (21%) 6% to 46%	ref ^a
Zone I, Stage 3 without Plus Disease	8	3 (38%) 9% to 76%	1.8 (0.5 to 6.2)
Zone II, Stage 2 or 3 with Plus Disease	34	7 (21%) 9% to 38%	1.0 (0.3 to 2.9)

^aThis is the reference category. All other groups were compared to this category.

CI = confidence interval

Table 3.

Re-treatment* of Study Eyes by Category of Type 1 ROP at Enrollment

	Zone I, any Stage with Plus Disease	Zone I, Stage 3 without Plus Disease	Zone II, Stage 2 or 3 with Plus Disease	All Eyes
Enrolled & Treated	19	8	34	61
Re-treated for early failure	0 (0%)	1 (13%)	2 (6%)	3 (5%)
Re-treated for late recurrence of ROP	4 (21%)	2 (25%)	5 (15%)	11 (18%)
Re-treated for persistent avascular retina	3 (16%)	1 (13%)	7 (21%)	11 (18%)
No additional treatment	12 (63%)	4 (50%)	20 (59%)	36 (59%)

* Re-treatment included photoablative therapy or intravitreal bevacizumab at investigator discretion.