Short-term retinal detachment risk after treatment of type 1 retinopathy of prematurity with laser photocoagulation versus intravitreal bevacizumab

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PURPOSE To perform a stratified comparison of the short-term risk of retinal detachment after treatment of type 1 retinopathy of prematurity treated with panretinal photocoagulation laser versus intravitreal bevacizumab.

METHODS The medical records of consecutive infants treated for type 1 ROP between 2010 and 2018 were retrospectively reviewed. An a priori decision was made to divide infants into two groups, those treated before postmenstrual age (PMA) of 36 0/7 weeks and those treated at or after PMA of 36 0/7 weeks. The primary outcome was presence of any retinal detachment (stage 4A, 4B, or 5) during the 8 weeks following treatment.

RESULTS A total of 222 eyes of 115 infants were included. In eyes treated before 36 0/7 weeks' PMA, retinal detachment occurred in 0 of 34 eyes treated initially with bevacizumab compared with 9 of 56 (16%) treated with laser ($P = 0.0112$); in eyes treated at or after 36 0/7 weeks, in 0 of 2 eyes treated with bevacizumab and 1 of 130 eyes (0.8%) treated with laser.

CONCLUSIONS The short-term risk of retinal detachment among infants requiring treatment for type 1 ROP prior to 36 0/7 weeks' PMA was lower in eyes treated with intravitreal bevacizumab than in eyes treated with laser, presumably due to the faster effect of bevacizumab in eyes that have more aggressive ROP. (J AAPOS 2019;23:260.e1-4)

Retinopathy of prematurity (ROP) is a potentially blinding condition affecting premature infants. Because of the immature retinal vasculature, a fibroproliferative retinopathy may develop and cause tractional retinal detachments, an important cause of severe visual impairment in infants with ROP.[1-3] The Early Treatment of Retinopathy of Prematurity study (ET-ROP) established panretinal photocoagulation laser (laser) as an effective treatment for high-risk prethreshold (type 1) ROP (any stage, zone I, plus; stage 3, zone I, without plus; or stage 2 or 3, zone II, plus).[1,4] Despite the efficacy of laser, 30 of 331 of eyes (9.1%) with type 1 ROP treated with laser in ET-ROP had a poor structural outcome (macular fold, retinal detachment involving the macula, or retrolental tissue or mass).[4] Of the 963 laser-treated eyes in the Postnatal Growth and Retinopathy of Prematurity study (G-ROP1), 58 (6%) developed a retinal detachment, and an additional 11 (1.1%) developed a macular fold.[5]

The Bevacizumab Eliminated the Angiogenic Threat of Retinopathy of Prematurity study (BEAT-ROP) highlighted the potential efficacy of intravitreal injection of bevacizumab for treating ROP, which recurred in 6 of 140 eyes (4%) treated with 0.625 mg of intravitreal bevacizumab and 32 of 146 eyes (22%) treated with laser[6]; however, there are limited additional data comparing structural outcomes in patients treated with intravitreal bevacizumab versus laser for ROP.[7,8] Generally, intravitreal bevacizumab works faster than laser, because bevacizumab directly binds to VEGF receptors, whereas laser works by destroying the source of VEGF production; therefore, there is a theoretical benefit to using bevacizumab in certain clinical situations, for example, where ROP is progressing rapidly. The purpose of the present study was to evaluate this potential benefit by comparing the short-term risk of retinal detachment in eyes treated with laser versus eyes treated with intravitreal bevacizumab.

Subjects and Methods

This study was approved by the Albany Medical College Institutional Review Board and complied with the US Health Insurance Portability and Accountability Act of 1996. The medical records of consecutive infants treated for ROP at the Duker Children's Hospital at Albany Medical Center between September 1, 2010,

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and September 10, 2018, were retrospectively reviewed. To be eligible for inclusion, patients had to have an initial treatment for ROP with either laser or intravitreal bevacizumab and had to have follow-up diagnostic dilated fundus examinations (DFE) using indirect ophthalmoscopy for at least 8 weeks following the initial procedure. Infants were screened and treated in accordance with the recommendations of the American Academy of Pediatrics policy statement on ROP.[1] We intended to exclude patients who received both laser and bevacizumab simultaneously or within 7 days of each other; however, no such occurrences were noted. Patients who received retreatment after 7 days but within 8 weeks of initial ROP treatment were included in the primary outcome analysis (retinal detachment at 8 weeks) and the retreatments were noted. Retreatments between 8 and 20 weeks of initial treatment were noted in a post hoc manner. Infants who died within 8 weeks of ROP treatment were excluded from primary analysis, because they had not had their 8-week follow-up DFE. Deaths occurring after 8 weeks were not noted in this study. Eyes that were treated but did not meet the strict criteria for type 1 ROP were excluded.

Initial treatments were performed with either laser or intravitreal bevacizumab. One ophthalmologist (GPB) performed both diagnostic DFE prior to treatments and all treatments. Prior to 2013, only laser was used. In those patients, panretinal photocoagulation laser was performed in a near confluent manner using indirect ophthalmoscopy and a 28 D lens. From 2013 onward, the decision of treatment modality between laser or bevacizumab was at the discretion of the ophthalmologist. When used, the dose of intravitreal bevacizumab varied from 0.375 to 0.625 mg per eye. Generally, bevacizumab was favored for "aggressive" ROP (type 1 in zone I), in infants deemed medically unstable by the attending neonatologist, and/or in infants in whom the ophthalmologist had a poor view of the posterior segment. All intravitreal bevacizumab injections were performed at the bedside in the neonatal intensive care unit using intravenous sedation. All infants receiving laser were intubated and received general anesthesia in the operating room. DFE using indirect ophthalmoscopy was performed on all patients 1 week after each procedure. Infants receiving bevacizumab continued to receive weekly or more frequent DFE for at least 1 month after treatment and every 1-2 weeks thereafter. Infants receiving panretinal photocoagulation received weekly or more frequent DFE until regression was clearly noted, after which DFE were spaced out at the discretion of the ophthalmologist in accordance with American Academy of Pediatrics guidelines.[1]

The primary outcome measure of this study was the presence or absence of retinal detachment (stage 4A, 4B, or 5) in each treated eye within the first 8 weeks following treatment. We decided a priori to divide the patients into two subgroups based on postmenstrual age (PMA) at initial treatment: <36 0/7 weeks' and ≥36 0/7 weeks' PMA. A two-tailed Fisher exact test was used to compare the risk of retinal detachment in eyes treated with bevacizumab versus laser. Comparisons between groups and subgroups for baseline characteristics (eg, BW, GA, PMA at treatment) and secondary outcomes (eg, short-term mortality) were made using the Fisher exact test for proportions and two-sample, two-tailed, unequal variance *t* tests for continuous measures.

Table 1. Outcomes of eyes treated for type 1 retinopathy of prematurity

PMA	Total	Laser	IVB	*P* value
<36 weeks				
Patients, no.	45	28	17	
Eyes, no.	90	56	34	
BW	694.8	658.6	754.6	0.152
GA	24.8	24.65	25.04	0.436
PMA	34.75	34.81	34.65	0.502
RD, eyes (%)	9 (10)	9 (16.1)	0	0.0122
≥36 weeks				
Patients, no.	70	69	1	
Eyes, no.	132	130	2	
BW	737.2	730.2	1220	
GA	25.6	25.57	27.43	
PMA	38.21	38.23	37.14	
RD, eyes (%)	1 (0.7)	1 (0.8)	0	
Total				
Patients, no.	115	97	18	
Eyes, no.	222	186	36	
BW	720.62	709.52	780.44	0.28
GA	25.28	25.3	25.18	0.78
PMA	36.86	37.24	34.76	<0.001
RD, eyes (%)	10 (4.5)	10 (5.3)	0	0.373

BW, birth weight; *GA*, gestational age; *IVB*, intravitreal bevacizumab; *PMA*, postmenstrual age; *RD*, retinal detachment.

Results

Of 139 consecutive infants treated for type 1 ROP during the study period, 2 were excluded for insufficient data, and 7 died within 8 weeks of ROP treatment and were excluded from analysis of the primary outcome (retinal detachment at 8 weeks). Of the remaining 130 infants (259 treated eyes), 15 patients (30 eyes) were excluded because neither eye was type 1, and 7 eyes were excluded because only the fellow eye was type 1. Analysis of the primary outcome included 222 eyes of 115 patients: 186 eyes of 97 patients were treated with laser; 36 eyes of 18 infants were treated with intravitreal bevacizumab (Table 1). Forty-five infants (90 eyes) were treated before 36 0/7 weeks' PMA, of whom 28 (56 eyes) were treated with laser and 17 (34 eyes) were treated with bevacizumab. Seventy infants (132 eyes) were treated at ≥36 0/7 weeks' PMA, of whom 69 (130 eyes) were treated with laser and 1 (2 eyes) was treated with bevacizumab.

Of the eyes treated at <36 0/7 weeks' PMA, 9 of 56 laser-treated eyes (16%) developed a retinal detachment in the 8 weeks following treatment, whereas none of 34 eyes treated with bevacizumab developed a retinal detachment ($P = 0.012$). See Figure 1. There was no significant difference between infants treated with laser and infants treated with bevacizumab in mean BW (658.6 vs 754.6 g, resp.; $P = 0.152$), GA (24.65 vs 25.04 weeks; $P = 0.436$), or PMA at treatment (34.81 vs 34.65 weeks; $P = 0.502$).

Of the 130 eyes with type 1 ROP treated with at ≥36 0/7 weeks' PMA, only 1 eye (0.8%) developed a retinal detachment, whereas none of the 2 eyes treated with bevacizumab in this cohort developed a retinal detachment. Statistical comparisons of BW (730.2 vs 1220 g), GA

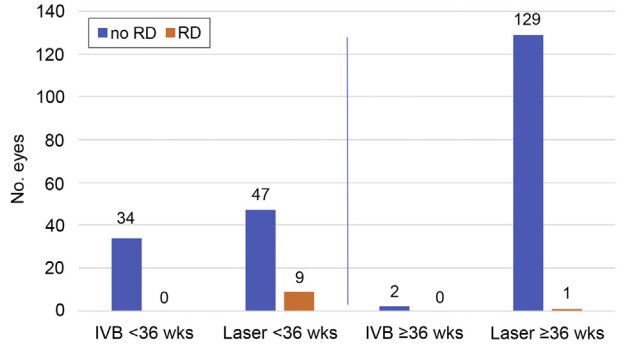

FIG 1. Incidence of retinal detachment (*RD*): eyes treated with bevacizumab (*IVB*) or panretinal photocoagulation (*Laser*) before 36 weeks' postmenstrual age versus at or after 36 weeks' postmenstrual age.

(25.57 vs 27.43 weeks), and PMA at treatment (38.23 vs 37.14 weeks) were not possible because of the small number of infants treated with bevacizumab. Eyes treated with laser at ≥36 0/7 weeks' PMA were less likely to develop a retinal detachment than those treated at <36 0/7 weeks (1 of 130 eyes compared to 9 of 56 eyes [$P = 0.0001$]).

Characteristics of the eyes that developed retinal detachment following laser are provided in Table 2. Ten eyes developed retinal detachment, 7 within 2 weeks of initial treatment; 8 developed stage 4B or 5. Death within 8 weeks of treatment occurred in 7 of 137 infants (5.1%). There was no significant difference in mortality within 8 weeks of treatment between infants treated with laser and infants with bevacizumab (6/118 [5.1%] vs 1/19 [5.3%]; $P = 1.00$). All 7 infants who died before their 8-week fundus examination showed signs of ROP regression after treatment, and no infant developed a retinal detachment before death. Retreatments within 8 weeks following initial treatment occurred in 16 of 186 eyes (9%) treated with laser and in 6 of 36 eyes (17%) treated with bevacizumab ($P = 0.14$ [Fisher exact test]). All retreatments occurring within 8 weeks of the initial treatment were panretinal photocoagulation. Of the 37 eyes excluded for not meeting the criteria for type 1, all had DFE at or after 8 weeks and none developed a retinal detachment.

A post hoc analysis was performed to examine retreatments and retinal detachments in patients where data was available up to 20 weeks after initial ROP treatment. By 20 weeks after treatment, 22 of 36 eyes (61%) initially treated with bevacizumab were retreated, 4 eyes with a second intravitreal bevacizumab injection and 20 eyes with laser, whereas 18 of 186 eyes (10%) initially treated with laser were retreated with laser. No additional retinal detachments were noted in any eyes by extending data collection to 20 weeks.

Discussion

In our study cohort, eyes requiring treatment for type 1 ROP before 36 0/7 weeks' PMA had a significantly lower short-term rate of retinal detachment if initially treated with intravitreal bevacizumab than with laser. Eyes with type 1 ROP in patients treated with laser at or after 36 0/7 weeks' PMA had a lower rate of retinal detachment (0.8%) than eyes treated with laser before 36 0/7 weeks' PMA. At Albany Medical College, the current preference is typically to offer patients with type 1 ROP under 36 0/7 weeks' PMA treatment with bevacizumab and those at or after 36 0/7 weeks' PMA treatment with laser. Using this treatment algorithm, we observed retinal detachment in 1 of 164 treated eyes (0.6%), which compares favorably to retinal detachments observed in eyes treated with only laser in both our study (10 of 186 eyes [5.3%]) and G-ROP-1, which noted short- and long-term retinal detachments in 6% of eyes treated with laser. Also, by limiting bevacizumab to patients with <36 0/7 weeks' PMA, most patients received laser and were spared from the possible systemic risks of bevacizumab.

With regard to ROP, anti-VEGF agents work by directly binding to and inactivating VEGF, whereas laser retinal photocoagulation works by destroying hypoxic retina, the source of the VEGF. Therefore, a clinical response is seen more rapidly for bevacizumab than for laser. Both subjective and computerized analysis have determined that infants treated with bevacizumab for ROP show more rapid regression of plus disease than do those treated with laser.[7,9] We hypothesized that the faster treatment effect of intravitreal bevacizumab may offer benefit over laser, particularly for infants with more aggressive ROP.

We chose PMA at time of treatment for ROP as a marker of disease aggression, because it was objectively measured and easily reproducible for future studies to validate or refute our findings. While International Classification of Retinopathy of Prematurity (I-CROP) classifications offer more refined measures of disease severity, there is subjectivity in each of these classifications.[10] Interexpert variability has been demonstrated in the evaluation of stage (40%), plus (18%), and zone (8%).[11] Expert agreement is higher, however, on the simple presence or absence of type 1 ROP.[11]

Identifying subgroups that may benefit from bevacizumab is particularly important amid safety concerns about bevacizumab in premature infants.[12,13] Plasma concentrations of VEGF in infants have been demonstrated to diminish for 7 weeks after bevacizumab injection.[14] Morin and colleagues[15] reported that among 125 nonrandomized infants treated with bevacizumab or laser for ROP, the two groups had similar cognitive and language Bayley scores, but the former group had lower motor scores. The use of bevacizumab for ROP also has raised questions about the long-term effects of intravitreal bevacizumab on the retinal vasculature, the risk of early failure, and late recurrence of ROP, including retinal detachment.[1,16-18] These are important concerns that must be weighed against the benefits of bevacizumab.

There are a number of limitations to our study. There was a relatively modest number of retinal detachments among the treated infants. However, there was still a

Table 2. Characteristics of 10 eyes of 6 infants that developed retinal detachment following treatment with laser retinal photocoagulation

Patient	Eye	PMA at treatment, weeks	ROP diagnosis at treatment	Highest stage RD	Treatment until RD first noticed, weeks
1	R	34.57	Stage 3, zone I, pre-plus	4B	1
1	L		Stage 3, zone I, pre-plus	4B	1
2	R	33.29	Stage 3, zone II, plus	4B	6
2	L		Stage 3, zone II, plus	5	6
3	R	34.86	Stage 3, zone I, plus	5	2
3	L		Stage 3, zone I, plus	5	2
4	R	43.57	Stage 3, zone II, plus	4A	2
5	L	35.29	Stage 3, zone II, plus	4A	5
6	R	35.57	Stage 2, zone I, plus	4B	2
6	L		Stage 2, zone I, plus	5	2

PMA, postmenstrual age; *RD*, retinal detachment.

statistically significant benefit in the subgroup discussed. We chose a short-term structural outcome measure, which has two drawbacks. Retinal detachments as late as 3 years have been reported with bevacizumab; thus our study may miss late retinal detachments.[1,17,18] Our data do not address the indications for retreatment after bevacizumab. Also, it would be ideal to measure visual acuity explicitly. Six-year follow-up data from ET-ROP demonstrated visual acuity of ≤20/200 in 64 of 70 eyes (91.4%) with retinal detachment after treatment with laser for ROP; therefore, we felt that retinal detachment would be a reasonable predictor of future poor vision.[2] This study was conducted at a single center, with one ophthalmologist making diagnosis and treatment decisions. Systematic biases with regard to these decisions as well as with regard to neonatal intensive care unit practices and treatment techniques may affect the generalizability of the results. The assignment of treatment modality was not randomized, and after 2013, bevacizumab was generally reserved for ROP that was more posterior and aggressive. However, assigning more aggressive disease to the bevacizumab group would bias results against a benefit to bevacizumab. Because we still found a benefit, the presence of such bias would not change the study results. The study period was long, and practices (besides use of bevacizumab) may have changed, altering our results in an unrecognized manner.

There are many factors to consider in choosing treatment modality for patients with ROP. Our study demonstrated less retinal detachments in eyes with type 1 ROP treated with intravitreal bevacizumab compared with those treated with laser among patients whose PMA at treatment was <36 0/7 weeks. Further study in a larger patient cohort is needed to confirm these findings.

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