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Retinal Detachment after Treatment of Retinopathy of Prematurity with Laser versus Intravitreal Anti–Vascular Endothelial Growth Factor

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Purpose: To compare rates of short-term retinal detachment (RD) of infants treated for type 1 retinopathy of prematurity (ROP) with intravitreal anti–vascular endothelial growth factor (VEGF) therapy with infants treated with laser therapy. The choice between these 2 treatments remains controversial. Comparative data are limited and describe re-treatment rates rather than retinal structural outcomes predictive of long-term vision. Anti–vascular endothelial growth factor acts faster than laser therapy, which may be beneficial for more aggressive ROP.

Design: Nonrandomized, comparative cohort study.

Participants: The study included 1167 eyes of 640 infants treated for type 1 ROP. Among these, 164 eyes received anti-VEGF therapy and 1003 eyes received laser therapy.

Methods: Pretreatment and posttreatment examinations and treatments were completed by ophthalmologists with expertise in ROP. The study was a secondary analysis of data from the retrospective Postnatal Growth and Retinopathy of Prematurity Study (G-ROP) 1 study (2006–2012) and the prospective G-ROP 2 study (2015–2017).

Main Outcome Measures: Rate of RD (ROP stages 4A, 4B, or 5) within 8 weeks of initial treatment, an end point predictive of poor long-term vision. The results were stratified by postmenstrual age (PMA) at treatment as occurring before versus at or after 36 weeks and 0 days, because earlier disease may be considered more aggressive.

Results: Among 458 eyes treated before PMA 36 weeks and 0 days, the short-term RD rate was higher after laser therapy (29/368 eyes [7.9%]) than after anti-VEGF therapy (0/90 eyes [0%]; $P < 0.001$). Of 709 eyes treated at or after PMA 36 weeks and 0 days, short-term RD risk did not differ between groups (laser [20/635 eyes], 3.1%; anti-VEGF [1/74 eyes], 1.4%; $P = 0.27$).

Conclusions: Anti–vascular endothelial growth factor therapy results in better short-term structural outcomes than laser therapy when type 1 ROP is treated before 36 weeks' PMA. After this age, both treatments have very low rates of short-term RD. The faster action of anti-VEGF agents likely is responsible for these findings. *Ophthalmology 2021;128:1188-1196 © 2020 by the American Academy of Ophthalmology*

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Retinopathy of prematurity (ROP) is a potentially blinding condition. Careful screening is required to identify infants who require treatment to minimize the risk of blindness.[1] The Early Treatment of ROP Study established panretinal photocoagulation laser eye surgery as an effective method of reducing blindness in infants with type 1 prethreshold ROP. Despite the efficacy of laser photocoagulation, 9.1% of 331 eyes with type 1 ROP treated with laser therapy showed a poor structural outcome.[2]

Intravitreal injection of anti–vascular endothelial growth factor (VEGF) agents for treatment of type 1 ROP has been reported and shows promising results.[3] The Bevacizumab Eliminates the Angiogenic Threat of ROP Study demonstrated a higher need for re-treatment in eyes with type 1 ROP in zone 1 or posterior zone 2 treated with laser therapy versus anti-VEGF agents: 26% versus 4%, respectively.[4] Barry et al[5] reported fewer short-term retinal detachments (RDs) in infants treated for type 1 ROP with anti-VEGF compared with laser specifically before postmenstrual age (PMA) 36 weeks and 0 days. Earlier PMA was considered by the authors to be a surrogate measure for more aggressively acting disease that was preferable to zone of disease as a marker of disease severity because zone depends on the subjective judgment of the examiner, whereas PMA typically is a known value. The authors hypothesized that the faster-acting effect of anti-VEGF injection versus laser therapy demonstrated a greater relative benefit in the context of

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earlier PMA because earlier disease generally is more aggressive. However, the study was a single-center study with a limited number of eyes treated with anti-VEGF agents.

We sought to evaluate further the hypothesis that infants treated with anti-VEGF agents for type 1 ROP before PMA 36 weeks 0 days demonstrate fewer short-term RDs than infants treated with laser therapy using data from the Postnatal Growth and ROP (G-ROP) studies, 2 large North American multicenter studies.[6–8]

Methods

We conducted a secondary analysis of data from the G-ROP 1 and 2 studies.[6–8] These studies were approved by the institutional review boards of the Children's Hospital of Philadelphia (the study headquarters) and all participating hospitals (Appendix A, G-ROP group investigators, available at www.aaojournal.org) and adhered to the tenets of the Declaration of Helsinki. The requirement for informed consent was waived because of the retrospective nature of the study. Clinical data were collected at each hospital by trained data abstractors covering a period from 2006 through 2012 retrospectively at 29 hospitals in G-ROP 1 and from 2015 through 2017 prospectively at 41 hospitals in G-ROP 2.[6–8] During the study periods, ophthalmologists with expertise in ROP practicing at each hospital determined the presence and severity of ROP using International Classification of ROP terminology during serial diagnostic examinations and made decisions about treatment methods using their clinical judgment. The results of these diagnostic examinations and treatments, including stage, zone, presence of plus disease, timing and type of ROP treatment, as well as the results of posttreatment ROP examinations were collected. In G-ROP 1, posttreatment outcomes were collected through age 15 months, and in G-ROP 2, posttreatment examination results were collected through PMA 50 weeks. Extensive medical and demographic information also were collected for these studies.

For the current analysis, we included infants treated with laser or anti-VEGF therapy for type 1 ROP in one or both eyes during G-ROP 1 or 2. Exclusion criteria included initial treatment with pars plana vitrectomy, use of the other treatment method (e.g., laser therapy after anti-VEGF therapy or vice versa) within 7 days of the initial treatment, treatment for ROP not meeting type 1 criteria, and insufficient outcome data at 8 weeks, including death within 8 weeks of initial ROP treatment. Both G-ROP 1 and 2 were observational studies, and choice of treatment method and anti-VEGF dosage were at the discretion of the treating ophthalmologist.

The primary outcome for the current analysis was the development of RD (ROP stages 4A, 4B, or 5) within 8 weeks after treatment for type 1 ROP. This outcome was chosen as a representation of short-term treatment failure. The primary outcome was compared between eyes treated with laser therapy and eyes treated with anti-VEGF agents. Treated eyes were stratified a priori by their PMA at treatment, which was categorized as treatment before 36 weeks 0 days' PMA or treatment at or after 36 weeks 0 days' PMA. The choice of time point was based on the aforementioned single-center study conducted at Albany Medical Center, which suggested a difference between groups before 36 weeks 0 days' PMA, but not after.[5] The rationale for this distinction was that ROP reaching criteria for type 1 disease at an earlier PMA generally is more aggressive with faster progression and may show a preferential benefit for a faster-acting treatment method. Of note, we did not use a time-to-event analysis because time to RD over the short period of 8 weeks after treatment would not add meaningful information in the context of whether simple failure to halt the acute progression of ROP occurred. Treated children typically are followed up closely during this period, and progression is likely to be identified in a timely fashion.

Secondary outcomes for the current analysis included a comparison of short-term RD rates between eyes receiving laser therapy versus anti-VEGF agents (1) with stratification by the most posterior zone of ROP at the time of treatment instead of PMA at treatment and (2) with no stratification at all, as well as the short-term rate of re-treatment (re-treatment during the first 8 weeks after the initial treatment).

Cluster bootstrap analysis was used to account for intereye correlation when determining statistical significance, because some infants received treatment of type 1 ROP in both eyes, and the number of RDs in the anti-VEGF treatment group was too low for statistical modeling.[9] The 95% confidence intervals for the RD rates were calculated based on the 2.5% percentile and 97.5% percentile of 2000 bootstrap replications. Comparisons of the RD rates after laser and anti-VEGF therapy were based on normal approximations of 2000 bootstrap replications. A generalized estimating equation was used for comparison of retreatment rates and number of retreatments between laser and anti-VEGF therapy. For these comparisons, adjustment for birth weight (BW) and gestational age could not be made because of the small number of outcome events.

Results

A total of 818 of 14 966 eyes (5.5%) in the G-ROP 1 study and 378 of 7960 eyes (4.7%) in the G-ROP 2 study were treated for type 1 ROP. Among these treated eyes, 7 eyes from the G-ROP 1 study and 22 eyes from the G-ROP 2 study were excluded for the current analysis, including 13 eyes that received a second treatment method within 7 days of the initial treatment, 1 eye that initially was treated with pars plana vitrectomy, and 15 eyes of infants who died within 8 weeks of initial treatment. Therefore, a total of 1167 eyes of 640 infants (811 eyes from the G-ROP 1 study and 356 eyes from the G-ROP 2 study) were included in this study (Fig 1). One hundred sixty-four eyes were treated initially with anti-VEGF agents and 1003 eyes were treated initially with laser therapy. One hundred forty-seven of 164 eyes (89.6%) treated with anti-VEGF agents received bevacizumab, whereas 17 of 164 eyes (10.4%) received ranibizumab. Infants treated with anti-VEGF agents showed lower mean BW (658 g vs. 709 g; $P = 0.01$) and lower mean PMA at treatment (35.8 weeks vs. 36.7 weeks; $P = 0.001$) than infants treated with laser therapy, respectively (Table 1). Among 1167 included eyes, 458 eyes (39.2%) were treated before a PMA of 36 weeks 0 days, and 709 eyes (60.8%) were treated at or after PMA of 36 weeks 0 days. Infants with eyes treated before PMA of 36 weeks 0 days showed a lower mean BW (663 g vs. 726 g; $P < 0.001$) and mean gestational age (24.2 weeks vs. 25.3 weeks; $P < 0.001$) than infants with eyes treated at or after PMA of 36 weeks 0 days, respectively. Within these subgroups based on PMA at treatment, infants treated with anti-VEGF agents before 36 weeks' PMA showed a lower mean BW (621 g vs. 674 g; $P = 0.02$) than infants treated with laser therapy before 36 weeks' PMA. No significant differences were found in gestational age or PMA at treatment between eyes receiving anti-VEGF agents and eyes receiving laser therapy within treatment subgroups before and after PMA of 36 weeks. Of the 8 infants who were excluded because of death within 8 weeks of initial treatment, 4 were treated with only laser therapy, 2 were treated with only anti-VEGF agents, and 2 were treated with both laser and anti-VEGF therapy.

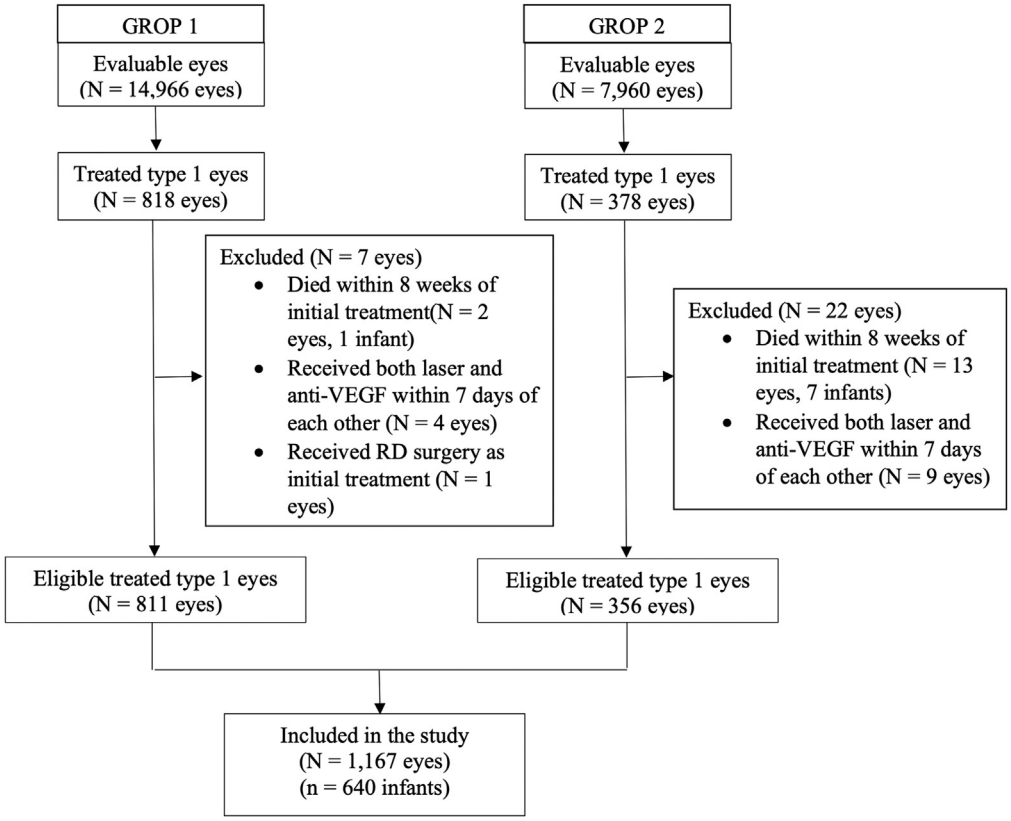

Figure 1. Flowchart of eligible eyes included and excluded in the study. RD = retinal detachment; VEGF = vascular endothelial growth factor.

When treatment for type 1 ROP occurred before PMA of 36 weeks 0 days, eyes treated with anti-VEGF agents were less likely to demonstrate a RD within 8 weeks after treatment (0/90 eyes with RD [0%]) than eyes treated with laser therapy (29/368 eyes with RD [7.9%]; $P < 0.001$; Table 2; Fig 2). In contrast, when treatment occurred at or after PMA of 36 weeks 0 days, no significant difference was found in RDs within 8 weeks after treatment between eyes treated with anti-VEGF agents (1/74 eyes with RD [1.4%]) and eyes treated with laser therapy (20/635 eyes with RD [3.1%]; $P = 0.27$).

When all included eyes were considered without stratification by PMA at treatment, fewer short-term RDs were observed in eyes treated with anti-VEGF agents (1/164 eyes with RD [0.6%]) than in eyes treated with laser therapy (49/1003 eyes with RD [4.9%]; $P < 0.001$). When stratified by zone of ROP, fewer short-term RDs were observed among eyes treated for type 1 ROP in zone 1 with anti-VEGF agents (1/79 eyes with RD [1.3%]) compared with eyes treated with laser therapy (12/155 eyes with RD [7.7%]; $P = 0.02$). Eyes with type 1 ROP in zone 2 also were less likely to demonstrate RD within 8 weeks when treated with anti-VEGF agents (0/85 eyes with RD [0%]) compared with eyes treated with laser therapy (37/843 eyes with RD [4.4%]; $P < 0.001$; Table 2).

Among eyes treated with laser therapy, more RDs were noted in eyes treated before PMA of 36 weeks 0 days (29/368 eyes with RD [7.9%]) than at or after 36 weeks 0 days (20/635 eyes with RD [3.1%]; $P = 0.01$). No difference was found in the rate of short-term RD after laser therapy if ROP at treatment was in zone 1 (12/155 eyes with RD [7.7%]) or zone 2 (37/843 eyes with RD [4.4%]; $P = 0.22$). With regard to re-treatment, 27 of 164 eyes (16.5%) initially treated with anti-VEGF agents and 73 of 1003 eyes (7.3%) initially treated with laser therapy required re-treatment within 8 weeks of initial treatment ($P = 0.03$). Among infants treated before PMA of 36 weeks 0 days, re-treatments occurred in 14 of 90 eyes (15.6%) initially treated with anti-VEGF agents and in 41 of 368 eyes (11.1%) initially treated with laser therapy ($P = 0.45$). Among infants treated at or after PMA of 36 weeks 0 days, re-treatment was performed in 13 of 74 eyes (17.6%) treated with anti-VEGF agents and in 32 of 635 eyes (5.0%) initially treated with laser therapy ($P = 0.053$; Table 3).

Discussion

We found a short-term structural benefit of treating type 1 ROP with intraocular anti-VEGF injection compared with laser therapy when treatment was required before 36 weeks 0 days' PMA. Although fewer short-term RDs seemed to occur overall in eyes treated with anti-VEGF agents than in eyes treated with laser therapy, the overall benefit of anti-VEGF agents over laser therapy was driven by the subgroup of eyes that were treated before 36 weeks' PMA, who presumably had more aggressive ROP and among whom the rates of short-term detachments were 7.9% after laser therapy and 0% after anti-VEGF treatment. In contrast, no significant difference was found in short-term detachments between treatment groups after 36 weeks 0 days' PMA. The concept of using PMA of less than 36 weeks 0 days at time of treatment of type 1 ROP as a relative marker of disease aggression instead of zone of ROP was introduced by Barry

Table 1. Baseline Characteristics of 1167 Eyes of 640 Infants Treated for Type 1 Retinopathy of Prematurity, Stratified by Method of Treatment and Postmenstrual Age at Treatment

Characteristic	Postmenstrual Age <36 Weeks			Postmenstrual Age ≥36 Weeks			Total		
	Laser Therapy (n = 368 Eyes)	*Anti-VEGF Treatment (n = 90 Eyes)*	P *Value*	*Laser Therapy (n = 635 Eyes)*	*Anti-VEGF Treatment (n = 74 Eyes)*	P *Value*	*Laser Therapy (n = 1003 Eyes)*	*Anti-VEGF Treatment (n = 164 Eyes)*	P *Value*
Birth weight (g)			0.02			0.44			0.01
Mean (SD)	673.6 (138.0)	620.9 (131.3)		729.2 (207.4)	702.9 (201.1)		708.8 (186.8)	657.9 (170.8)	
Median	650.0	610.0		682.0	655.0		670.0	628.0	
Range	380.0–1235.0	390.0–875.0		380.0–1692.0	370.0–1273.0		380.0–1692.0	370.0–1273.0	
Gestational age (wks)			0.40			0.99			0.12
Mean (SD)	24.2 (1.0)	24.0 (1.4)		25.3 (1.6)	25.3 (1.7)		24.9 (1.5)	24.6 (1.7)	
Median	24.0	24.0		25.0	25.0		25.0	24.0	
Range	22.0–28.0	22.0–27.0		22.0–31.0	22.0–32.0		22.0–31.0	22.0–32.0	
PMA at first type 1 treatment			0.98			0.25			0.001
Mean (SD)	34.1 (1.0)	34.1 (0.9)		38.2 (2.0)	37.8 (1.7)		36.7 (2.6)	35.8 (2.3)	
Median	34.0	34.0		38.0	37.0		36.0	35.0	
Range	30.0–35.0	32.0–35.0		36.0–46.0	36.0–42.0		30.0–46.0	32.0–42.0	
Gender, no. (%)			0.96			0.09			0.25
Female	158 (42.9)	39 (43.3)		293 (46.1)	24 (32.4)		451 (45.0)	63 (38.4)	
Male	210 (57.1)	51 (56.7)		342 (53.9)	50 (67.6)		552 (55.0)	101 (61.6)	
Ethnicity, no. (%)			0.73			0.07			0.52
Hispanic or Latino	35 (9.5)	9 (10.0)		59 (9.3)	2 (2.7)		94 (9.4)	11 (6.7)	
Not Hispanic or Latino	175 (47.6)	48 (53.3)		397 (62.5)	42 (56.8)		572 (57.0)	90 (54.9)	
Unknown	158 (42.9)	33 (36.7)		179 (28.2)	30 (40.5)		337 (33.6)	63 (38.4)	
Race, no. (%)			0.27			0.21			0.04
White	194 (52.7)	50 (55.6)		348 (54.8)	33 (44.6)		542 (54.0)	83 (50.6)	
Asian/Asian American	10 (2.7)	4 (4.4)		18 (2.8)	2 (2.7)		28 (2.8)	6 (3.7)	
Black	75 (20.4)	9 (10.0)		139 (21.9)	9 (12.2)		214 (21.3)	18 (11.0)	
American Indian/ Alaskan Native	6 (1.6)	0 (0.0)		1 (0.2)	0 (0.0)		7 (0.7)	0 (0.0)	
Native Hawaiian/other Pacific Islander	2 (0.5)	0 (0.0)		4 (0.6)	0 (0.0)		6 (0.6)	0 (0.0)	
Other	46 (12.5)	11 (12.2)		40 (6.3)	6 (8.1)		86 (8.6)	17 (10.4)	
Unknown	35 (9.5)	16 (17.8)		82 (12.9)	21 (28.4)		117 (11.7)	37 (22.6)	
Greater than 1 race checked	0 (0.0)	0 (0.0)		3 (0.5)	3 (4.1)		3 (0.3)	3 (1.8)	
Birth location, no. (%)			0.07			0.80			0.28
Inborn	158 (42.9)	52 (57.8)		373 (58.7)	45 (60.8)		531 (52.9)	97 (59.1)	
Outborn	210 (57.1)	38 (42.2)		262 (41.3)	29 (39.2)		472 (47.1)	67 (40.9)	
Stage, zone, plus at type 1 ROP treatment, no. (%)			0.08			0.14			<0.001
Stage 1, zone I, plus	6 (1.6)	7 (7.8)		0 (0.0)	3 (4.1)		6 (0.6)	10 (6.1)	
Stage 2, zone I, plus	11 (3.0)	5 (5.6)		3 (0.5)	1 (1.4)		14 (1.4)	6 (3.7)	
Stage 2, zone II, plus	35 (9.5)	5 (5.6)		63 (9.9)	5 (6.8)		98 (9.8)	10 (6.1)	
Stage 3, zone I, no plus	15 (4.1)	6 (6.7)		6 (0.9)	2 (2.7)		21 (2.1)	8 (4.9)	
Stage 3, zone I, plus	67 (18.2)	28 (31.1)		13 (2.0)	8 (10.8)		80 (8.0)	36 (22.0)	
Stage 3, zone I, preplus	20 (5.4)	9 (10.0)		14 (2.2)	10 (13.5)		34 (3.4)	19 (11.6)	
Stage 3, zone II, plus	205 (55.7)	30 (33.3)		494 (77.8)	45 (60.8)		699 (69.7)	75 (45.7)	
Type 1 ROP, not specified, not specified	0 (0.0)	0 (0.0)		4 (0.6)	0 (0.0)		4 (0.4)	0 (0.0)	
Type 1 ROP, not specified, plus	0 (0.0)	0 (0.0)		1 (0.2)	0 (0.0)		1 (0.1)	0 (0.0)	
Type 1 ROP, zone II, plus	9 (2.4)	0 (0.0)		35 (5.5)	0 (0.0)		44 (4.4)	0 (0.0)	
Type 1 ROP, zone II, preplus	0 (0.0)	0 (0.0)		2 (0.3)	0 (0.0)		2 (0.2)	0 (0.0)	

(*Continued*)

Table 1. (Continued.)

Characteristic	Postmenstrual Age <36 Weeks			Postmenstrual Age ≥36 Weeks			Total		
	Laser Therapy (n = 368 Eyes)	*Anti-VEGF Treatment (n = 90 Eyes)*	P Value	*Laser Therapy (n = 635 Eyes)*	*Anti-VEGF Treatment (n = 74 Eyes)*	P Value	*Laser Therapy (n = 1003 Eyes)*	*Anti-VEGF Treatment (n = 164 Eyes)*	P Value
Anti-VEGF agent, no. (%)									
Bevacizumab		85 (94.4)			62 (83.8)			147 (89.6)	
Ranibizumab		5 (5.6)			12 (16.2)			17 (10.4)	

PMA = postmenstrual age; SD = standard deviation; ROP = retinopathy of prematurity; VEGF = vascular endothelial growth factor.
P values are from logistic regression with generalized estimating equation to account for the correlation between eyes within the same infant.

et al,[5] who reported short-term structural superiority of treatment with anti-VEGF agents compared with laser therapy in this subgroup in a single-center cohort. Our larger, multicenter study validates those earlier findings.

A faster mechanism of action of anti-VEGF treatment compared with laser therapy may explain our study findings. Tractional RD is the primary source of blindness in eyes with type 1 ROP.[10,11] Laser photocoagulation ablates hypoxic avascular retina, the primary source of excessive VEGF and subsequent fibrovascular proliferation in ROP. By destroying this source of VEGF, laser therapy can be effective in preventing progression to RD from type 1 ROP. Response to laser therapy typically takes 1 week or more to be visible on clinical examination, presumably because VEGF present in the vitreous at the time of laser treatment takes time to clear. In contrast, visible regression of ROP is faster if treated with anti-VEGF agents because intravitreal anti-VEGF agents rapidly sequester VEGF in the vitreous at the time of treatment.[12,13] This difference in rapidity of effect would be expected to have a more pronounced effect with ROP that is progressing more quickly. Shah et al[14] demonstrated fewer RDs in eyes with aggressive posterior ROP treated with anti-VEGF agents compared with laser therapy. These findings also support the hypothesis that anti-VEGF treatment demonstrates greater efficacy than laser therapy for rapidly progressing ROP.

Although zone is a traditional marker of disease severity, PMA and zone of ROP are closely related, and there are advantages to using PMA as a marker of ROP aggression. Natural history data from the Cryotherapy for ROP Study demonstrated that ROP follows a typical course tied to developmental age (PMA) and that developmental age is a more reliable indicator of ROP risk than chronologic age.[15] More posterior ROP occurs earlier in development and the more posterior the location of ROP, generally the more

Table 2. Retinal Detachment Rates within 8 Weeks after Treatment of Type 1 Retinopathy of Prematurity with Laser Therapy and Intravitreal Anti–Vascular Endothelial Growth Factor Treatment, Stratified by Postmenstrual Age at Treatment and Zone of Disease

	Laser Therapy*	Anti–Vascular Endothelial Growth Factor Treatment*	P Value*
PMA <36 wks (n = 458 eyes)			<0.001
No./total no. (%)	29/368 (7.9)	0/90 (0.0)	
95% CI	4.7%–11.3%	NA‡	
PMA ≥36 wks (n = 709 eyes)			0.27
No./total no. (%)	20/635 (3.1)	1/74 (1.4)	
95% CI	1.6%-4.9%	0.0%-4.5%	
Zone I (n = 234 eyes)†			0.02
No./total no. (%)	12/155 (7.7)	1/79 (1.3)	
95% CI	3.1%–13.2%	0.0%–4.3%	
Zone II (n = 928 eyes)†			<0.001
No./total no. (%)	37/843 (4.4)	0/85 (0.0)	
95% CI	2.8%–6.1%	NA‡	
Total			<0.001
No./total no. (%)	49/1003 (4.9)	1/164 (0.6)	
95% CI	3.4%–6.5%	0.0%–2.0%	

CI = confidence interval; NA = not available; PMA = postmenstrual age.
*Based on bootstrap method.
†Five eyes with unknown zones were excluded.
‡Could not be calculated because of 0 retinal detachments.

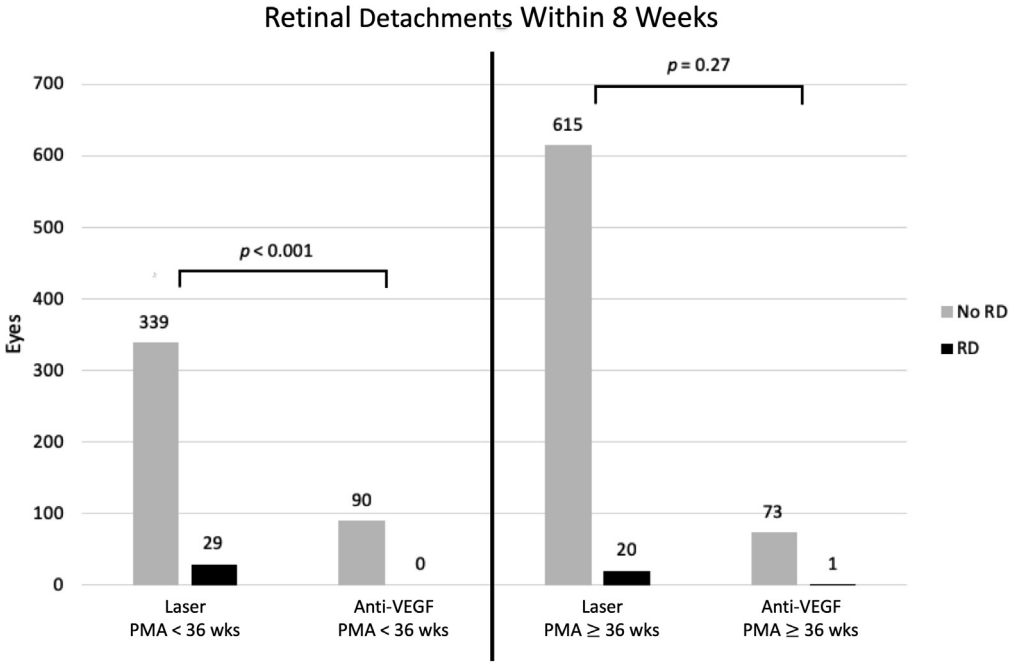

Figure 2. Bar graph showing retinal detachments (RDs) within 8 weeks after treatment for type 1 retinopathy of prematurity with intravitreal anti–vascular endothelial growth factor (VEGF) versus laser photocoagulation, stratified by postmenstrual age (PMA) before and after 36 weeks at time of treatment.

aggressive the ROP state. Presumably, type 1 ROP in zone 1 involves greater area of avascular retina, higher VEGF production, and more aggressive ROP when compared with type 1 ROP in zone 2. Many studies have used zone 1 as a marker of aggression of type 1 ROP.[4,16–18] Although zone of ROP is defined clearly in the International Classification of ROP,[19] clinical distinction of zone 1 from zone 2 is subjective and carries significant interobserver variability, even among experienced clinicians.[20] Perhaps such variability explains why we observed no difference in rate of RD between laser-treated eyes in zone 1 compared with zone 2. In contrast to zone, PMA at diagnosis is a known objective measure and therefore is easier to reproduce across physicians and institutions. Our data suggest that diagnosis of type 1 ROP before PMA of 36 weeks 0 days may be a more practical clinical marker of RD risk, and therefore disease aggression, than zone of disease.

We chose a short-term outcome for this study, development of RD within 8 weeks of treatment, because this is a

Table 3. Characteristics of Re-treatment within 8 Weeks after Initial Treatment with Laser Therapy or Intravitreal Anti–Vascular Endothelial Growth Factor Treatment Stratified by Postmenstrual Age at Initial Treatment

	Postmenstrual Age <36 Weeks			Postmenstrual Age ≥36 Weeks			Total		
	Laser Therapy (n = 368 eyes)	*Anti–VEGF Treatment (n = 90 Eyes)*	P *Value*	*Laser Therapy (n = 635 Eyes)*	*Anti–VEGF Treatment (n = 74 Eyes)*	P *Value*	*Laser Therapy (n = 1003 Eyes)*	*Anti–VEGF Treatment (n = 164 Eyes)*	P *Value*
No. of re-treatments, no. (%)			0.46			0.07			0.10
0	327 (88.9)	76 (84.4)		603 (95.0)	61 (82.4)		930 (92.7)	137 (83.5)	
1	40 (10.9)	12 (13.3)		29 (4.6)	13 (17.6)		69 (6.9)	25 (15.2)	
2	1 (0.3)	2 (2.2)		3 (0.5)	0 (0.0)		4 (0.4)	2 (1.2)	
Retreatment rate, no. (%)	41 (11.1)	14 (15.6)	0.45	32 (5.0)	13 (17.6)	0.053	73 (7.3)	27 (16.5)	0.03
First retreatment type, no. (%)			0.06			0.22			0.31
Laser	37 (90.2)	7 (50.0)		24 (75.0)	12 (92.3)		61 (83.6)	19 (70.4)	
Anti-VEGF agent	4 (9.8)	7 (50.0)		8 (25.0)	1 (7.7)		12 (16.4)	8 (29.6)	

VEGF = vascular endothelial growth factor.

more direct sign of treatment failure, as opposed to disease reactivation. In addition, many RDs after laser therapy occur within this period,[5,21] and the half-lives of most anti-VEGF agents suggest that their effects will occur primarily in the first 8 weeks after treatment.[22–24] Although long-term visual acuity would be an ideal clinical outcome, data from the Early Treatment of ROP Study suggest that RD is associated closely with poor long-term visual outcomes and is a good proxy for such long-term outcomes.[11] Finally, short-term risk of RD is more directly relevant to long-term visual outcome than "disease recurrence requiring treatment," which has been the focus of prior studies comparing anti-VEGF and laser treatments; the goal of treatment for ROP is to prevent imminent progression to RD. If acute progression is not halted, prognosis is poor. Nevertheless, it is important to recognize the need for long-term monitoring of eyes treated with anti-VEGF agents for late reactivation that may benefit from additional treatment.

The large number of treated eyes in our study enabled a comparison of laser and anti-VEGF therapies stratified by PMA at treatment. The geographically and racially diverse sample across many hospitals and many different treating physicians improves the generalizability of the findings. However, potential limitations should be considered. Despite the large overall number of treated eyes in this study, the number of eyes treated with anti-VEGF agents in some subgroups, such as treatment at or after PMA of 36 weeks, may have limited the power to detect differences between groups. Infants were not randomized to treatment method. If a tendency existed to use anti-VEGF for what was perceived to be more aggressive ROP, this would bias the results toward worse outcomes for anti-VEGF eyes, which would not change the conclusions for the groups treated before PMA of 36 weeks 0 days, but may change the conclusions for the group treated at or after PMA of 36 weeks 0 days, in which a statistical difference was not found. With regard to outcome, we considered only RD and not other adverse structural outcomes, such as macular folds, data for which were available for G-ROP 1, but not G-ROP 2. Macular fold was considered a poor structural outcome in the Early Treatment of ROP Study and is associated with poor long-term visual acuity.[10] In G-ROP 1, 11 eyes receiving laser therapy demonstrated macular fold without RD.[21] We did not consider longer-term outcomes that may influence clinician treatment choice. Eyes treated with anti-VEGF agents may have persistent avascular retina, placing them at risk for late reactivation and RD, even years after initial treatment.[25–29] Additional treatment for eyes receiving anti-VEGF agents may need to be considered, including after the 8-week end point reported in this study. Reported rates of re-treatment after initial monotherapy with anti-VEGF agents have varied considerably.[3–5]

Our study also did not address safety concerns about the use of anti-VEGF agents for ROP.[30,31] Systemic VEGF levels are depressed for up to 12 weeks after intraocular bevacizumab for ROP with uncertain effects on the developing brain, lung, and kidneys.[32–35] Systemic VEGF levels recover more rapidly after ranibizumab injection, but are still suppressed initially.[36–40] Studies comparing neurodevelopmental outcomes between infants treated with laser therapy versus anti-VEGF agents have yielded inconclusive results. Some show no adverse effect from anti-VEGF agents,[3,41,42] and others suggest worse motor outcomes and higher mortality among infants treated with bevacizumab compared with laser therapy.[43,44] These studies should be interpreted with caution, because treatment methods generally were not randomized and sicker infants tended to be treated with anti-VEGF agents instead of laser therapy.[45] Finally, ideal dosing of bevacizumab for ROP has yet to be established.[46–48] Wallace et al[49] recently demonstrated good results with 0.004 mg, considerably less than the 0.625 mg used in the Bevacizumab Eliminates the Angiogenic Threat of ROP Study.

The decision of whether to treat type 1 ROP with laser therapy or intravitreal anti-VEGF injections remains a complicated, multifaceted one. Our data confirm a clear short-term structural benefit of anti-VEGF treatment over laser therapy before PMA of 36 weeks 0 days and suggest that the more objective measure of PMA at type 1 diagnosis may be preferable to the subjective judgment of zone of disease. However, this benefit must be considered along with other risks and benefits, including long-term structural outcomes, long-term visual acuity outcomes, and short-term and long-term safety data of patients treated with anti-VEGF agents.

Footnotes and Disclosures

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Data collection: Barry, Tomlinson, Fisher, Binenbaum

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Abbreviations and Acronyms:
BW = birth weight; **G-ROP** = Postnatal Growth and Retinopathy of Prematurity Study; **PMA** = postmenstrual age; **RD** = retinal detachment; **ROP** = retinopathy of prematurity; **VEGF** = vascular endothelial growth factor.

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