

Original Investigation | CLINICAL TRIAL

Refractive Outcomes Following Bevacizumab Monotherapy Compared With Conventional Laser Treatment

A Randomized Clinical Trial

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IMPORTANCE Children born prematurely who develop retinopathy of prematurity (ROP) often develop myopia, and those who require laser treatment may develop very high myopia, which has considerable clinical consequences.

OBJECTIVE To report refractive outcomes in preterm infants who developed ROP in zone I or zone II posterior as stage 3+ ROP or aggressive posterior ROP (APROP).

DESIGN, SETTING, AND PARTICIPANTS All infants received intravitreal bevacizumab or laser therapy in a prospective, stratified, randomized, controlled, masked, multicenter clinical trial, Bevacizumab Eliminates the Angiogenic Threat for ROP (BEAT-ROP). Children who received intravitreal bevacizumab or laser in the BEAT-ROP clinical trial, with treatment randomized by infant, underwent cycloplegic retinoscopic refraction at a mean age of 2½ years. Fifteen centers with both pediatric and vitreoretinal ophthalmologists participating in level 3 neonatal intensive care units in academic centers with institutional review board approval were included in the trial. Of the originally enrolled 150 infants (300 eyes) in the BEAT-ROP clinical trial, 13 infants (26 eyes) died (6 received intravitreal bevacizumab; 7 received laser) and 19 eyes had intraocular surgery (6 infants bilaterally). Thus, 45 eyes (19 infants bilaterally) were excluded, leaving 131 infants (255 eyes, including 21 eyes that received a successful second treatment for recurrence).

INTERVENTIONS Follow-up of the BEAT-ROP cohort.

MAIN OUTCOMES AND MEASURES Spherical equivalent refractive outcomes and their distribution by ROP zone and treatment.

RESULTS Refractions were available for 109 of 131 eligible infants (83.2%) and 211 of 255 eyes (82.7%). Mean (SD) spherical equivalent refractions were as follows: zone I, -1.51 (3.42) diopters (D) in 52 eyes that received intravitreal bevacizumab and -8.44 (7.57) D in 35 eyes that received laser treatment ($P < .001$); and zone II posterior, -0.58 (2.53) D in 58 eyes that received intravitreal bevacizumab and -5.83 (5.87) D in 66 eyes that received laser treatment ($P < .001$). Very high myopia (≥ -8.00 D) occurred in zone I in 2 of 52 (3.8%) eyes that received intravitreal bevacizumab and in 18 of 35 (51.4%) eyes that received laser treatment ($P < .001$). Very high myopia occurred in zone II posterior in 1 of 58 (1.7%) eyes that received intravitreal bevacizumab and in 24 of 66 (36.4%) eyes that received laser treatment ($P < .001$).

CONCLUSIONS AND RELEVANCE More very high myopia was found in eyes that received laser treatment than in eyes that received intravitreal bevacizumab. This difference is possibly related to anterior segment development that is present with intravitreal bevacizumab but minimal or absent following laser treatment.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT00622726

JAMA Ophthalmol. 2014;132(11):1327-1333. doi:10.1001/jamaophthalmol.2014.2772
Published online August 7, 2014.

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Group Information: The Bevacizumab Eliminates the Angiogenic Threat for Retinopathy of Prematurity (BEAT-ROP) Cooperative Group members are listed in the eAppendix in the Supplement.

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Advances in the treatment for retinopathy of prematurity (ROP) are allowing better prevention of blindness due to retinal detachment; however, the visual rehabilitation of these children does not end with ROP regression. One important problem frequently found to affect these children is the development of myopia, especially very high myopia, which has considerable structural and functional consequences.¹

The refractive outcomes of prematurity, both without²⁻⁶ and with ROP,⁴⁻⁶ have been established. The myopia in children born prematurely without ROP, termed *myopia of prematurity*,³⁻⁷ is negatively correlated with birth weight and gestational age. It tends to be of low magnitude and lessens with age.^{3,5,7} The myopia in children born prematurely who develop ROP that does not require treatment, called *myopia of spontaneously regressed ROP*,^{3-5,7-11} is similarly negatively correlated with birth weight and gestational age but is also correlated with ROP severity. Myopia in these children usually plateaus at approximately age 2½ years, tends to be of slightly higher magnitude, and does not decrease with age.¹²

The Early Treatment for ROP (ETROP) clinical trial¹³ was designed to determine whether earlier laser treatment (high-risk prethreshold, 1 eye [treatment group]) would produce better functional and structural outcomes than later laser therapy (threshold ROP, fellow eye [control group]). While the Cryotherapy for ROP (CRYO-ROP) clinical trial¹⁴ compared threshold ROP in both: cryotherapy, 1 eye (treatment group), and no treatment, fellow eye (control group). Other studies,¹⁵⁻¹⁸ as well as the CRYO-ROP⁷ and ETROP^{19,20} trials, described markedly increased myopia following peripheral retinal ablation for ROP. Refractive outcomes of the ETROP study^{19,20} revealed an increased prevalence of myopia and high myopia in eyes that had developed ROP requiring laser therapy than in eyes with ROP that regressed spontaneously without treatment. The ETROP study also found an increased prevalence of high myopia (≥ -5 diopters [D]) in eyes with high-risk prethreshold ROP treated for zone I disease than in those treated for zone II disease. Both of these refractive findings were attributed to the severity of ROP.

The objective of the present article is to report the refractive outcomes in children aged 2½ years, especially with myopia, following monotherapy with the anti-vascular endothelial growth factor (VEGF) agent bevacizumab for ROP (treatment group) compared with myopia following laser peripheral retinal ablation (control group) from the Bevacizumab Eliminates the Angiogenic Threat for ROP (BEAT-ROP) clinical trial.²¹

Methods

The study protocol was approved by the institutional review boards at all 15 participating hospitals and conformed to the requirements of the US Health Insurance Portability and Privacy Act. Parents or guardians of the infants provided written informed consent before enrollment in the randomized trial and at entry into the long-term portion of the

study. No financial compensation was provided. The study had an independent data and safety monitoring board and was conducted in accordance with a previously published protocol.²¹

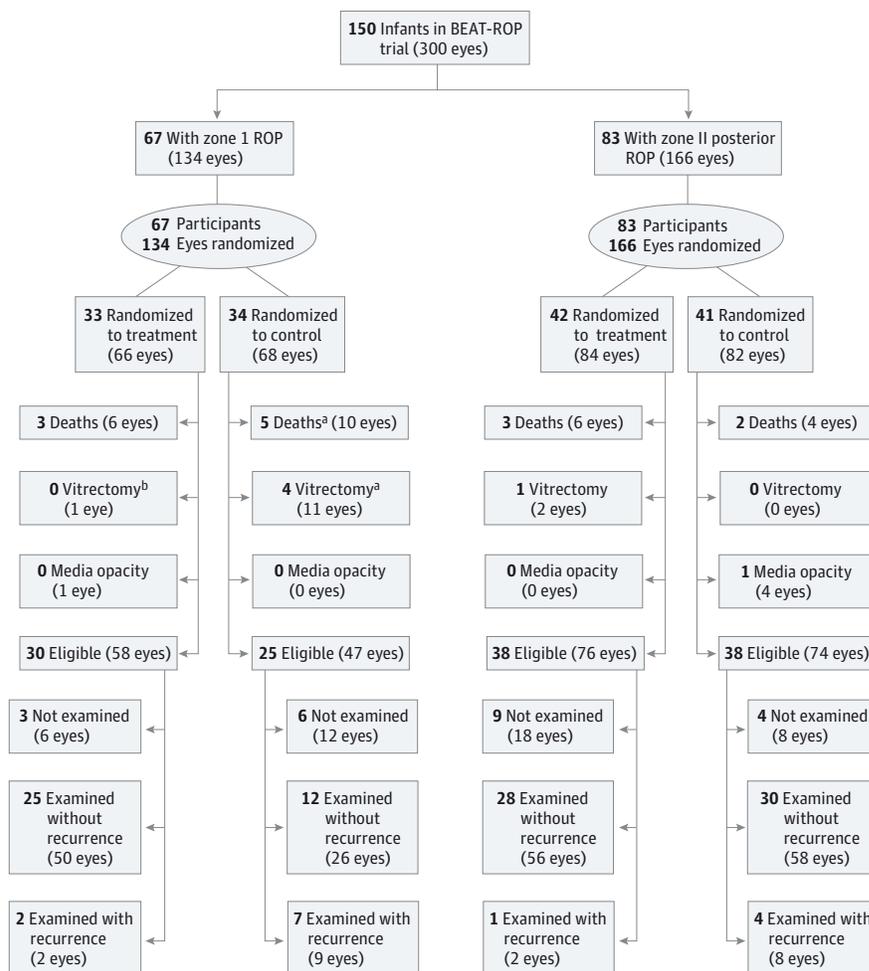
Participants in the BEAT-ROP clinical trial were 150 infants with a birth weight of 1500 g or less and a gestational age of 30 weeks or less who were enrolled between March 13, 2008, and August 4, 2010, at 1 of 15 participating centers. In this clinical trial, infants (both eyes) had ROP in zone I or zone II posterior with stage 3+ ROP or aggressive posterior ROP (APROP), ranging from high-risk prethreshold disease (type 1) of ETROP¹³ to the threshold disease of CRYO-ROP.¹⁴ Each infant was determined to have zone I or zone II posterior ROP and was stratified by zone. Each infant was then randomized to receive treatment in both eyes as either intravitreal bevacizumab monotherapy or near confluent laser therapy. The use of intravitreal bevacizumab, 0.625 mg (0.025 mL), was given with a 31-gauge 5/16-inch needle at the bedside after topical anesthesia and antiseptic drops were administered. Laser therapy was performed in the operating room under general anesthesia.

Of the original 300 eyes (150 infants), 255 eyes (131 infants) were eligible to be included in this cycloplegic retinoscopic refractive study at a mean age of 2½ years. The exclusions were (1) 26 eyes (13 infants who died; 6 infants in the intravitreal bevacizumab arm and 7 infants in the laser arm), (2) 13 eyes of 8 infants (bilateral vitrectomies in 5 infants) who developed recurrent ROP and ultimately underwent vitrectomy for retinal detachment (2 eyes in the intravitreal bevacizumab arm and 11 eyes in the laser arm; 1 infant who received laser treatment required vitrectomy in both eyes prior to death and is counted under deaths), (3) 1 eye in the intravitreal bevacizumab arm required vitrectomy for hemorrhage occluding the macula following nonaccidental trauma, and (4) 5 eyes of 4 infants (1 infant with bilateral opacities) underwent surgery for lenticular (4 eyes) or corneal (1 eye) opacities (1 in the intravitreal bevacizumab arm and 4 in the laser arm) (Figure 1).

Unmasked practicing pediatric ophthalmologists performed the cycloplegic retinoscopic refractions. These refractive errors were divided into 6 categories by the amount of spherical equivalence as follows: very high myopia (≥ -8 D), high myopia (< -8 to -5 D), low myopia (< -5 to -1 D), emmetropia (< -1 to $+1$ D), low hyperopia ($> +1$ to $+4$ D), and high hyperopia ($> +4$ D). These refractive categories were chosen based on previous studies.^{7,19,20}

Descriptive statistics were performed, calculating the mean (SD) refractive errors and frequencies (percentage) to investigate the prevalence of each category of refractive error according to treatment modality received and zone of ROP. Additionally, comparing mean refractive errors between treatment modalities and determining the correlation between refractive errors and laser applications in the laser arm were performed using a mixed-effects model. The percentage of eyes with very high myopia was compared using a generalized linear model with logit link. All statistical analyses were performed using SAS for Windows, version 9.3 (SAS Inc). $P < .05$ was considered statistically significant for all comparisons.

Figure 1. Bevacizumab Eliminates the Angiogenic Threat for Retinopathy of Prematurity (BEAT-ROP)



Infants were stratified by ROP zone and randomized between 2 treatment modalities: intravitreal bevacizumab (treatment group) and laser treatment (control group).

^a One infant who died had undergone bilateral vitrectomy.

^b Nonaccidental trauma.

Results

Refractions were performed on 211 of 255 eyes (109 of 131 infants), representing 82.7% of eyes and 83.2% of infants eligible for involvement in this refraction study. These refractions represent 70.3% of 300 eyes and 72.7% of 150 infants in the original BEAT-ROP cohort.²¹ The 109 infants undergoing refraction included 56 infants in the intravitreal bevacizumab arm and 53 infants in the laser arm. The infants who underwent refraction had been stratified previously according to the zone of ROP at randomization: 87 eyes of 46 infants with ROP in zone I and 124 eyes of 63 infants with ROP in zone II posterior (Figure 1). The mean age of these infants at the time of refraction was 2.5 (0.9) years. Their baseline clinical characteristics are listed in the Supplement (eTable 1).

The Table provides the mean (SD) of the spherical equivalent refractive error (SE) for all eligible children at age 2½ years. The eyes of infants who received intravitreal bevacizumab had significantly less SE compared with eyes that received laser therapy ($P < .001$). For children with zone I ROP, the mean SE was -1.51 (3.42) D in the intravitreal bevacizumab group (27 in-

fants, 52 eyes) and -8.44 (7.57) D in the laser group (19 infants, 35 eyes) ($P < .001$). For children with zone II posterior ROP, the mean SE was -0.58 (2.53) D in the intravitreal bevacizumab treatment arm (29 infants, 58 eyes) and -5.83 (5.87) D in the laser arm (34 infants, 66 eyes) ($P < .001$). There was no significant difference in myopia between zones of ROP in either treatment arm ($P = .24$ in the intravitreal bevacizumab arm and $P = .26$ in the laser arm after adjustment for the number of laser applications).

Figure 2 and Figure 3 show the percentage of eyes in each of the 6 refractive error categories at age 2½ years. All infants (with or without recurrence) who received intravitreal bevacizumab had a significantly lower percentage of eyes with very high myopia compared with eyes that received laser, regardless of the zone of ROP ($P < .001$). Among all eyes that received treatment for zone I ROP, very high myopia developed in 2 of 52 eyes (3.8%) in the intravitreal bevacizumab arm and in 18 of 35 eyes (51.4%) of the laser arm ($P < .001$) (Figure 2). In zone II posterior ROP, very high myopia developed in 1 eye (1.7%) in the intravitreal bevacizumab treatment arm and in 24 of 66 eyes (36.4%) in the laser treatment arm ($P < .001$) (Figure 3).

Table. Cycloplegic Retinoscopic Refractive Error at Age 2½ Years

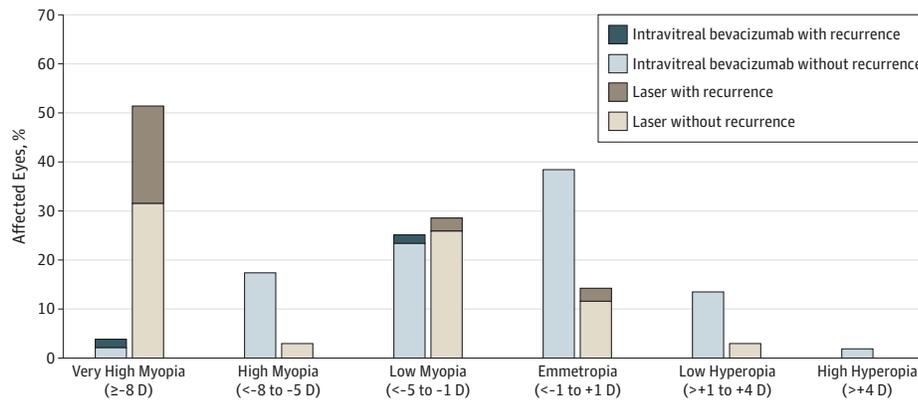
Spherical Equivalent Refractions, D	Intravitreal Bevacizumab		Laser	
	Without Recurrence	With Recurrence	Without Recurrence	With Recurrence
Zone I (87 eyes) ^a	(50 Eyes)	(2 Eyes)	(26 Eyes)	(9 Eyes)
Mean (SD)	-1.36 (3.34)	-5.25 (4.60)	-7.34 (7.44)	-11.61 (7.42)
Median (range)	-0.50 (-8.00 to 6.00)	-5.25 (-8.50 to -2.00)	-4.69 (-24.88 to 2.00)	-10.00 (-22.00 to 0.75)
Zone II posterior (124 eyes) ^b	(56 Eyes)	(2 Eyes)	(58 Eyes)	(8 Eyes)
Mean (SD)	-0.63 (2.56)	0.88 (0.00)	-5.20 (5.77)	-10.42 (4.58)
Median (range)	0.00 (-13.00 to 2.50)	0.88 (0.88 to 0.88)	-4.00 (-19.00 to 3.50)	-11.50 (-15.00 to -2.63)

Abbreviation: D, diopters.

^a For zone I, the 52 eyes in the intravitreal bevacizumab group represent 90% of eligible eyes, and the 35 eyes in the laser group represent 74% of eligible eyes. The mean (SD) spherical equivalent refractions for the intravitreal bevacizumab group were -1.51 (3.42) D (median [range], -0.56 [-8.56 to 6.00] D) and for the laser group were -8.44 (7.57) D (median [range], -8.00 [-24.88 to 2.00] D) (*P* < .001).

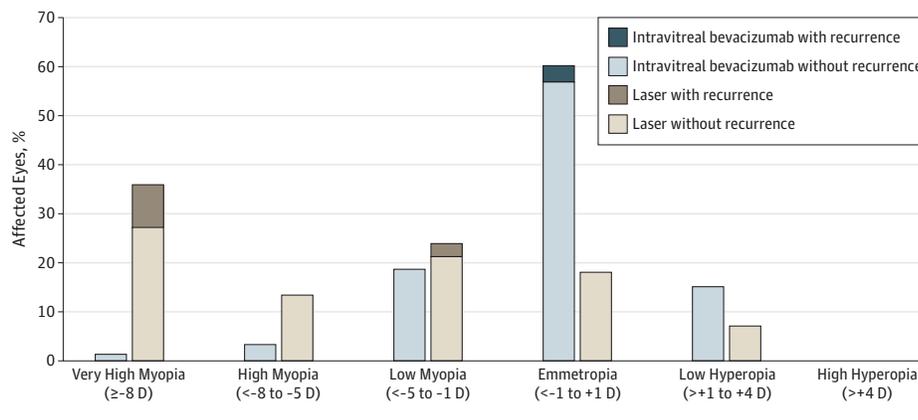
^b For zone II posterior, the 58 eyes in the intravitreal bevacizumab group and the 66 eyes in the laser group represent 76% of eligible eyes in each group. The mean (SD) spherical equivalent refractions for the intravitreal bevacizumab group were -0.58 (2.53) D (median [range], 0.00 [-13.00 to 2.50] D) and for the laser group were -5.83 (5.87) D (median [range], -4.88 [-19.00 to 3.50] D) (*P* < .001).

Figure 2. Zone I Distribution of Refractive Error by Treatment Modality



Distribution of spherical equivalent refractive error at age 2½ years in eyes that received treatment for stage 3+ retinopathy of prematurity or aggressive posterior retinopathy of prematurity in the Bevacizumab Eliminates the Angiogenic Threat for Retinopathy of Prematurity clinical trial. Data are presented according to treatment modality.

Figure 3. Zone II Posterior Distribution of Refractive Error by Treatment Modality



Distribution of spherical equivalent refractive error at age 2½ years in eyes that received treatment for stage 3+ retinopathy of prematurity or aggressive posterior retinopathy of prematurity in the Bevacizumab Eliminates the Angiogenic Threat for Retinopathy of Prematurity clinical trial. Data are presented according to treatment modality.

In addition, the mean SE of 17 eyes (with ROP in both zones) successfully retreated with laser for recurrence was -11.05 (6.09) D, and 13 of these 17 eyes (76.5%) had very high myopia. The mean SE of 4 eyes (with ROP in both zones) successfully retreated with intravitreal bevacizumab was -2.19 (4.42) D, and 1 of these 4 eyes (25.0%) had very high myopia.

In the laser arm, the myopia was greater if more laser applications were administered (*P* = .007). The myopia increased -0.14 (0.05) D for every 100 laser applications given. Data in the Supplement (eTable 2) indicate the mean laser applications in each zone without and with recurrence. The mean laser applications were 2526 (1162) (35 eyes) in zone I and 1954

(1288) (66 eyes) in zone II posterior. The mean laser applications were 1990 (467) in zone I (26 eyes) and 1567 (476) in zone II posterior (58 eyes) without retreatment. The mean laser applications were 4072 (1198) in zone I (9 eyes) and 4766 (1811) in zone II posterior (8 eyes) with retreatment. There were significantly more applications in retreated eyes ($P < .001$ for both zones).

Discussion

In the BEAT-ROP clinical trial with 83.2% of eligible infants (70.3% of all enrolled infants) undergoing cycloplegic refractions at age 2½ years of age, more myopia, especially very high myopia, was found in eyes that received peripheral retinal ablation than in eyes that received an intravitreal anti-VEGF agent. We believe that these findings support the continued use of anti-VEGF agents in the treatment of ROP and are an important consideration for the treating ophthalmologist.

At least 3 etiologic factors are responsible for the myopia reported in the present study regarding the eyes of premature infants with ROP: (1) prematurity, (2) the severity of ROP, and (3) changes related to treatment administered for stage 3+ ROP or APROP (related either to retinal ablation [laser treatment] or anti-VEGF therapy [intravitreal bevacizumab]). The possibility of peripheral retinal ablation contributing to the increased myopia seen following treatment for ROP has been raised by previous investigators,¹⁵⁻¹⁸ but this cause is often given less credence in favor of increased severity of ROP being solely responsible for the myopia following treatment.^{7,19,20}

Our study found no significant difference in the severity of myopia in ROP between zone I and zone II posterior within each treatment arm. Thus, comparing the myopia of each treatment arm suggests that the severity of ROP (zones I and II posterior) is not the primary etiologic factor.

In eyes matched for the severity of ROP (zone or stage), there was significantly increased myopia between both zones together and each zone separately in eyes that received laser compared with those that received intravitreal bevacizumab ($P < .001$). This finding suggests a possible significant contribution of the laser ablation to the increased myopia seen in infants who received laser treatment. Supporting this result, a few case series²²⁻²⁵ found similar low levels of myopia following intravitreal bevacizumab monotherapy for ROP.

The distribution of refractive errors is interesting. The highest percentage of eyes that received intravitreal bevacizumab was for those that were emmetropic after treatment (38.5% of zone I and 60.3% of zone II posterior). Bimodal distribution with 2 peaks in the percentage of eyes treated by laser was very high myopia (51.4% of zone I and 36.4% of zone II posterior) and low myopia (28.6% of zone I and 24.2% of zone II posterior) (Figures 2 and 3).

Retreatment for recurrence of ROP was determined to be the end point of the BEAT-ROP clinical trial²¹; thus, evaluation of eyes that received additional therapy allows further insight into the potential contribution of treatment modality to the significant refractive differences between the 2 treatment arms. In the group of eyes with recurrent ROP in which

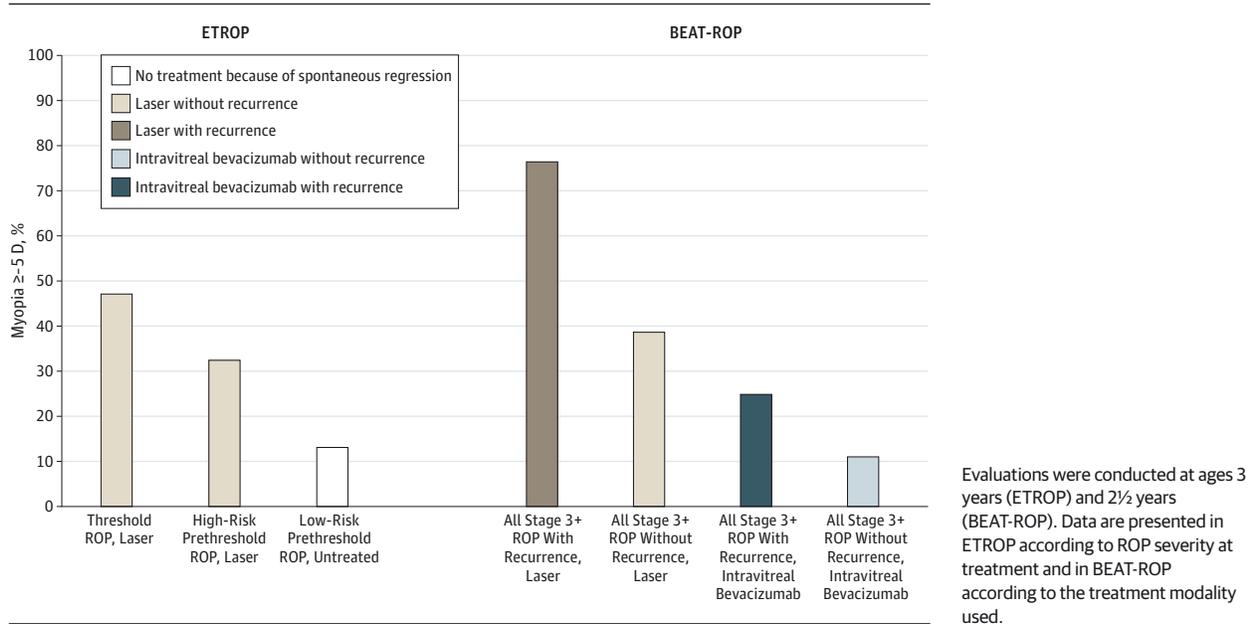
retreatment was successful, there was a much higher incidence of very high myopia in 13 of 17 eyes receiving additional laser (76.5%) vs those 1 of 4 eyes receiving additional intravitreal bevacizumab (25.0%). These data, combined with the finding of increased myopia with more laser applications, support the possibility that laser treatment may contribute to the very high myopia that develops.

To better understand the importance of these findings, it is necessary to appreciate them in the setting of the current standard of care for ROP derived from the ETROP clinical trial.¹³ It is difficult to make direct comparisons between the ETROP and BEAT-ROP²¹ studies; however, because both studies used the same revised international classification^{26,27} and enrolled infants with either stage 3+ ROP or APROP, some comparisons can be made. A historical comparison of ETROP and BEAT-ROP was compiled to highlight some similarities and differences in the myopia of these studies (Figure 4). In the ETROP study,^{19,20} the control group (laser treatment at threshold ROP) had a slightly greater percentage of eyes with myopia of -5 D or higher (high and very high myopia as defined in the present study) than the experimental group (laser treatment at high-risk prethreshold ROP). In the BEAT-ROP clinical trial,²¹ the laser treatment control group ranged from high-risk prethreshold ROP to threshold ROP. The percentage of eyes with myopia of -5 D or greater was between that seen following laser treatment for both the control and experimental eyes in the ETROP clinical trial. In contrast, the percentage of eyes with myopia of -5 D or greater after intravitreal bevacizumab treatment in the BEAT-ROP cohort was far less than that seen following peripheral retinal ablation. The myopia following anti-VEGF monotherapy for ROP in the eyes that received intravitreal bevacizumab in the BEAT-ROP trial was similar to the myopia of spontaneously regressed ROP^{19,20} seen in the untreated eyes in the ETROP trial.

It has been well established that the myopia of prematurity, both with and without ROP,^{8,9,28-30} is nonaxial, consisting of (1) steepening of the cornea, (2) decreased anterior chamber depth, and (3) increased lenticular thickness. It is thought that these anterior segment changes are the result of an arrested state of development following premature birth, which is caused by many factors.^{11,15}

Although purely speculative at this juncture, it is possible that intravitreal bevacizumab allows for minimal disruption of the local growth factor milieu and signaling pathways necessary for development of the anterior segment. As hypothesized previously,^{11,15} the incomplete development of the retina in prematurity with or without ROP may alter local ocular growth signals. It has been shown³¹ that the peripheral retina in the eyes of very preterm infants will vascularize or differentiate only to the location of the anterior termination of endothelial cell precursors at birth. Thus, retinal vessels may never reach the ora serrata, especially in very immature infants.³² Some studies^{10,14} have proposed that the absence of full migration of retinal vessels to the ora serrata and the arrested maturation of photoreceptors may decrease the levels of the local growth factors required for signaling pathways involved in anterior segment development. As previously reported and demonstrated,²¹ intravitreal bevacizumab allows

Figure 4. Percentage of Eyes at ≥ -5 Diopters or Greater in the Early Treatment for Retinopathy of Prematurity (ETROP) Compared With Bevacizumab Eliminates the Angiogenic Threat for Retinopathy of Prematurity (BEAT-ROP) Trials



the continued development of the retinal vessels beyond the neovascular ridges, which is minimal or absent following laser treatment. It is possible that this development could allow the continuation of local growth factor expression and signaling pathways necessary for a more normal anterior segment with minimal myopia. Furthermore, a more normal eye with a less steep cornea, without a shallow anterior chamber and with decreased lens thickness, would be less prone to later angle-closure glaucoma that occasionally afflicts laser-treated eyes.⁸ Although these theories are intriguing, they are still speculative and require further investigation.

As with any study, the present one has limitations to be considered: (1) 22 of 131 infants (16.8%) were lost to follow-up; (2) the population included primarily Hispanic infants, which raises concerns for possible selection bias with less applicability of these results to other populations (however, a previous study³³ reported no difference in the incidence of ROP between Hispanic infants and white non-Hispanic infants); and (3) concern for any potential observer bias in the refraction data is important to consider because many of the investigators

(M.G.H., A.A.N., and E.A.P.), including the principal investigator (H.A.M.-H.), performed the refraction for some, but not all, of the infants. However, all refractions were performed by qualified pediatric ophthalmologists who were held to the utmost ethical standards required in routine patient care or in any research endeavor.

Conclusions

A significantly increased prevalence of myopia and very high myopia was identified in the eyes of children with stage 3+ ROP or APROP treated with laser compared with intravitreal bevacizumab monotherapy in both zone I and zone II posterior ROP in the BEAT-ROP clinical trial. Longer-term refractive outcomes of this study, including the biometric components, visual acuity, and visual field, are necessary. In addition, the establishment of the long-term safety of intravitreal bevacizumab and a refinement of the dose of intravitreal bevacizumab compared with other anti-VEGFs, as well as a follow-up schedule to detect all recurrences, are essential.

ARTICLE INFORMATION

Submitted for Publication: July 22, 2013; final revision received January 3, 2014; accepted January 6, 2014.

Published Online: August 7, 2014.
doi:10.1001/jamaophthalmol.2014.2772.

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Acquisition, analysis, or interpretation of data: All authors.

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Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Chuang.

Obtained funding: Mintz-Hittner.

Administrative, technical, or material support: All authors.

Study supervision: Mintz-Hittner.

Conflict of Interest Disclosures: None reported.

Funding/Support: This study was supported by National Eye Institute core grant EY10608 for analysis of the data (A.Z.C.), by Research to Prevent Blindness, Inc, Hermann Eye Fund and Alfred W. Lasher III Research Funds for collection and management of the data (H.A.M.-H.), and by The University of Texas-Health Science Center/Center for Clinical and Translational Science/Clinical Research Unit Clinical and Translational Science Award grant UL1 RR024148 for design and conduct of the study (H.A.M.-H.).

Role of the Sponsor: The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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