Treatment of non–type 1 retinopathy of prematurity in the Postnatal Growth and Retinopathy of Prematurity (G-ROP) study

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PURPOSE To determine the prevalence and characteristics of eyes treated for retinopathy of prematurity (ROP) not meeting currently recommended early treatment (type 1) criteria.

METHODS This was a secondary analysis of data from the Postnatal Growth and ROP (G-ROP) study, a retrospective cohort study of 7,483 infants undergoing ROP examinations and treatment at 29 North American hospitals between January 2006 and June 2012. Medical records were reviewed to determine the prevalence and characteristics of eyes treated for ROP less severe than type 1 ROP.

RESULTS Of 1,004 eyes that received ROP treatment, 126 eyes of 91 infants (0.8% of all eyes; 12.5% of treated eyes) underwent treatment for ROP less severe than type 1. Mean age at treatment was 38 weeks' post-menstrual age (range, 32-49 weeks). Reasons for treatment included type 1 ROP in the fellow eye (43%), stage 3 ROP with pre-plus in the treated eye (30%), concerning structural changes in the retina (7%), persistent stage 3 ROP for ≥6 weeks without regression (6%), stage 3 ROP with no plus disease in the treated eye (5%), stage 3, zone III ROP with plus disease (3%), logistical considerations (3%), or stage 2 disease in the treated eye (2%).

CONCLUSIONS Of all eyes treated for ROP, 1/8 were treated for disease less severe than currently recommended type 1 criteria. Clinician judgment of risk for permanent vision impairment superseded recommended treatment criteria and was usually related to type 1 disease in the fellow eye or pre-plus vascular changes in one or both eyes. (J AAPOS 2019;23:332.e1-6)

Retinopathy of prematurity (ROP) is a potentially blinding, vasoproliferative disorder of the developing retinal vasculature. The benefit of ablative treatment in reducing the risk of retinal detachment was first documented for threshold ROP (defined as 5 contiguous clock hours or 8 total clock hours of stage 3 and plus disease in zone I or II) in the Multicenter Trial of Cryotherapy for Retinopathy of Prematurity (CRYO-ROP)[1-5]; current treatment recommendations are based on the results of the Early Treatment for Retinopathy of Prematurity (ETROP) randomized clinical trial.[6-10] Peripheral retinal ablation is now recommended for eyes diagnosed with type 1 prethreshold ROP, defined as zone I, any stage ROP with plus disease; zone I, stage 3 ROP with or without plus disease; or zone II, stage 2 or 3 ROP with plus disease.[7] Continued serial examinations are recommended for type 2 prethreshold ROP, defined as zone I, stage 1 or 2 ROP without plus disease or zone II, stage 3 ROP without plus disease.[7] Treatment recommendations were not made for zone III disease.

The decision to treat progressive ROP is based on clinician judgment and consideration of these guidelines. Evidence suggests that clinicians not infrequently treat eyes with ROP that do not meet criteria for type 1 ROP.[11,12] In a survey-based study of pediatric ophthalmologists involved in ROP treatment in the United Kingdom, 27% of 654 eyes receiving treatment were diagnosed with ROP milder than type 1 ROP.[11] In a study of 1444 eyes of 722 infants from 6 institutions in the United States, Gupta and colleagues[12] found that 13 of 137 eyes (9.5%) treated for ROP were treated with a clinical diagnosis less severe than type 1 ROP. Reasons for treatment in these studies included the fellow eye being treated for type 1 ROP, concerning early structural changes in the retina, and persistent ROP at an advanced postmenstrual age (PMA).[12]

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The purpose of the present study was to determine the prevalence and characteristics of eyes treated for ROP not meeting type 1 criteria in a multicenter cohort of at-risk infants examined in North America. Through analysis of these data and discussions with site investigators, we also sought to understand the reasons for treating ROP that had not yet progressed to type 1 disease.

Subjects and Methods

This study is a secondary analysis of data collected as part of the Postnatal Growth and ROP (G-ROP) study, a multicenter retrospective cohort study of infants undergoing ROP screening at 29 hospitals in the United States and Canada between 2006 and 2012. Institutional review board approval for the study was obtained at all study hospitals.[13] Infants were enrolled if they underwent ROP screening and had a known birth weight (BW), gestational age (GA), and sufficient postnatal weight measurement data before 36 weeks' postmenstrual age (PMA), because the study's primary aim was the development of a postnatal weight gain ROP predictive model. Enrolled infants had been examined by trained pediatric ophthalmologists or retina specialists with ROP expertise, following the local institutional protocols, until retinal vascular maturity or disease regression. Data collected included BW, GA, date of birth, date at each examination, ROP examination findings (stage, zone, and presence of plus or pre-plus disease) using the International Classification of Retinopathy of Prematurity (ICROP),[14] date and type of all treatments, and extensive medical and demographic information. All treated eyes were classified as type 1 ROP, type 2 ROP, or neither type 1 nor type 2 ROP, according to the ETROP definitions described above.

The primary outcomes of the current analysis were the numbers and proportions of treated eyes that had an ROP diagnosis that was not severe enough to meet the criteria for type 1 disease ("non–type 1 ROP"). The secondary outcomes consisted of the characteristics of these eyes and the presumed reasons for treating earlier than the published guidelines. These reasons were identified based on a review of the literature, an open-ended questionnaire sent to all G-ROP investigators inquiring about potential reasons infants with ROP not meeting type 1 criteria might be treated at their institution, and detailed medical records review, including ophthalmology consult notes and ROP treatment procedure notes to ascertain the potential reasons for treating eyes with non–type 1 ROP. If applicable, a study eye could be categorized as meeting more than one reason for treatment of non–type 1 disease. Some non–type 1 treated eyes were classified as having no clear reason other than the ROP diagnosis and the treating ophthalmologist's opinion that such disease mandated treatment due to the perceived risk of adverse visual outcome if the eye were untreated.

Results

Of 7,483 infants in the G-ROP study, 1,004 eyes of 514 infants received treatment for ROP. Of 91 infants, from 24 of 29 study hospitals, 126 eyes (0.8% of all eyes in the G-ROP study, or 12.5% of all treated eyes in the G-ROP study) received treatment for non–type 1 ROP (Table 1). On average, infants with one or both eyes treated for non–type 1 ROP were treated at a developmental age 1 week's PMA later than infants treated for ROP meeting type 1 criteria in both eyes. However, these two groups did not differ significantly with respect to BW, GA, sex, maternal race or ethnicity, or birth location.

Of the 91 infants with at least one eye treated for non–type 1 ROP, 54 (59%) with one eye having non–type 1 ROP and the other having type 1 ROP were treated bilaterally, 35 (38%) with both eyes having non–type 1 ROP infants were treated bilaterally, and 2 (2%) were treated unilaterally in the eye with non–type 1 ROP (the fellow eye, which had a less severe diagnosis, was not treated). Of the 126 eyes that were treated for non–type 1 ROP, 102 (81%) had type 2 ROP and 24 (19%) had ROP not meeting criteria for either type 1 or type 2 ROP. Laser photocoagulation was used to treat 122 eyes (97%), and intravitreal injection of anti-vascular endothelial growth factor was used in 4 eyes (3%). The ICROP diagnoses for these eyes are presented in Table 2. The majority of eyes (66%) had stage 3, zone II ROP with pre-plus disease.

The reasons for treating eyes with non–type 1 ROP are provided in Table 3. The most common reason was concurrent treatment of type 1 ROP in the fellow eye (43% of eyes). Nine eyes (7%) of 5 infants were treated for structural changes concerning for an impending visual complication of ROP. Specific structural changes as documented in the medical record by the examining ophthalmologists included "traction with increased stage 3 elevation," "neovascularization elevated with traction," "risk of retinal fold," "elevated traction with possible neovascular ridge," and "traction with gliotic ridge." Four eyes (3%) of 2 infants were treated for logistical considerations, including concurrent anesthesia for non-ROP procedures and impending discharge. For example, 1 infant was found to have bilateral stage 3, zone II ROP with pre-plus disease on examination under anesthesia while undergoing neurosurgery for hydrocephalus, and the ophthalmologist decided to treat with laser photocoagulation while the patient was anesthetized "as [the] infant is at high risk of developing type 1 ROP, rather than continue with twice weekly monitoring." Another infant with bilateral stage 3, zone II ROP with pre-plus disease was treated because the "parents live too far away to follow up weekly." Some investigators indicated that they would generally treat persistent ROP or avascular retina beyond 50 weeks' PMA. However, in our sample of 126 eyes, the PMA at treatment ranged from 32 to 49 weeks, which indicates that persistent ROP beyond 50 weeks' PMA was not a reason for treatment in our cohort. Other investigators indicated that they would treat stage 3 ROP that persisted without evidence of regression for 6 weeks or more from the initial diagnosis of stage 3 disease. In our sample, 8 eyes (6%) of 4 infants met this criterion (range, 8-12 weeks). Finally, 47 eyes (38%) did not fall into any of the above categories and had no clear reason for treating non–type 1

Table 1. Demographic information for infants receiving treatment for pre-type 1 ROP in one or both eyes and for infants meeting type 1 criteria in both eyes

Characteristic	Infants receiving treatment for pre–type 1 ROP in one or both eyes (n = 91)	Infants receiving treatment for type 1 ROP in both eyes (n = 423)	*P* value
BW, g, mean ± SD	742 ± 233	709 ± 197	0.22
GA, weeks, mean ± SD	25 ± 1.6	25 ± 1.5	0.97
PMA at treatment, weeks, mean ± SD	38 ± 3.2	37 ± 2.7	0.0004
Sex, no. (%)			0.85
Female	41 (45.1)	186 (44.0)	
Male	50 (54.9)	237 (56.0)	
Maternal ethnicity, no. (%)			0.21
Hispanic or Latino	5 (5.5)	41 (9.7)	
Not Hispanic or Latino	46 (50.6)	231 (54.6)	
Unknown	40 (44.0)	151 (35.7)	
Maternal race, no. (%)			0.69
White	42 (46.2)	224 (53.0)	
Asian/Asian American	3 (3.3)	13 (3.1)	
Black/African American	25 (27.5)	90 (21.3)	
American Indian/Alaskan Native	0 (0.0)	4 (1.0)	
Native Hawaiian/other Pacific Islander	0 (0.0)	3 (0.7)	
Other	10 (11.0)	37 (8.8)	
Unknown	11 (12.1)	52 (12.3)	
Birth location, no. (%)			0.68
Inborn	43 (47.3)	210 (49.7)	
Outborn	48 (52.8)	213 (50.4)	

BW, birth weight; *ETROP*, Early Treatment of Retinopathy of Prematurity Study; *GA*, gestational age at birth; *PMA*, postmenstrual age; *ROP*, retinopathy of prematurity.

ROP other than the ROP diagnosis. Of these eyes, 38 eyes (30%) had stage 3 ROP with pre-plus disease in the treated eye, 6 (5%) had stage 3 ROP with no plus disease in the treated eye, and 3 (2%) had stage 2 ROP in the treated eye.

Discussion

In this multicenter cohort of 7,483 premature infants treated between 2006 and 2012, 12.5% of treated eyes had an ROP diagnosis that did not meet type 1 criteria. This rate is slightly higher than a previously reported rate of 9.5% of 137 treated eyes of 70 infants from 6 centers in the United States between 2006 and 2015.[12] However, our study found differences in the prevalence of different reasons for treating eyes with non–type 1 ROP. In addition, one-third of eyes treated for non–type 1 ROP in our study had no clear reason other than a diagnosis of stage 3, zone II ROP with pre-plus disease, a novel finding that suggests ophthalmologists may view this diagnosis as sufficiently high enough to warrant early treatment.

The most common reason for treating eyes before they attained type 1 criteria in the G-ROP cohort was concurrent treatment of type 1 ROP in the fellow eye. This situation occurred in 43% of the infants in our sample, a much higher rate than the 15.4% reported by Gupta and colleagues.[12] Multiple prior large ROP studies have shown a high degree of concordance between fellow eyes with acute ROP. For example, in the CRYO-ROP study, infants had threshold ROP in both eyes 38.1%-85.7% of the time, depending on postconceptional age.[15] In the ETROP study, 79.1% of infants had high-risk prethreshold disease bilaterally at the time of enrollment.[7] In the most recently completed Telemedicine Approaches to Evaluation of Acute-Phase Retinopathy of Prematurity (e-ROP) study, the severity of ROP (type 1, type 2, milder, or none) was identical in both eyes in 72.7% of imaging sessions.[16] Given the high degree of concordance between eyes, ophthalmologists may opt to treat both eyes concurrently, even if only one eye has reached type 1 ROP, given the high likelihood of developing type 1 ROP in the fellow eye. This is especially the case if the treatment modality planned is laser photocoagulation since sedation and often intubation is needed for ROP laser procedures. Concurrent treatment

Table 2. ICROP classification of 126 eyes receiving treatment for ROP not meeting ETROP type 1 criteria

ETROP Type	ICROP classification	No. eyes (%)
Type 2	Stage 3, zone II, pre-plus	83 (66)
	Stage 3, zone II, no plus or pre-plus	18 (14)
	Stage 2, zone I, no plus or pre-plus	1 (1)
Not type 1 or type 2	Stage 2, zone II, pre-plus	12 (10)
	Stage 2, zone II, no plus or pre-plus	4 (3)
	Stage 3, zone III, plus	5 (4)
	Stage 3, zone III, pre-plus	3 (2)

ETROP, Early Treatment of Retinopathy of Prematurity Study; *ICROP*, International Classification of Retinopathy of Prematurity; *ROP*, retinopathy of prematurity.

Table 3. Reasons for treatment of 126 eyes receiving treatment for ROP not meeting ETROP type 1 criteria

Reason for treatment	No. infants (%)	No. eyes (%)	No. eyes by ICROP diagnosis						
			S3Z2PP	S3Z2−	S2Z1−	S2Z2PP	S2Z2−	S3Z3+	S3Z3PP
Type 1 ROP in fellow eye	54 (59)	54 (43)	32	7	1	10	3	1	
Concerning structural changes[a]	5 (5)	9 (7)	4	4					1
Logistical considerations[b]	2 (2)	4 (3)	4						
Persistent stage 3 ROP for ≥6 weeks without regression	4 (4)	8 (6)	7	1					
Stage 3, zone III ROP with plus disease, presumably treated as if in zone II	2 (2)	4 (3)						4	
No clear reason other than diagnosis									
Stage 3 pre-plus in treated eye	19 (21)	38 (30)	36						2
Stage 3 no plus in treated eye	3 (3)	6 (5)		6					
Stage 2 in treated eye	2 (2)	3 (2)				2	1		
Total	91 (100)	126 (100)	83	18	1	12	4	5	3

ETROP, Early Treatment of Retinopathy of Prematurity Study; *ICROP*, International Classification of Retinopathy of Prematurity; *ROP*, retinopathy of prematurity; *S3Z2PP*, stage 3 zone II pre-plus; *S3Z2−*, stage 3 zone II no plus or pre-plus; *S2Z1−*, stage 2 zone I no plus or pre-plus; *S2Z2PP*, stage 2 zone II pre-plus; *S2Z2−*, stage 2 zone 2 no plus or pre-plus; *S3Z3+*, stage 3 zone III plus; *S3Z3PP*, stage 3 zone III pre-plus.
[a]Traction, retinal fold.
[b]Difficult follow-up, already under anesthesia for other procedure.

avoids the need for a second sedation, intubation, or general anesthesia for treatment of the second eye soon after the first procedure.

In our cohort, 33% of eyes treated for non–type 1 ROP had no clear reason other than a diagnosis of stage 3, zone II ROP with pre-plus disease in the worse eye (with an equal or less severe diagnosis in the fellow eye), the second most common circumstance in which non–type 1 eyes were treated. This finding suggests that some ophthalmologists continue to view this level of ROP as warranting early treatment. All of these eyes would meet criteria for type 2 ROP. In the ETROP study, treatment of eyes with type 2 prethreshold ROP did not result in improved outcomes compared to waiting for progression to threshold disease.[9] However, the ETROP study was conducted prior to the incorporation of pre-plus disease into ICROP in 2005.[14] Therefore, it is unclear whether treating type 2 eyes with pre-plus disease would result in better visual or structural outcomes.

Worrisome structural findings in the retina were the reason for treatment of non–type 1 eyes in 7% of cases. Vitreoretinal traction and risk of developing macular fold were the most commonly cited structural changes that prompted treatment. In addition to signifying a potentially developing retinal detachment, visible retinal traction on indirect ophthalmoscopy is a risk factor for the development of macular ectopia, which was correlated with worse visual outcomes in the CRYO-ROP and ETROP studies.[17-19] However, studies have not shown clearly that treating eyes with signs of retinal traction prevents the development of macular ectopia.[7,17] Concerning structural changes were a much more common reason (69%) for early treatment in the study by Gupta and colleagues.[12] This difference may be due in part to an older PMA at time of treatment. The 9 eyes in their study that underwent treatment for concerning structural changes were treated at a PMA of 38-47 weeks, which is greater than the mean PMA at treatment of infants in our study.

Prior studies have suggested that some ophthalmologists may treat eyes with persistent, active stage 3 ROP after PMA 41 weeks.[12] Fourteen (11%) eyes in our study were treated with stage 3 ROP after PMA 41 weeks, but many of these eyes had characteristics suggestive of other possible reasons, such as type 1 ROP in the fellow eye, concerning structural changes, or logistical considerations. In addition, in responses to questionnaires, G-ROP investigators suggested duration of disease might be a more important consideration than a specific PMA threshold. Six or more weeks was one cited duration after which treatment for persistent stage 3 without signs of regression would be considered. However, there are no data to evaluate the hypothesis that treating such eyes results in better visual or structural outcomes.

Strengths of this study include the geographically and racially diverse multicenter cohort representative of infants undergoing ROP examinations in North America documented using ICROP; the large sample of clinicians, whose behavior was captured through study of ROP screening at a diverse set of institutions; and the large sample of over 1,000 treated eyes.

Our study has limitations. Although there was a perceived benefit on the part of ophthalmologists to treating non–type 1 ROP, primarily stage 3 pre-plus, our study only examined clinician behavior. Therefore, while it is possible that in some circumstances earlier treatment may be beneficial with regard to visual outcomes, this hypothesis requires explicit evaluation in a prospective study. Another potential limitation is that infants may have been treated for reasons that were neither documented in consult or operative notes nor revealed to us when questioning investigators at participating hospitals. For example, scheduling constraints or availability of treating ophthalmologists could be practical factors affecting treatment decisions in some cases. Third, this study included data from 2006-2012, largely prior to the publication of the Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity (BEAT-ROP) study.[20] Practice patterns may have changed with the increased use of anti-VEGF injections, which do not require general anesthesia, making bilateral sequential treatment more practical. Finally, our study was a secondary analysis of retrospectively collected data. The data were collected by trained and certified data abstractors,[13] but there was no photographic documentation and confirmation of ROP staging, regimented screening schedules or treatment rules, or prospective documentation of treatment rationale. If some clinicians documented type 1 disease in borderline or non–type 1 cases, the actual treatment rate of non–type 1 ROP may be higher. Nevertheless, this study does provide a glimpse into the "real world" behavior of ophthalmologists making ROP treatment decisions, which might not be as well captured when ophthalmologists are aware they are being observed in a prospective study.

We found that approximately 1 in 8 treated eyes with ROP were treated for disease that did not meet the criteria for type 1 pre-threshold ROP. The most common reason was the presence of type 1 ROP in the contralateral eye, but the presence of pre-plus disease with stage 3 ROP alone constituted a substantial proportion of eyes as well. Ultimately, treatment guidelines are evidence-based suggestions for reducing the risk of an adverse visual outcome from ROP, and clinician judgment is the final arbiter for treatment decisions. Understanding the circumstances in which clinicians vary from recommendations is helpful, so that those circumstances might be considered in the development and revision of future guidelines. Such information may also possibly encourage further investigation of the potential benefit or lack of benefit of treatment of non–type 1 disease, such as pre-plus disease, nonresolving stage 3 fibrovascular tissue, or structural changes, such as traction or folds, that may develop prior to or even without progression to type 1 pre-threshold ROP.

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