Objective: To examine the frequency and timing of progression from type 2 to type 1 retinopathy of prematurity (ROP) in the Early Treatment for Retinopathy of Prematurity Study.

Methods: Infants with prethreshold ROP that was no worse than low risk in 1 or both eyes, based on the RM-ROP2 model, were examined every 2 to 4 days for at least 2 weeks. Using the Early Treatment for Retinopathy of Prematurity Study–defined classification of eyes as having type 1 or type 2 prethreshold ROP, we analyzed the time to conversion from type 2 to type 1. Data were analyzed for 1 randomly selected eye for each child.

Results: Of 294 eyes at first diagnosis of type 2 ROP, 65 (22.1%) progressed to type 1 (mean [SD] interval, 9.0 [6.6] days; median, 7.0 days). Of 217 eyes with type 2 ROP that had an examination in less than 7 days, 25 (11.5%) were diagnosed with type 1 ROP in less than 7 days. Of 200 eyes that continued to have type 2 disease at the first follow-up examination and underwent a subsequent examination, 24 (15.7%) of the 153 eyes that had an examination in <7 days) developed type 1 ROP in less than 7 days. The risk of progression from type 2 to type 1 in less than 7 days was greatest between 33 and 36 weeks' postmenstrual age, regardless of zone of retinopathy.

Conclusions: Type 1 ROP can be identified with weekly examinations in most eyes with initial diagnosis of type 2 ROP; a small subset progresses to type 1 in less than 7 days.

Trial Registration: clinicaltrials.gov Identifier: NCT00027222


Despite significant advances in the neonatal and ophthalmologic treatment of premature infants, retinopathy of prematurity (ROP) remains an important cause of childhood blindness today. Several multicenter randomized studies have been undertaken during the last 3 decades to develop ways of optimizing treatment outcomes for severe ROP. These have led to the development of strategies designed to improve the detection of sight-threatening ROP.

In the Early Treatment for Retinopathy of Prematurity (ETROP) Study, a protocol requiring more frequent screening than that typically conducted was developed to promptly identify eyes with prethreshold ROP (see Table 1 for definitions used in the ETROP Study, adapted from the International Classification of ROP). According to the ETROP Study design, eyes with prethreshold ROP were designated as having high risk or low risk for progression to an unfavorable anatomic outcome based on a risk analysis model, RM-ROP2. This model took into account not only the ROP characteristics of the eye but also demographic characteristics of the baby as well as pace of disease; it was based on data from the Cryotherapy for ROP Study. Prethreshold eyes judged to be at high risk were entered into a randomized trial comparing eyes treated at high-risk prethreshold with eyes managed conventionally (ie, either treated at threshold or observed if ROP regressed). Early treatment reduced unfavorable outcomes in eyes with high-risk prethreshold ROP. Infants whose eyes were judged to have low-risk prethreshold ROP based on the RM-ROP2 risk analysis model were examined at 2- to 4-day intervals for at least 2 weeks until the ROP began to regress or until it had progressed to high-risk prethreshold disease, making the infant eligible for randomization.

From the results of the ETROP Study, a clinical algorithm that was based only on structural characteristics of eyes with prethreshold ROP and that could be used to
make treatment and follow-up decisions was developed. Eyes were designated as having type 1 ROP if they had zone 1 ROP with plus disease; zone 1, stage 3 ROP without plus disease; or zone 2, stage 2 or 3 ROP with plus disease. Peripheral retinal ablation was recommended in these eyes. The remaining eyes with prethreshold ROP, ie, those eyes with zone 1, stage 1 or 2 ROP without plus disease or with zone 2, stage 3 ROP without plus disease, were designated as having type 2 ROP. In this article, we examine the timing and frequency of progression of eyes with type 2 ROP (based on the clinical algorithm) to type 1 ROP. These data may help examiners optimize the frequency of screening examinations required for individual infants in order to improve detection of type 1 ROP.

### METHODS

Premature infants who survived to 28 days in 26 study centers in the United States and whose birth weight was less than 1251 g had serial examinations to detect ROP. The initial examination was performed by 42 days of age, and all examinations were performed by study-certified ophthalmologists. If an infant developed ROP, informed consent was obtained from the parents for further examinations within the context of the ETROP Study protocol. Infants were enrolled from October 1, 2001, through September 30, 2002. Details of the protocol have been published previously.6,9

Briefly, routine ROP examinations were conducted to detect ROP, and when prethreshold ROP developed, a risk determination was made using the RM-ROP2 model.7 If the risk of progression in 1 or both eyes to an unfavorable structural (anatomic) outcome in the absence of treatment was determined to be 15% or higher (high-risk prethreshold), the parents of the infant were offered entry in the randomized trial in which the eye selected at random was the eye with no ROP or ROP that was less than prethreshold. This left 294 infants with ROP that was less than prethreshold. There were 828 infants who developed prethreshold ROP in 1 or both eyes. Table 2 shows the ROP characteristics of these infants. At the time of the first examination documenting prethreshold disease, the prethreshold ROP was high risk in 1 or both eyes of 411 infants, who were eligible for enrollment in the randomized ETROP Study. The remaining 417 infants had low-risk prethreshold ROP in 1 or both eyes. Among these 417 infants with low-risk prethreshold ROP, 23 had ROP that met the criteria for type 2 ROP in the worse eye or in both eyes. One eye was randomly selected for this analysis for these 394 infants. For eyes with type 2 prethreshold ROP that progressed to type 1 in an interval less than 1 week, the number of days following the previous disease designation was documented and the timing of conversion was grouped by postmenstrual age in weeks.

### RESULTS

There were 828 infants who developed prethreshold ROP in 1 or both eyes. Table 2 shows the ROP characteristics of these infants. At the time of the first examination documenting prethreshold disease, the prethreshold ROP was high risk in 1 or both eyes of 411 infants, who were eligible for enrollment in the randomized ETROP Study. The remaining 417 infants had low-risk prethreshold ROP in 1 or both eyes. Among these 417 infants with low-risk prethreshold ROP, 23 had ROP that met the criteria for type 1 ROP; the remaining 394 had ROP that met the criteria for type 2 ROP in the worse eye or in both eyes. One eye was randomly selected for this analysis for these 394 infants. For 100 infants who had type 2 ROP in only 1 eye, the eye selected at random was the eye with no ROP or with ROP that was less than prethreshold. This left 294 eyes with type 2 ROP that were included in the current analyses. Among the 294 eyes with low-risk prethreshold ROP that was type 2 at the first examination, 65 (22.1%) developed type 1 disease. The mean (SD) interval between first diagnosis of type 2 ROP and the diagnosis of type 1 ROP was 9.0 (6.6) days (median, 7.0 days).

The 294 eyes that had low-risk prethreshold ROP with type 2 characteristics had a protocol-mandated ophthalmoscopic examination every 2 to 4 days for at least 2...
weeks. As shown in Table 3, between the first and second examinations, 25 eyes (11.5% of the 217 that had a second examination in <7 days) were diagnosed with type 1 ROP within less than 7 days of diagnosis of type 2 ROP. Most of these eyes (23 eyes) were in the group examined within the study-required maximum reexamination limit of 4 days after detection of low-risk prethreshold ROP. Also shown in Table 3 are data indicating that on a second follow-up examination of 200 of the 202 eligible eyes that continued to have type 2 ROP, 24 eyes (15.7% of the 153 that had a second follow-up examination in <7 days) had developed type 1 ROP within less than 7 days from the previous examination.

The timing of diagnosis of type 1 ROP by postmenstrual age is shown in Table 4. The risk of conversion from type 2 to type 1 ROP in less than 7 days was greatest between 33 and 36 weeks' postmenstrual age. However, there were a few eyes with type 2 ROP in zone 2 that converted to type 1 ROP even through 43 to 44 weeks' postmenstrual age. The late conversion to type 1 ROP that occurred in some eyes is not due to missed examinations, since all eyes shown in Table 4 with conversion had an examination that showed type 2 ROP less than 7 days prior to the examination that showed type 1 ROP.

### Table 2. Status of Selected Eyes for All Patients Who Developed Prethreshold Retinopathy of Prematurity in 1 or Both Eyes

<table>
<thead>
<tr>
<th>Status</th>
<th>Patients, No.</th>
<th>Eyes, No.</th>
<th>Progression From Type 2 to Type 1 ROP, Mean (SD) [Median], d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prethreshold patients, total</td>
<td>828</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First prethreshold examination high risk in 1 or both eyes</td>
<td>411</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First prethreshold examination low risk in both eyes or 1 eye low risk and 1 eye not prethreshold</td>
<td>417</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First examination type 1 ROP in 1 or both eyes</td>
<td>23</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First examination type 2 ROP with neither eye type 1</td>
<td>394</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never progressed to type 1 ROP</td>
<td></td>
<td>229b</td>
<td></td>
</tr>
<tr>
<td>Progressed to type 1 ROP</td>
<td></td>
<td>65b</td>
<td>9.0 (6.6) [7.0]</td>
</tr>
<tr>
<td>Not prethreshold ROP</td>
<td></td>
<td>100</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: ROP, retinopathy of prematurity.

a One eye randomly selected.
b These are the only eyes included in Table 3 and Table 4.
c The randomly selected eye was less than prethreshold in these patients in whom only 1 eye developed prethreshold ROP.

**Table 3. Days From First or Second Diagnosis of Type 2 Prethreshold Retinopathy of Prematurity to the Next Examination for Selected Low-Risk Prethreshold Eyes With Type 2 Retinopathy of Prematurity; Characteristics at the First Examination and Status at the Next Examination**

<table>
<thead>
<tr>
<th>Time From First or Second Diagnosis of Type 2 ROP to Next Examination, d</th>
<th>Type 1 ROP</th>
<th>Type 2 ROP</th>
<th>Not Prethreshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>First diagnosis[a]</td>
<td>Status at second examination</td>
<td>Status at third examination</td>
<td></td>
</tr>
<tr>
<td>1-4</td>
<td>23 (12.7)</td>
<td>134 (74.0)</td>
<td>24 (13.3)</td>
</tr>
<tr>
<td>5-6</td>
<td>2 (5.6)</td>
<td>27 (75.0)</td>
<td>7 (19.4)</td>
</tr>
<tr>
<td>≥7</td>
<td>7 (9.7)</td>
<td>41 (56.9)</td>
<td>24 (33.3)</td>
</tr>
<tr>
<td>Total</td>
<td>32</td>
<td>202</td>
<td>55</td>
</tr>
<tr>
<td>Second diagnosis[b]</td>
<td>Status at third examination</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-4</td>
<td>18 (14.9)</td>
<td>86 (71.1)</td>
<td>17 (14.0)</td>
</tr>
<tr>
<td>5-6</td>
<td>6 (18.8)</td>
<td>21 (65.6)</td>
<td>5 (15.6)</td>
</tr>
<tr>
<td>≥7</td>
<td>2 (4.3)</td>
<td>35 (74.5)</td>
<td>10 (21.3)</td>
</tr>
<tr>
<td>Total</td>
<td>26</td>
<td>142</td>
<td>32</td>
</tr>
</tbody>
</table>

Abbreviation: ROP, retinopathy or prematurity.

[a] Five of 294 eyes with type 2 prethreshold ROP at the first examination did not have a second examination.
b Two of 202 eyes with type 2 prethreshold ROP at the second examination did not have a third examination.

Improved outcomes reported for the ETROP Study, which enrolled only infants with birth weights less than 1251 g, are based on a study design requiring ROP examinations that were more frequent than conventional ROP examination schedules. The purpose of this increased examination frequency was to allow maximum separation of earlier-treated eyes from conventionally managed eyes (ie, eyes treated only if threshold severity was reached). The study protocol also required treatment within 48 hours for eyes with high-risk prethreshold ROP that were randomized to earlier treatment. This, too, was an integral part of a study design that attempted to maximize the difference in treatment times between earlier-treated and conventionally managed eyes.

**COMMENT**

Improved outcomes reported for the ETROP Study, which enrolled only infants with birth weights less than 1251 g, are based on a study design requiring ROP examinations that were more frequent than conventional ROP examination schedules. The purpose of this increased examination frequency was to allow maximum separation of earlier-treated eyes from conventionally managed eyes (ie, eyes treated only if threshold severity was reached). The study protocol also required treatment within 48 hours for eyes with high-risk prethreshold ROP that were randomized to earlier treatment. This, too, was an integral part of a study design that attempted to maximize the difference in treatment times between earlier-treated and conventionally managed eyes.
The results of the ETROP Study have raised interest in the optimal timing and frequency of screening examinations. Previous studies of treatment of ROP, including the Cryotherapy for ROP Study and the Supplemental Therapeutic Oxygen for Prethreshold ROP study, were not designed with such tight follow-up criteria. In the former, follow-up of near-treatment-level ROP was indicated in a week or less; in the Supplemental Therapeutic Oxygen for Prethreshold ROP study, follow-up was weekly at most. The ETROP Study, on the other hand, was designed to address the importance of treating eyes with slightly less severe ROP than the threshold severity that had demonstrated benefit from retinal ablation. Therefore, shorter follow-up intervals were designed as part of the trial to separate 2 treatment arms of the ETROP Study as much as possible. The analysis reported here examines the rate and timing of progression from type 2 ROP to type 1 ROP and might be interpreted as providing data that suggest more frequent ROP examinations would be worthwhile. However, the ETROP Study was not designed to test the effect of increasing the frequency of ROP examinations, and study investigators did not follow a rigid schedule of when to perform examinations. Further, the ETROP Study was not designed to determine whether a delay in detection and treatment of type 1 ROP had a detrimental effect on the ultimate visual or structural outcome of the eye. It was also not designed to address when to stop examining the infant, although investigators tended to rely on a previous article that stated that the risk of developing serious disease was minimal if there were 3 “signs of retinal vascular maturation: full retinal vascularization into zone 3, and mild stage 1 or 2 ROP first developing in zone 3.”

These observations highlight a weakness of the current analysis. To define more precisely the timing of progression of eyes with type 2 ROP to type 1 ROP, more frequent and rigidly controlled follow-up ROP examinations would be required. Thus, the results of the present study must be interpreted cautiously with this limitation in mind.

The analysis presented in this article shows that progression to type 1 ROP occurs at an interval of a week or more in most eyes that have type 2 ROP. However, eyes that are newly diagnosed with type 2 ROP have approximately a 12% to 16% risk of developing type 1 disease within 6 days, and this risk extends to at least the second follow-up examination. Risk of rapid progression from type 2 to type 1 ROP beyond the second follow-up examination cannot be estimated because of the limitations of the protocol. The risk of rapid progression appears greatest between 33 and 36 weeks' postmenstrual age, but the risk of progression to ROP requiring treatment extends through 43 to 44 weeks' postmenstrual age; however, such progression is rare after 41 weeks.

This study has not addressed whether examinations at intervals more frequent than weekly would result in better visual or structural outcomes in eyes with type 2 ROP. However, data from the ETROP Study do offer some information about the timing and frequency of progression to type 1 disease. Other variables play a role in rapid progression from type 2 ROP to type 1 ROP, including postmenstrual age at onset of disease and rate of progression of retinopathy. These and other factors must guide clinical judgment in scheduling screening examinations for ROP. In addition, it seems prudent to recall that infants enrolled in the ETROP Study all had birth weights less than 1251 g and were cared for in neonatal intensive care units in the United States. Thus, timing intervals and screening criteria may not be generalizable to other countries, especially those with rapidly developing neonatal care systems.

Recent ROP examination guidelines published by the American Academy of Pediatrics, the American Academy of Ophthalmology, and the American Association for Pediatric Ophthalmology and Strabismus have taken findings from the ETROP Study into consideration. These guidelines were developed by experts in the field to aid ophthalmologists in determining the frequency of ROP examinations. Findings in this article complement these guidelines and offer data that may help nurseries and ophthalmologists determine optimal timing for ROP examinations. Clinical judgment will allow ophthalmologists to develop an appropriate approach to ROP examinations for the individual infant.
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REFERENCE


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