

Preliminary Results of Treatment of Eyes With High-Risk Prethreshold Retinopathy of Prematurity in the Early Treatment for Retinopathy of Prematurity Randomized Trial

FOR SOME time retinopathy of prematurity (ROP) has been the subject of intense research activity. Experimental studies have increased our understanding of normal and abnormal retinal vascular development particularly with respect to the roles of oxygen-influenced vascular endothelial growth factor^{1,2} that works synergistically with oxygen-independent insulinlike growth factor 1.³ A low serum insulinlike growth factor 1 is said to predict ROP.³ However, insulinlike growth factor 1 is expressed by many tissues and the low serum level, therefore, could be a general marker of a sick infant at risk of ROP rather than a specific marker for retinal disease.⁴ Oxygen remains firmly center stage in ROP pathogenesis, and concomitant with basic studies, neonatal research is exploring the safe upper and lower limits of arterial oxygen saturation. Looking first at higher levels, a randomized controlled trial, comparing arterial oxygen saturation ranges of 91% to 94% with 95% to 98%, reported no difference in infant growth, neurodevelopment, or rates of ROP.⁵ Exploring “what constitutes the lower safe limit”^{6(p366)} was stimulated, in part, by a recent study, showing that infants with target arterial oxygen saturation levels of 94% to 98% (but not measured) had a much higher incidence of ROP requiring treatment compared with those reared in target arterial oxygen saturation levels of 70% to 90%, with no increase in neurological morbidity in the latter group.⁶ A different outcome to the increased neonatal deaths was reported 30 years ago, that resulted from the policy of restricting inspired oxygen in incubators to prevent ROP.⁷

*See also pages 1684
and 1697*

Progress in the treatment of severe ROP has been nothing short of revolutionary. The International Classification of ROP (ICROP) in 1984⁸ provided the first description of this condition that allowed detailed comparison between medical centers and so generated a wave of clinical research that continues today, making ROP one of the most robust evidence-based subjects of ophthalmology. For the first time in 1988 the preliminary results of the Multicenter Trial of Cryotherapy for Retinopathy of Prematurity (CRYO-ROP) demonstrated that treatment is effective in reducing ROP-induced blindness.⁹ It really is difficult to overestimate the effect of this research—one of the milestones in pediatric ophthalmology.

The follow-up of the CRYO-ROP study cohort has shown that the beneficial effect of cryotherapy is main-

tained long-term.¹⁰ However, it has also demonstrated that this treatment is no panacea, because 10 years after treatment 45.4% of the treated eyes had a visual acuity of 20/200 or worse. The indication for treatment in the CRYO-ROP study was threshold ROP, when the risk of blindness untreated was about 50%.⁹ Threshold was defined as 5 or more continuous or 8 cumulative clock hours of stage 3 ROP in zone I or II in the presence of plus disease (ie, dilation and tortuosity of posterior pole retinal vessels in at least 2 quadrants, meeting or exceeding that of a standard photograph). This has remained unchanged for the past 15 years, although there has been an informal trend toward early treatment. All this led to the design of the Early Treatment for Retinopathy of Prematurity (ETROP) Randomized Trial whose preliminary findings are reported in this issue of the ARCHIVES.^{11,12} The prethreshold ROP criteria were set as follows: zone I, any ROP less than threshold; zone II, stage 2 with plus disease and stage 3 without plus disease; and stage 3 with plus disease but less than threshold. At prethreshold ROP, data derived from the natural history cohort of the CRYO-ROP study were entered into a computerized risk model (RM-ROP2) to determine if there was a high ($\geq 15\%$) or low risk ($< 15\%$) of progression to retinal detachment. High-risk eyes were randomized to prethreshold early treatment or conventional management (treatment at threshold) and low-risk eyes were followed up conservatively.

The RM-ROP2 risk model was highly effective in predicting the behavior of high- and low-risk eyes of progressing to retinal detachment. Overall, ETROP reports that early treatment significantly improved both functional and structural outcomes. The eyes that benefited structurally most from early treatment were those with especially aggressive disease, that is, zone I, stage 3 ROP. Less dramatic benefits for structure and function were observed in zone I, stages 1 and 2 ROP without plus disease, and zone II, stage 3 ROP with plus disease, while treatment of zone II, stage 2 ROP with plus disease demonstrated benefit only in structural outcome.

Functional outcome in ETROP, as in CRYO-ROP, was measured by gratings. This was one of the most exciting spin-offs of CRYO-ROP for it promoted a child-centered approach to clinical practice and research and greatly increased interest in quantifying the vision of children. The behavioral grating test of visual acuity is influenced by factors that are not the direct consequence of ROP such as nystagmus and neurological insults. This does not reflect test deficiency but rather the complexity of the substrates that contribute to a behavioral re-

sponse compared with ophthalmoscopic assessment of retinal structure. In addition, vision assessment must be placed in the context of the developing infant; the deficit will only become measurable when the age-normal visual acuity exceeds the limit imposed by the retinal damage—at which point visual development will become asymptotic. At an early stage of visual development, one cannot assume that a moderate visual deficit would be measurable, so it is likely that with time, some of the visual acuities currently reported by ETROP to be normal at 9 months of age will fail to develop normally and subsequently fall outside the normal range.

Posterior ROP (zone I) is particularly aggressive. In CRYO-ROP prethreshold zone I disease was observed in only 7%, but the incidence was much higher in the Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity (STOP-ROP) Trial¹³ and in ETROP it affected 23% of the eyes. Although almost all of these eyes were classified by the model as high risk, intriguingly in ETROP zone I disease displayed a more benign course than previously observed. The temporal behavior of ROP progression was similar in 2 randomized controlled studies separated by 1 decade.¹⁴ The higher incidence of zone I disease may in part reflect the improved survival of the most immature infants. Another possibility is the increased recognition that zone I ROP does not always present with the classic morphologic features and progress through stages 1 through 3. Hopefully, this will be included in the revisions to ICROP that are being considered.

Mathematical expertise of the highest quality, to implement the RM-ROP2 risk model, is not always immediately in hand at the crib side. So, it is especially helpful that the preliminary report of ETROP contains a simple clinical ICROP-based algorithm that supports the clinician when deciding whether an infant requires treatment. The following criteria have been set for eyes with type 1 or type 2 ROP. Type 1 ROP is defined as follows: zone I, any stage of ROP with plus disease; zone I, stage 3 with or without plus disease; or zone II, stage 2 or 3 with plus disease. Type 2 ROP is defined as follows: zone I, stage 1 or 2 with no plus disease; or zone II, stage 3 with no plus disease. In addition to treatment at threshold, according to ETROP, intervention should be considered for type 1 prethreshold ROP, whereas eyes with type 2 prethreshold ROP can be followed up conservatively and treated only if there is progression either to type 1 prethreshold ROP or threshold ROP. Had the ICROP-based algorithm been used in this study instead of the RM-ROP2, it would have resulted in 38% fewer high-risk neonates or infants being treated and with no increase in unfavorable outcome. On the not so safe assumption that ROP behaves identically now as it did in the mid 1980s of the CRYO-ROP study, it is anticipated that early treatment will result in 8% of the infants weighing less than 1251 g requiring intervention, an increase of 2%. But this highlights the dilemma of ROP research, balancing long-term benefits to sight against the increased examinations required to identify neonates and infants timously and also the greater risk of systemic complications from performing treatment at an early age.

Blindness from ROP is largely preventable. It is responsible for 5% to 8% of childhood blindness in high-

tk;3income countries, whereas in middle-income countries this rises to about 40% and affects infants with a wider range of birth weight and gestational age.¹⁵⁻¹⁷ This greatly increases the requirement for screening in countries where ophthalmic expertise is particularly sparse—one of the greatest challenges to reduce ROP-induced blindness worldwide. There is no easy fix to this screening dilemma, but ETROP offers more than a glimmer of hope for the future. The presence of plus disease (retinal arteriolar tortuosity and venous congestion) is one of the key differences between type 1 and type 2 prethreshold ROP as defined by ETROP that requires treatment or observation, respectively. But the diagnosis of plus disease, especially if mild, is far from easy and remains one of the least robust aspects of ROP diagnosis.¹⁸ We have just entered an exciting era of ROP research in which clinical observations can be measured and some components of plus disease can be quantified from digitized photographs,¹⁹ or semiautomatically directly from digitally acquired images.^{20,21} There is still some way to go, but it hardly needs a crystal ball to envisage, that in the foreseeable future, an automatic objective measure of plus disease could be obtained from 1 digital image of the vessels close to the optic disc. Screening could then be undertaken by nonmedical personnel and the expert ophthalmologist consulted only, via telemedicine, when plus disease is present. Perhaps this will become an example of how technological advance can promote access to health in countries with limited health resources.

The ETROP has grown out of CRYO-ROP and is a logical development from that groundbreaking study. Building on this research expertise and the unique database so created has permitted the development of risk models that will have major impact on clinical practice. The further refining of the indications for treatment by ETROP will undoubtedly improve the outcome of many neonates and infants with severe ROP.

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ARCHIVES Web Quiz Winner

Congratulations to the winner of our August quiz, Norman C. Charles, MD, New York University Medical Center, New York, NY. The correct answer to our August challenge was conjunctival sarcoidosis. For a complete discussion of this case, see the Clinicopathologic Reports, Case Reports, and Small Case Series section in the September ARCHIVES (Akpek EK, Ilhan-Sarac O, Green WR. Topical cyclosporin in the treatment of chronic sarcoidosis of the conjunctiva. *Arch Ophthalmol*. 2003;121:1333-1335.

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