Laser Therapy Versus Anti-VEGF Agents for Treatment of Retinopathy of Prematurity

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Introduction

Retinopathy of prematurity (ROP) is characterized by abnormal retinal neurovascular development that occurs in preterm infants. Although in high-income countries up to 8% of childhood blindness is due to ROP, in middle-income countries this number rises to 40%.[1] Moreover, as methods to ensure survival of preterm infants improve, the prevalence of ROP continues to increase.[2,3] Worldwide, approximately 10% of births occur before the full gestational age defined as 37 weeks. The risk of developing ROP is inversely proportional to the infant's gestational age and to its weight at the time of delivery, with most cases occurring in infants born at earlier than 28 weeks of gestation and weighing <1251 g.[2,4] Although studies looking at ROP prevalence in various developed-world countries differ in the selection criteria for the infants at risk, incidence of any ROP ranges from 33% to 73%, whereas severe ROP was reported in 10% to 26% of patients.[2]

Understanding the pathology of ROP and its current treatments requires an understanding of the normal retinal vascular development. Retinal angiogenesis in humans begins at approximately 16th week of gestation, with vessels growing from the optic disc radially outwards. Normally, new vessels grow out from existing ones until they reach the ora serrata at around the time of full-term birth. In utero, the development of the sensory retina outpaces that of the retinal vasculature, and the resulting physiological hypoxia leads to the secretion of vasoactive factors such as vascular endothelial growth factor (VEGF), which, in turn, stimulate blood vessel growth.[5]

Premature birth, however, can disrupt normal retinal development and result in ROP. Two phases of ROP have been described.[3] Phase I is characterized by the arrest of normal retinal vessel growth after a

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preterm birth. This arrest is thought to be due to exposure of the developing eye to nonphysiological hyperoxia of ambient air; in addition, the eye loses the nutrients and growth factors vital to orderly retinal angiogenesis that would have been supplied by the mother. In the subsequent phase II, metabolic demands of the developing retina lead to upregualtion of hypoxia-induced factors and to neovascularization at the border of vascularized and avascular retina. In severe cases, the neovascularization undergoes cicatricial changes that lead to partial or total retinal detachment and even blindness.

■ ROP Classification

The International Classification of ROP describes the severity of this disease based on location, stage, and extent.[6] For the purposes of localizing the disease, the retina is divided into 3 zones. Zone I, the posterior pole, is the retina within a circle centered on the optic disc with a radius equal to twice the disc-macula distance; zone II is concentric with zone I, whereas its radius extends to the distance from the disc to the nasal ora serrata; and zone III comprises the remaining crescent of temporal retina.

Staging of ROP is based on the appearance of the clinically visible demarcation between the vascularized and avascular retina. This demarcation is a flat line in stage 1, a raised ridge in stage 2, and extraretinal neovascular proliferation overlying the ridge in stage 3. In more severe ROP, marked arterial tortuosity and venous engorgement are seen; this is called ''plus disease'' and is thought to be due to shunting through the areas of neovascularization. Presence of stage 3 ROP with plus disease in either 5 contiguous or 8 total clocks hours within zones I or II indicates ''threshold disease''—disease with a 50% chance of progression to retinal detachment and very poor visual prognosis.[6,7] Retinal detachment is divided into subtotal (stage 4 ROP) or total detachment (stage 5 ROP).

■ First Attempts of ROP Treatment: Retinal Cryoablation

The first widely studied treatment for ROP was ablation of non-vascularized retina by cryotherapy. In the CRYO-ROP study, 291 premature infants with bilateral threshold disease had 1 eye treated with cryotherapy, whereas the other served as control.[8] The initial results were encouraging, and at 10-year follow-up, cryotherapy showed significantly better visual acuity and fundus anatomy in the treated eyes.[9] Treatment reduced blindness by 17% and total retinal detach-

ment by 20%; as expected, it constricted the visual fields somewhat (by ~7%) but had no effect on contrast sensitivity.

Nevertheless, a disturbingly high percentage of treated eyes, 44.4%, had visual acuity of 20/200 or worse, including no light perception. The authors acknowledged that the high percentage may reflect the severity of ROP at the time of treatment, although they argued that "treatment of milder ROP will result in unnecessary treatment of a substantial number of eyes," and that improved outcomes of eyes treated earlier in the course of the disease may be due to improved prognosis in these eyes even without treatment.[9]

■ Risk Stratification

Consequently, the natural history of infants in the CRYO-ROP study was examined retrospectively to determine the risk factors for progression from prethreshold to threshold disease.[10] Prethreshold eyes were defined as having any ROP in zone I; stage 2 ROP with plus disease in zone II; or stage 3 ROP in zone II without plus disease or with plus disease but with neovascularization that spans fewer than 5 contiguous or 8 total clock hours. A computerized risk-model algorithm (called RM-ROP2) was devised for evaluating these risk factors. The model considered race, birth weight, and gestational age, as well as location and severity of ROP at the time of diagnosis. In subsequent studies, eyes that were predicted by the algorithm to have a ≥15% chance of developing an unfavorable outcome such as retinal detachment or blindness were dubbed high risk, whereas low-risk eyes were those predicted to have a <15% chance of developing an unfavorable outcome.

The most significant factors in determining the risk of disease progression were the location and severity of ROP at the time of diagnosis. This finding allowed the formation of a simpler and more practical system of risk stratification, based entirely on the ocular features of the disease and not relying on computerized modeling. Prethreshold ROP eyes were described as either type 1 or type 2. The higher risk type 1 eyes are characterized by the presence of any stage ROP with plus disease in zone I, or stage 3 disease without plus disease also in zone I, or stage 2 with plus disease in zone II. Of these, 63% progressed to threshold disease and 36% had an unfavorable structural outcome at 3 months. In contrast, the lower risk type 2 eyes are characterized by the presence of stage 1 or 2 disease without plus disease in zone I, or stage 3 disease without plus disease in zone II. Of these, only 14% progressed to threshold disease and only 5% had an unfavorable structural outcome at 3 months.[10]

■ Treatment of ROP Using Laser Therapy: The Early Treatment for Retinopathy of Prematurity (ETROP) Study

Now that it was possible to identify high-risk prethreshold eyes, investigators hypothesized that treating them earlier would result in improved functional outcomes. The ETROP study was organized to test this hypothesis.[11] In this study, infants weighing <1251 g at birth were screened for prethreshold ROP within 6 weeks of birth. Eyes with prethreshold ROP were evaluated using the RM-ROP2 algorithm described above. High-risk prethreshold eyes were randomized either to "early treatment"—retinal ablation within 48 hours of diagnosis, or to "conventional treatment"—observation and subsequent cryoablation if threshold disease developed. Of note, early treatment was performed by laser therapy, since by the time the ETROP study was initiated it had been shown to result in better visual outcomes and fewer adverse effects than cryotherapy. Low-risk prethreshold eyes were followed until ROP regressed or until high-risk features were identified. At 9 months of corrected age, functional outcome was evaluated by Teller grating acuity cards, and retinal structural outcome was determined by dilated fundus examination.[11]

Altogether, 828 infants were identified as having prethreshold disease, of whom 401 had high-risk features and were randomized to the 2 treatments as described above. At 9 months of age, although unfavorable visual acuity (defined as >4 SDs below the age-appropriate mean) was seen in 19.5% of the eyes managed conventionally, it was seen only in 14.5% of the eyes treated early ($P = 0.01$). The data for retinal structural outcomes were even more encouraging: unfavorable outcomes (defined as a macular fold, retinal detachment involving the macula, or a retrolental tissue obscuring the posterior pole) were seen in 15.6% of the eyes managed conventionally, but only in 9.1% of the eyes treated early ($P<0.001$).[11]

A follow-up reassessment of visual and anatomic outcomes was performed at 6 years.[12,13] Unlike at the age of 9 months, no significant difference in visual acuity was found between eyes treated early by laser or conventionally by cryotherapy. However, when visual acuity outcomes were subdivided by prethreshold severity types, a statistically significant benefit of early treatment was seen in type 1 eyes, where early treatment resulted in an unfavorable outcome in 25.1%, whereas conventional management resulted in an unfavorable outcome in 32.8%. The highest benefit was noted in eyes with the highest burden of disease at the time of diagnosis; conversely, there was no statistical difference in visual acuity outcomes between early and conventional treatment in the least-affected type 2 eyes. Interestingly, the benefit of early treatment on structural outcome continued to persist at 6 years for all eyes, although, again, it

was most pronounced in eyes with the more severe or extensive forms of ROP.[12,13]

■ Treatment of ROP Using Anti-VEGF Agents: The BEAT-ROP Study

The mechanism of action for both cryotherapy and laser treatment is the destruction of cells in the avascular retina that produce vasoactive compounds such as VEGF. A more direct and rapid approach to counteracting VEGF activity became available in 2004, when the Food and Drug Administration approved the use of the monoclonal anti-VEGF antibody, bevacizumab, in treatment of metastatic colon cancer. Soon, it was used off-label for ophthalmologic diseases characterized by neovascularization,[14] and reports on its use in severe ROP began appearing soon thereafter (see Wallace and Wu,[15] table 1). The BEAT-ROP (bevacizumab eliminates the angiogenic threat of ROP) study was the first, and to date, the only randomized, prospective trial to assess the efficacy of this agent in treatment of ROP.[16]

The highest rates of disease recurrence after ablation treatment were previously noted in eyes affected by stage 3 ROP with plus disease located within zone I (up to 50% recurrence) or posterior zone II (up to 20%).[11] Consequently, 150 infants with this disease burden were randomized to either conventional laser treatment or intravitreal injection of bevacizumab, with the primary outcome of the study defined as recurrence of neovascularization at 54 weeks of postmenstrual age. The rate of ROP recurrence was significantly higher in infants with zone I disease treated by laser (42%) than in those treated with bevacizumab (6%, $P = 0.003$). In infants with posterior zone II disease, a higher recurrence rate with laser treatment was also observed (12% vs. 5% with bevacizumab), but the difference was not statistically significant ($P = 0.27$). This may be at least in part due to the study sample not being large enough to detect such a difference; the investigators predicted a need for at least 50 participants per each zone II treatment group, but were able to enroll only about 40 patients per group. Nevertheless, the rate of recurrence with laser treatment remained significantly higher when both zone I and posterior zone II data were examined together (26% vs. 6% with bevacizumab, $P = 0.002$). Finally, in contrast to ablation therapy, bevacizumab eyes showed continued vascular growth into the peripheral retina.[16]

Importantly, the initial report from the BEAT-ROP group did not show visual outcomes, making it difficult to compare the functional significance of its results to those of the ETROP study. Although not equivalent, participants' refractive outcomes at 2.5 years of age were recently reported.[17] Approximately 70% of children who had been

enrolled in the original study underwent cycloplegic refraction, and the eyes of children who were treated with bevacizumab had significantly less spherical equivalent (SE) refractive error than those who received laser. In eyes with zone I ROP, the mean SE (± SD) was −1.51 ± 3.42 D for those treated with bevacizumab and −8.44 ± 7.57 D for those treated with laser ($P<0.001$); for posterior zone II ROP, the mean SE (± SD) was −0.58 ± 2.53 D for those treated with bevacizumab and −5.83 ± 5.87 D for those treated with laser ($P<0.001$).

Myopia of prematurity is thought to be due to altered anatomy of the anterior segment, including corneal steepening, shallowing of the anterior chamber, and increased lenticular thickness.[18] Because bevacizumab allows for subsequent retinal vascular growth anteriorly, BEAT-ROP investigators make an intriguing speculation that bevacizumab treatment may result in less myopia by creating an improved growth factor milieu necessary for normal anterior segment development.[17]

■ Laser Treatment Versus VEGF Antagonists for ROP

Publication of the BEAT-ROP study sparked a lively debate among pediatric ophthalmologists and pediatric retina specialists regarding the optimal treatment of acute ROP. In addition to addressing the limitations of the BEAT-ROP study itself, this debate also questions the wisdom of using bevacizumab, and anti-VEGF agents in general, for treatment of ROP.

A persistent critique about the BEAT-ROP study was its lack of protection against investigator bias, as its primary outcome, ROP recurrence, was dependent on decisions made by unmasked investigators.[15,19] In an attempt to increase the rigor of the study, BEAT-ROP investigators included ophthalmologists at an independent reading center who were masked to the treatment, but their contribution to assessing ROP recurrence was limited[16] and investigator bias remains a concern. The study population size was much smaller than that of CRYO-ROP or ETROP studies; as described above, it was too small even to detect whether bevacizumab treatment was beneficial in zone II disease, one of the stated goals of the study. Furthermore, the patient population in BEAT-ROP was >50% Hispanic; white and black patients each constituted ~20% of the study population. Although Hispanic and white non-Hispanic children have been previously reported to have similar susceptibility to ROP, the course of disease in the 2 groups was significantly different.[20] Given that genetic factors may play a significant role in ROP susceptibility and progression,[21,22] the results of this study may not be applicable to other populations. Another puzzling aspect of the BEAT-ROP trial is its lack of visual acuity assessment. As the purpose of ROP treatment is to preserve sight, such an assessment seems

essential; reporting refraction outcomes[17] is insufficient, and unfortunately does not facilitate a direct comparison of outcomes of this study to those of prior ones.

Another important criticism of treating ROP with bevacizumab is that in the BEAT-ROP study, the time to recurrence of ROP was significantly longer in the bevacizumab-treated infants (16.0 ± 4.6 wk after treatment) than in those who received laser retinal ablation (6.2 ± 5.7 wk).[16] Indeed, ROP recurrence after bevacizumab has been observed as late as 35 weeks after treatment (~69 wk of postmenstrual age),[23] a finding that emphasizes the need for prolonged follow-up of children treated with bevacizumab. Such extended follow-up, however, may be hampered by poor parental compliance.[24] In addition, fundus examinations would become more difficult as patients age and may eventually require examinations under anesthesia. Of note is the fact that the BEAT-ROP study followed up only out to 54 weeks postmenstrual age. The very late recurrences in the bevacizumab group might have been missed at this end point.

Perhaps the most important criticism, however, concerns the lack of safety data regarding bevacizumab. Broad knockdown of VEGF causes retinal cell apoptosis and outer nuclear layer thinning in animal models of ROP,[25] and repeated administration of anti-VEGF agents may contribute to geographic atrophy in adult patients.[26] Its effect on long-term retinal health in preterm infants remains unknown. In addition, intravitreal bevacizumab is known to penetrate systemic circulation and cause a decrease in serum VEGF levels for 2 weeks or longer after administration.[15,27] Reducing VEGF levels systemically in a premature infant is likely to disrupt the development of a variety of organs, including brain, lungs, and kidneys.[22] The effect of VEGF deprivation on the developing brain in premature infants is unknown. Furthermore, citing the importance of VEGF for lung development, several groups expressed concerns that 4 of 5 infant deaths in the bevacizumab arm of the BEAT-ROP study were due to pulmonary problems.[27,28] Although a 50% dilution of the adult bevacizumab concentration was used in the BEAT-ROP study, it has been pointed out that a preterm infant's vitreous volume is one fourth that of an adult, and an infant's blood volume is <3% of that of an adult.[22] Bevacizumab escaping into systemic circulation in an infant may thus reach much higher concentrations than it would in an adult.

Problematic though it may be, ROP treatment with anti-VEGF agents has several distinct advantages over laser therapy. First, anti-VEGF agents immediately reduce ocular and intravitreal levels of VEGF, and may therefore be more effective in severe, aggressive disease; in contrast, retinal ablation destroys VEGF-producing cells, but is not expected to affect elevated VEGF levels present in the vitreous gel. Anti-VEGF agents also seem to allow more extensive development of the

retina anteriorly, where it may exert normalizing influence on the developing anterior segment and prevent myopia of prematurity. By avoiding ablation of the peripheral retina, anti-VEGF treatment may preserve the subjects' peripheral visual fields. Unlike laser therapy, intravitreal injection may be performed in infants with opaque cornea, lens, or vitreous, or in patients with poorly dilating pupils. Finally, it is important to emphasize the ease of intravitreal injection for both the infant and the ophthalmologist, even into the eyes of a premature infant. In contrast, laser treatment causes significant stress both to the treated eyes and to the infant as a whole, usually requiring intubation, sedation, and anesthesia. This would be a significant factor in medically unstable infants. In addition, significantly more training and equipment is necessary for laser ablation therapy.[29]

■ Future Directions

It seems that if bevacizumab is to be used more widely going forward, a carefully controlled assessment of its long-term safety for overall infant development is necessary. An initial step might be the determination of the minimal dose of bevacizumab that is required for effective ROP treatment. For now, in the absence of such an assessment, it may be wise to limit the use of intravitreal bevacizumab to the most severe cases of ROP that are highly predisposed to retinal detachment, namely stage 3 with plus disease within zone I. It is in these cases that this anti-VEGF agent has been shown to be most beneficial, although its administration would oblige extended follow-up on behalf of practitioners as well as of the patients and their families. In less severe cases of high-risk ROP, however, laser ablation therapy is likely to be safer yet just as effective.

Other anti-VEGF agents have recently emerged and some of these may be less likely to enter the systemic circulation than bevacizumab, and they may have a better safety profile or even be superior to bevacizumab in treating ROP. Ranibizumab is already being used in some centers. In addition, numerous compounds other than VEGF antagonists are currently being investigated for their use in treating ROP, including erythropoietin derivatives, insulin-like growth factor 1/insulin-like growth factor-binding protein 3, omega-3 fatty acids, neural guidance molecules, inflammatory mediators, and others.[22] More debates are sure to come!

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