Retinopathy of Prematurity: An Overview

Location, stage, and other clinical features guide the choice to treat versus observation.

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Retinopathy of prematurity (ROP) was first described by Terry and colleagues in 1942, and it was termed retrolental fibroplasia. Early attempts at surgical intervention and radiation treatment often resulted in poor visual outcomes. In the following decades, as more premature infants survived, ROP quickly became the leading cause of blindness among children in the United States.

ROP results from drastic environmental changes when an infant is born prematurely, which results in an abrupt withdrawal of nutrients and growth factors in addition to a relatively hyperoxic environment. These changes disrupt the fragile balance of vasculogenesis and angiogenesis that occurs in the developing fetal retina. As a result, normal growth of the retinal vasculature ceases, leading to an avascular peripheral retina. As the retina continues to mature, the combination of an avascular retina and increased metabolic activity leads to hypoxia. Levels of vascular endothelial growth factor (VEGF) increase with resultant retinal neovascularization.

The foundation of treatment for ROP has historically been peripheral retinal ablation: first with cryotherapy, followed by the current standard of laser photocoagulation. As we forge ahead in the treatment of ROP, intravitreal bevacizumab (Avastin, Genentech) has brought excitement and controversy. Case reports and series, as well as one clinical trial, Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity (BEAT-ROP), have demonstrated the efficacy of bevacizumab in this indication. Anti-VEGF treatment has been heralded as a potential “one-shot” fix for the treatment of ROP. Questions remain, however, regarding treatment with the agent, and peripheral retinal ablation remains the gold standard treatment for ROP.

ROP is a dynamic disease process with a delicate window of time to ensure proper treatment. The ophthalmologist and neonatologist must be aware of all facets of this disease that may contribute to the successful treatment of this potentially blinding condition. Risk factors for the development of ROP include infants’ birth weight, gestational age, and oxygen satu-
ration. Results from the Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity (STOP-ROP) trial showed that the use of supplemental oxygen to maintain oxygen saturation between 96% and 99% resulted in a lower risk of the progression to a threshold level of disease. Infants who received supplemental oxygen, however, had more adverse pulmonary outcomes and longer hospitalizations. In contrast, a meta-analysis showed that restricting supplemental oxygen reduced the progression to severe ROP but may result in adverse effects on long-term growth and development.

**SCREENING**

Screening guidelines for ROP recommended that all preterm infants weighing less than 1,500 g or those younger than 32 weeks gestational age should be evaluated. Infants should have a comprehensive examination including indirect ophthalmoscopy with scleral depression starting at 31 to 36 weeks of gestational age or approximately 4 to 9 weeks after birth. Based on clinical findings, examinations should be performed every 1 to 2 weeks and until there is complete retinal vascularization into zone 3 without prior zone 1 or zone 2 disease. For high-risk infants, or those requiring treatment, examinations should be performed more frequently until the disease regresses.

The capabilities of wide-field modalities have revolutionized the imaging of infants with ROP and have allowed the possibility for telemedical screening. Studies have shown that wide-field retinal imaging may be as sensitive as indirect ophthalmoscopy at identifying plus disease, but slightly less sensitive at determining prethreshold or threshold disease. The Stanford University Network for Diagnosis of Retinopathy of Prematurity (SUNDROP) initiative revealed that wide-field imaging was able to capture 100% of infants necessitating treatments. Despite these findings, the gold standard in screening continues to be indirect ophthalmoscopy by an ophthalmologist, with wide-field imaging providing disease documentation and allowing detailed comparison to evaluate the effect of treatment.

**CLINICAL TREATMENT**

Location, stage, and other clinical features guide the choice to treat versus simply observing an infant. Threshold disease is defined as 5 contiguous clock hours or 8 cumulative clock hours of stage 3 ROP in zone 1 or 2 with plus disease. Plus disease is a high-risk clinical feature consisting of poor pupillary dilation secondary to iris engorgement, vitreous haze, dilation, tortuosity of veins and arterioles, and hemorrhages. Eyes with poor dilation and vitreous haze make laser photocoagulation difficult, thus these eyes are ideal candidates for intravitreal bevacizumab treatment. Some eyes with high-risk features may warrant treatment. Type 1 ROP is defined as zone 1 or any stage with plus disease, zone 1 with stage 3 without plus disease, and zone 2 with stage 2 to 3 and plus disease. These type 1 eyes benefit from early treatment within 48 to 72 hours of diagnosis. Type 2 ROP is defined as zone 1 and stage 1 to 2 without plus disease or zone 2 and stage 3 without plus disease. These type 2 eyes may be observed for progression before treatment.

Aggressive posterior ROP (AP-ROP) is characterized by plus disease affecting all four quadrants. It is an aggressive form of the disease, and it requires immediate treatment. Infants with AP-ROP may also be good candidates for intravitreal bevacizumab, because laser photocoagulation for zone 1 disease is associated with complications such as macular dragging and retinal detachment. Although an arm of the Pan-VEGF Blockade for the Treatment of Retinopathy of Prematurity (BLOCK-ROP) clinical trial was initiated to evaluate intravitreal bevacizumab for the treatment of AP-ROP that progressed despite laser therapy, it was stopped due to a lack of enrollment.

**OTHER TRIALS**

In a multicenter clinical trial, infants weighing less than 1,251 g received serial ophthalmologic examinations showing that 66% of the infants developed ROP. Only 6% of the infants progressed to threshold disease.
necessitating treatment, however. The trial investigated cryotherapy for ROP (CRYO-ROP) to determine if treatment affected anatomic and functional outcomes. After 15 years follow-up, a statistically significant difference in unfavorable outcomes was found for treated compared with untreated eyes (30% vs. 51.9%). Almost 50% of eyes had a visual acuity of 6/60 or worse.10 Cryotherapy has several drawbacks, including portability, difficulty treating posterior locations, and higher refractive errors.

With the development of laser photocoagulation systems that use indirect ophthalmoscopy, retinal ablation of avascular retina has been shown to be safe and efficacious compared with cryotherapy. Studies have revealed that laser photocoagulation is associated with regression of avascular retina has been shown to be safe and efficacious compared with cryotherapy.15-18 Laser photocoagulation for posterior disease, however, often leads to significant myopia, macular dragging, and permanent visual field defects from retinal ablation. With the use of intravitreal bevacizumab, however, most eyes continue to vascularize into the far periphery, potentially reducing these complications. Long-term follow-up is needed to determine the final visual acuity outcomes and refractive errors in infants treated with bevacizumab.

Even with cryotherapy and laser photocoagulation proving to be efficacious for disease regression, a large proportion of infants still have poor visual acuity. The Early Treatment of ROP (ETROP) trial investigated whether earlier treatment with laser or cryotherapy of high-risk eyes would result in improved visual outcomes. ETROP defined high-risk prethreshold disease as type 1 and type 2, with type 1 eyes receiving treatment within 48 to 72 hours of diagnosis. Early treatment reduced unfavorable visual outcomes from 19.8% to 14.3% and decreased unfavorable anatomical outcomes from 15.6% to 9.0%. In ETROP, an additional 2% of eyes required treatment compared with what was found in CRYO-ROP.

Patterns used in laser photocoagulation influence the treatment course: using a confluent pattern and administering early re-treatment as needed was associated with a decrease in the risk of progression from 29.4% to 3.6%.13 Careful attention should be made to prevent skipping areas during treatment, which may increase the risk of continued disease progression. Although intravitreal bevacizumab is not without local and systemic risks, this treatment does not rely on the experience of the ophthalmologist as much as laser treatment, thus potentially reducing inter-hospital variation in treatment with bevacizumab compared with laser.

Anti-VEGF Treatment

The pathogenesis of ROP consists of 2 phases: vasoobliteration then neovascularization. VEGF levels increase as the avascular retina becomes increasingly hypoxic.3 Therefore, various anti-VEGF agents have been investigated for the off-label treatment of ROP, including bevacizumab, pegaptanib sodium (Macugen, Pfizer, Inc.), and ranibizumab (Lucentis, Genentech). As mentioned earlier, case reports have shown VEGF inhibitors may be effective at halting the progression of ROP, especially in cases where there are media opacities or poor dilation precluding adequate visualization for laser treatment.20

BEAT-ROP was a randomized, prospective, controlled clinical trial investigating the efficacy of bevacizumab for the treatment of stage 3 with plus disease affecting zone 1 or 2. The study included 140 eyes treated with bevacizumab (0.625 mg/0.025mL) and 146 eyes treated with laser photocoagulation. The BEAT-ROP study found that intravitreal bevacizumab significantly decreased the rate of recurrence (6%) versus laser (26%) for zone 1 and posterior zone 2 disease. More specifically, for zone 1, recurrence was 42% with the laser treatment and 4% with bevacizumab. For eyes with zone 2 disease, recurrence rates were 12% with the laser compared with 5% for bevacizumab. The results were not significant for zone 2 disease.

Clinically, these results highlight the potential utility of intravitreal bevacizumab in the treatment of ROP with zone 1 disease, as well as eyes that fail conventional laser treatment. Of note, the time to recurrence for eyes treated with intravitreal bevacizumab was 16 weeks compared with 6.2 weeks for those treated with laser. Therefore, ophthalmologists must ensure that these infants have close follow-up, including outpatient visits if they are discharged from the hospital. Regarding safety, preterm infants have a higher-than-average all-cause mortality rate of death, with the ETROP reporting a rate of 5.4%. The BEAT-ROP trial was not powered to determine safety.

CONCLUSION

There have been significant advances in the treatment of ROP during the past few decades, and cryotherapy, laser photocoagulation, and now angiogenic inhibitors have proven to be successful in the majority of cases, often allowing infants to achieve functional vision. Laser photocoagulation continues to be an important tool and remains the gold standard in the treatment of premature infants affected by the leading cause of childhood blindness in the United States. Newer agents targeting VEGF, however, have demonstrated short-term benefits as monotherapy, especially for zone 1 disease, or
when combined with standard laser. Current protocols stress the importance of early detection and treatment for these infants to obtain optimal visual results.

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