Concerns for Development After Bevacizumab Treatment of ROP

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Until recently, the treatment of potentially blinding retinopathy of prematurity (ROP) has been relatively straightforward. The 2003 publication1 of the multicenter ETROP (Early Treatment for Retinopathy of Prematurity) randomized trial indicated improved outcomes with the use of peripheral retinal ablation for eyes with type 1 ROP, defined as zone I ROP with plus disease (ie, abnormal dilation and/or tortuosity of the posterior pole vessels), zone I stage 3 ROP without plus disease, or zone II stage 2 or 3 ROP with plus disease. Among 401 infants with birth weights <1251 g at 26 US clinical centers, 342 of 370 survivors were examined at age 6 years.2 One in 4 had visual acuity worse than 20/200 in the laser-treated eye with type 1 ROP. This finding represents a marked improvement in visual function compared with the natural history of severe ROP found in untreated eyes in the CRYO-ROP (Cryotherapy for Retinopathy of Prematurity) study conducted 15 years earlier.3 In the earlier study, 52% of control (untreated) eyes with slightly worse than type 1 ROP had 20/200 or worse visual acuity.4

However, in CRYO-ROP,5 only 7% and, in ETROP,6 9.1% of eyes had zone I disease in the posterior retina within a few millimeters of the optic nerve. These eyes had a 31% likelihood of developing poor vision in ETROP2 and eyes in the CRYO-ROP study with this ROP severity had a 69% likelihood of poor vision without treatment.7

The increasing survival of lower birth weight and gestational age infants8 will likely lead to the occurrence of more zone I ROP requiring treatment. In the BEAT-ROP (Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity) trial,9,10 45% of the 150 infants enrolled for treatment had zone I stage 3 ROP with plus disease and 55% had posterior zone II disease. This US trial tested the hypothesis that intravitreal injection of bevacizumab was effective in preventing retreatment by 54 weeks’ postmenstrual age and reported benefit from a bevacizumab injection compared with conventional laser, in zone I disease in particular; this finding was also reported in observational studies.11–13 These results have led many ophthalmologists to consider intravitreal injection as a primary treatment, despite the small number of patients in BEAT-ROP and, thus far, no detailed results of visual function or long-term systemic effects.

There are several advantages to ROP treatment with a “simple” intravitreal injection. These advantages include requiring only a few minutes for the procedure under topical anesthesia or intravenous sedation versus 30 to 45 minutes per eye for laser with sedation and/or intubation. Other advantages include more rapid diminution of vessel dilation and tortuosity signifying resolving disease, perhaps preservation of the visual field,9,10 and less myopia14 in the long run.

However, concerns remain over intraocular injection of an anti–vascular endothelial growth factor (VEGF) drug with possible ocular and systemic effects. From the ophthalmic viewpoint, there are reports of recurrence requiring retreatment as

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late as 65 to 70 weeks’ postmenstrual age.\textsuperscript{15–17} Lepore et al\textsuperscript{18} reported that bevacizumab-treated eyes had significant vascular and macular abnormalities compared with laser-treated eyes on fluorescein angiography 9 months after treatment. Systemically, there are few data on later developmental status of children treated with anti-VEGF agents;\textsuperscript{19} despite the knowledge that the drugs are present in the serum for weeks after treatment.\textsuperscript{20}

The report from the Canadian Neonatal Network by Luu et al\textsuperscript{21} in this issue of Pediatrics shows that infants whose ROP was treated with intravitreal bevacizumab had an increased risk of motor impairment at 18 months compared with those treated with laser alone. The report acknowledges many weaknesses of such observational studies but, given that an adequately powered randomized controlled trial of an intravitreal anti-VEGF therapy compared with conventional laser to detect long-term systemic effects is not likely anytime soon, it should give pause for thought before opting for this therapy. The history of neonatology has numerous examples of therapies embraced because of short-term benefit without knowledge of longer term outcomes.

There are parallels with postnatal corticosteroid use, commonplace in the 1980s–1990s in preterm infants requiring ventilation beyond 1 week of age, largely because the therapy facilitated extubation and led to a reduction in chronic lung disease (CLD).\textsuperscript{22} However, a 2000 report linked early, short courses of postnatal corticosteroids with a significant increased risk of cerebral palsy.\textsuperscript{23} In an analysis of 20 studies, Doyle et al\textsuperscript{24} showed that there is a trade-off between the risk of death or cerebral palsy and CLD; when the CLD risk is low, corticosteroid use increases the risk of death or cerebral palsy, but when the CLD risk is high, the opposite scenario is true.

If the Canadian Neonatal Network study findings\textsuperscript{21} are supported by other neonatal networks collecting similar data, it will help define which infants might experience overall benefit from intravitreal bevacizumab therapy for acute ROP. The most immature infants with posterior disease will have greatest risks of adverse visual outcome and neurodevelopmental and motor impairments. Larger, more mature infants with less risk of neurodevelopmental impairment, many of whom are currently treated in middle-income countries,\textsuperscript{25–27} may have a worse long-term outcome after this therapy. We are not at the point that such conclusions can be drawn, but Luu et al\textsuperscript{21} have made an important step along the path.

**ABBREVIATIONS**

CLD: chronic lung disease  
VEGF: vascular endothelial growth factor

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