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Editorial

Bevacizumab for Retinopathy of Prematurity: Treatment When Pathology Is Embedded in a Normally Developing Vascular System

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Bevacizumab and other vascular endothelial growth factor (VEGF) inhibitors have emerged as potent treatments for advanced retinopathy of prematurity (ROP), adding to the use of laser to treat this disease.[1] The other treatment method is ablation of the peripheral retina, usually with a laser. Many clinicians now choose intravitreal bevacizumab (IVB) for zone I type 1 eyes or zone II posterior type 1 eyes, as recommended in a recent editorial.[2] These are eyes with the most severe ROP, and arguably a poorer prognosis, that otherwise would require extensive ablation of large areas of retina to control the disease.

It is easy to understand the lure of IVB. Its ease of administration and its effectiveness speak to its popularity. But there are many questions that remain unanswered about its use, including its safety, dosage, and effects on other organ systems, because bevacizumab is absorbed systemically. In this issue of *Ophthalmology*, Mintz-Hittner et al[3] (see page 1845) begin to address some of these concerns and provide us with valuable data about the clinical course of eyes treated with IVB. The information in their article will help guide ROP specialists, while leaving unanswered questions about its use.

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Ophthalmologists confront the boundary between normal eye development and disease when they choose IVB over laser retinal ablation. This is similar to other interventions in medicine. We often must balance the risk of harming a patient with the advantage of administering a potentially dangerous drug. These risk-versus-benefit decisions occur with cancer therapies, immune modulation, and so on. In the case of premature infants, the risk-to-benefit ratio remains unclear. Bevacizumab molecules spill into the circulation with effects measured there for more than 1 month.[4] The fellow eye in patients treated with VEGF inhibitors also may show improvement, a witness to the effect of remote interactions of VEGF inhibitors on other vascular beds. Already, reports of deleterious effects of bevacizumab on the premature infant's brain are emerging, although this is debated. What about other organ systems? Two systems merit mention.

Lungs in preterm infants are significantly underdeveloped. Pulmonary buds are highly vestigial at 22 weeks gestational age, and lung development is heavily influenced by VEGF, so much so that alteration of VEGF in knockout mice is a rare lethal mutation.[5] Precise spatial and temporal regulation of VEGF-A is required to promote proper vascular development and development of pulmonary buds in embryonic development.[6] Is it enough to have some VEGF to encourage proper pulmonary development? Depriving lungs, brain, and other organs of VEGF could have lasting deleterious effects—or not. We simply don't know. It may take years to know whether partially turning off VEGF is harmful to the infant.

The brain in preterm infants may be at-risk when exposed to bevacizumab.[7] In the case of neonatal jaundice (in preterm infants), where bilirubin management is an ever-present issue, certain toxins (e.g., bilirubin) will alter VEGF levels and thereby increase the porosity of the blood–brain barrier. Even without exposure to aggravating neurotoxins, the premature infant's blood–brain barrier is naturally more diaphanous than that of a full-term infant. Thus, circulating proteins and chemicals are more likely to see their way into the brain. These potentially harmful effects of anti-VEGF treatments will take some time to sort out. It may be years before we recognize any harmful or otherwise effects, and innovative strategies will be required to detect some of the more subtle findings.

The study by Mintz-Hittner et al addresses important issues and treatment decisions germane to the eye undergoing bevacizumab therapy. This article is a noteworthy and highly valued addition to our knowledge base on the subject and contains many important caveats. One standout is that prophylactic bevacizumab treatment for ROP should be avoided. Even the Early Treatment for Retinopathy of Prematurity Study showed a trend (statistically insignificant) toward worse outcomes with treatment of type 2 eyes. These were the less severely affected eyes, now recognized as often not requiring treatment.[8] That VEGF inhibitors can alter normal retinal vascularization forms the backbone of this study, so of course, unnecessary treatment is to be eschewed. Normal retinal vessel development also is under the influence of VEGF, so inhibition of VEGF runs the risk of causing normal retinal vessels to stop growing, and indeed, this is exactly the finding from this group. We know that this occurs when ROP eyes are treated, and this poses a conundrum. How long is it safe to wait for normal vascularization to recommence? What is the time frame during which vascularization is dormant, and does the peripheral avascular retina require treatment?

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The answer to some of these questions can be found in this study. For instance, 8.3% of eyes require more treatment, with the age range for recurrence being between 45.7 and 65.9 weeks' gestational age. The authors themselves note that this recurrence rate is not insignificant. Retreatment for recurrent ROP also was administered with IVB, an issue we will return to. In infants requiring retreatment, 3 eyes in 20 children developed some degree of retinal detachment. The assumption would be that retreatment is a risk factor for retinal detachment, but we have not been provided with outcomes for infants who did not require retreatment.

As helpful and reassuring as these data are, there are unanswered questions. The criteria for retreatment seem clear from this study, but should retreatment occur with more bevacizumab or with retinal ablation? A widespread assumption that laser treatment, but not bevacizumab, causes myopia is insufficiently proven. In the Cryotherapy for Retinopathy of Prematurity Study, there was no difference in myopia between treated eyes and untreated control eyes.[9] Data on lack of myopization after IVB treatment is not yet strong enough to make this assertion.

Is an avascular retina as a result of IVB a problem? From this study, we learn that it is—sometimes. The risk for ROP recurrence in this study of 51 weeks' gestational age on average (range, 45–65 weeks) is reassuring information, particularly given the very long-term follow-up in this study, but we may need many more years before we know it is safe to leave the retina partially without a blood supply. Additional questions to be answered include the most effective dose of bevacizumab, which anti-VEGF compound is most effective, and evaluation of other longer-term consequences to the treated eyes, because VEGF is involved in the development of many components of the eye.

The authors of this rich and thorough article should be congratulated. Not only have they systematically introduced a treatment for ROP, they now are carefully reconstructing and evaluating any harm or benefit that may befall infants who receive this treatment. Any treatment deserves our attention that reduces anesthesia time for infants; potentially reduces ocular complications such as myopia, cataract, and glaucoma; and is so easily administered. Anyone interested in ROP is urged to follow this team's work and to pay attention to this emerging treatment.

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Footnotes and Financial Disclosures

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