Published in final edited form as:

Retina. 2009 April ; 29(4): 562–564. doi:10.1097/IAE.0b013e31819a98b9.

The Use of Anti-VEGF Intravitreal Injections for Vision Threatening Stage 3 Retinopathy of Prematurity: Risk-Benefit Ratio

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Dear Editor

The authors, Mintz-Hittner and Kuffel, embarked on the use of Bevacizumab (Avastin) for retinopathy of prematurity (ROP) with great trepidation. We used half of the adult dose (the lowest reported in the literature) and initially, used it only for the most advanced cases of aggressive posterior retinopathy of prematurity (AP-ROP) which would have the worst possible outcomes. We were aware of the interactions of anti-VEGF drugs with VEGF and its receptors. We have worried about neurodevelopment and angiogenesis in the retina and central nervous system.

The first case ever injected by Dr. Mintz-Hittner was a 350 gram 22 week gestational age infant who was so critically ill that he could barely tolerate a retinal exam—let alone a laser surgery. His retinal vessels did not extend to the macula and was 31 weeks post conceptual age when he developed AP-ROP. Forty percent of the adult dose (0.50 mg) of Bevacizumab was injected into the vitreous of each eye (with parental consent and IRB emergency approval). The ROP disappeared within 48 hours and did not return for 11 weeks. Repeating the 0.50 mg of Bevacizumab caused complete regression of the ROP recurrence within 48 hours. Unfortunately, after another nine weeks, the infant died at post conceptual age of 50 weeks of total organ failure, and the eyes were obtained for pathology with extensive immunohistochemistry. There was no evidence of any retinal toxicity in this case that has been reported in detail showing the continued development of retinal vessels with the concomitant underlying development of rod and cone nuclei (outer nuclear layer), bipolar nuclei (inner nuclear layer), and ganglion cell neurons.¹ Thus, the articles cited by the corresponding authors are not new references for us. (Note that reference 3 in Kong, Mintz-Hittner, Penland, et. al is the same as the corresponding authors' reference 1.)

ROP is a two phase pathologic neovascularization. Phase I is hyperoxia associated with decreased levels of VEGF. Clinically, this occurs from 22 weeks to approximately 30 weeks post menstrual age. Most hypoxic episodes occur during phase I when adequate VEGF is especially necessary for neuroprotection. Phase II is hypoxia associated with increased

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The author has no financial interest regarding the information mentioned in this article.

levels of VEGF. Clinically, this occurs from 31 weeks to approximately 45 weeks post menstrual age. Anti-VEGF therapy should only be given during phase II.

Additionally, although the report published in *Retina* 28:831-838, 2008 did not report our electrophysiologic testing nor our fluorescein angiographic findings, all were normal, and a comparison from case 3 (570 gram 24 week gestational age infant) of the initial ROP photograph of the left eye at 2.5 months post natal age (Fig 1A) to a fluorescein angiogram of the same eye at 18 months post natal age (Fig 1B) demonstrate continued retinal vascularization. Of course, the retina of a 24 week gestational age infant never reaches the ora serrata in the best of circumstances.²

Following this case series for a mean of 18 months, at this time, has confirmed the positive development of vision in those cases that do not have severe developmental delay because of pre-existing severe intraventricular hemorrhage or periventricular leukomalacia (common complications of extreme prematurity). Electroretinograms are normal even for patients who do have severe central nervous system complications. Of course, visual evoked responses are present only in those infants without these severe central nervous system complications.

We definitely share Drs. Hosseini, Khalili, and Nowroozizadeh's concern about the RISKS of Bevacizumab in the developing retina and in fact in the very low birth weight infant in general. However, our group has found the BENEFITS of using intravitreal Bevacizumab alone (without laser) to be substantial:

- 1) The complications of laser are prevented completely. Ablation of the entire avascular peripheral retina is avoided. Cataracts, angle closure glaucoma, anterior segment necrosis, phthisis, and high myopia do not occur. Strabismus related to too little field to sustain binocular vision is prevented.
- 2) Fewer patients need to be treated. Bevacizumab offers a larger window of treatment so one can observe a few days to be sure that ROP is advancing and really needs to be treated.
- 3) The disease stops almost immediately. The anti-VEGF therapy not only inactivates the VEGF in the retina, but also that already in the vitreous. Plus disease is uniformly gone within 48 hours.
- 4) No potential complications of anti-VEGF therapy have been observed.
 - a) Bevacizumab administration for ROP Stage 3 at the same time or immediately following laser therapy might permit the drug to escape the natural retinal barrier despite its large molecular weight (149 KD).
 - b) Bevacizumab administration for ROP Stages 4 and 5 (following retinal detachment) is usually administered to eyes that have had laser therapy. This may permit the drug to escape the natural retinal barrier. Advanced disease itself with retinal detachment is associated with very high vitreous levels of VEGF.³ Further, Bevacizumab at these late stages of ROP can trigger contraction of membranes and accelerate retinal detachment.⁴

Despite these arguments which favor the use of intravitreal Bevacizumab without laser therapy for vision threatening ROP Stage 3, we still realize the need to gather evidence based data to confirm a favorable RISK-BENEFIT ratio prior to recommending its wide use for ROP in the NICU. Thus, the **BEAT-ROP** (Bevacizumab Eliminates the Angiogenic Threat of Retinopathy Of Prematurity) prospective, randomized, controlled, multi-center clinical trial has begun—under the watchful eye of the FDA-IND (NCT 00622726). We believe that no laser therapy is needed in combination with Bevacizumab for the angiogenic component of ROP and that Bevacizumab has no favorable effect on the tractional component of ROP.

Acknowledgments

We are thankful to the corresponding authors for their admonitions, but feel that the extremely positive response of acute vision threatening ROP to Bevacizumab warrants the cautious continuation of this clinical research.

Supported by NEI Core Grant EY010608-15; Research to Prevent Blindness, Inc. (New York, NY); and the Hermann Eye Fund (Houston, TX).

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Figure 1. Left eye of infant who was 570 grams and 24 weeks gestational age at birth. A. Color photograph at the age of 2.5 months. B. Fluorescein angiograph at 18 months of age. (Black arrows are identical vessels at the two time points; Yellow arrows are the extent of the retina at 2.5 months of age; White arrows are the extent of the retina at 18 months of age.)