

Retinopathy of Prematurity in the Time of Bevacizumab: Incorporating the BEAT-ROP Results into Clinical Practice

Darius M. Moshfeghi, MD - Palo Alto, California

Audina M. Berrocal, MD - Miami, Florida

Recently, the results of the Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity (BEAT-ROP) trial were published in the *New England Journal of Medicine* and careful review is important since the authors advocate for a change in the standard of care in the treatment of ROP.¹ The BEAT-ROP trial design was a prospective, multicenter, randomized, unmasked Phase II trial of intravitreal bevacizumab (0.625 mg in 0.025 ml) vs. conventional diode laser photocoagulation.¹ Eligible patients were 1500 g or less and 30 weeks gestational age or less with Stage 3+ ROP in Zone I or Zone II posterior disease in both eyes.¹ The primary outcome of the trial was modified from an absence of recurrence of Stage 3+ ROP in Zone I or Zone II posterior by 54 weeks to recurrence of retinal neovascularization requiring retreatment by 54 weeks.¹ Bevacizumab was injected 2.5 mm posterior to the limbus using a 31-gauge needle.¹ Based upon a pre-study analysis of the predicted efficacy of bevacizumab, the trial targeted 50 patients with Zone I disease and 100 patients with Zone II posterior disease, with a 1:1 randomization of bevacizumab: diode laser photocoagulation.¹ The authors elected to randomize based upon infants, not eyes, because of the threat of amblyopia induced by 1 eye receiving laser photocoagulation and potential exuberant inflammation and the other eye receiving an injection; each infant received the same therapy in both eyes.¹ At the time of full enrollment, 150 patients had been enrolled, 67 in Zone I (33 bevacizumab, 34 laser), and 83 in Zone II posterior (42 bevacizumab, 41 laser).¹ Of these, 143 were considered eligible for analysis, with 7 deaths before the 54 week primary outcome endpoint.¹ There was 1 protocol violation, a patient who inadvertently received bevacizumab when they should have received laser photocoagulation, and they were included in the laser group by virtue of the intent-to-treat analysis plan.¹

The BEAT-ROP demonstrated a beneficial effect for bevacizumab vs. laser in the treatment of Zone I, Stage 3+ ROP.¹ In the bevacizumab group, recurrence of retinal neovascularization requiring treatment was 6% at 54 weeks vs. 42% in the laser group, for an odds ratio of 0.09 favoring bevacizumab (95% confidence interval of 0.02–0.43).¹ No statistical difference was noted for Zone II posterior, Stage 3+ROP between bevacizumab and laser.¹ Recurrence rates were 5% vs. 12%, bevacizumab and laser, respectively.¹ Of the 7 deaths, 5 were in the bevacizumab group, 2 in the laser group, and this did not reach statistical significance.¹

The authors offered the following conclusions: (1) bevacizumab is superior to laser for treatment of Zone I, Stage 3+ ROP; (2) peripheral retinal vascularization continued as normal in the bevacizumab group, but not the laser group; and (3) “Becavizumab is an inexpensive drug that can be rapidly administered at the bedside by any ophthalmologist.”¹

Before ophthalmologists who screen and treat ROP consider a change from laser to bevacizumab for Zone I ROP, we caution them to consider the following points: (1) Safety was not demonstrated in the BEAT-ROP trial and indeed, the authors agree noting that the sample size was not adequate to speak to safety,¹ (2) time to recurrence was significantly different in the 2 treatment groups, (3) re-treatment decisions were verified after the fact, and (4) the primary endpoint was changed midway through the trial.¹

An important question to ask when evaluating a new therapy is, “Will this new therapy be better and as safe as the standard of care?” In the BEAT-ROP trial the answer to this question seems to be: yes it is better than the standard of care in reducing recurrences and yes it seems to be as safe as laser (longer follow up is needed).¹ The investigators did not identify any ocular toxicity.¹ Considering safety, two issues immediately come to the forefront. First, the BEAT-ROP study was not powered to evaluate safety.¹ Theoretically, systemic risks include thromboembolic events,² as well as failure of pulmonary maturation.³ Despite the authors’ belief that bevacizumab does not traverse the retina except in small quantities,¹ the retina has demonstrated permeability to bevacizumab in animal models without laser,^{4,5} in adult case reports demonstrating bilateral anti-VEGF effects following monocular injection,⁶ as well as in pediatric uveitides.^{7,8} We are concerned when 71% of the mortality occurred in the bevacizumab group (and all related to pulmonary issues), although this was not statistically significant.¹ Second, the authors noted that injections were performed about 2.5 mm posterior to the limbus.¹ The pars plana is not fully developed in a premature infant until approximately 6 months corrected age, and injection at any location greater than 1.5–2.0 mm posterior to the limbus potentially passes through full-thickness retina.⁹

The time to recurrence was significantly different between the 2 groups, 19.2±8.6 weeks vs. 6.4±6.7 weeks for bevacizumab and laser, respectively, in Zone I eyes.¹ Similarly, the age at treatment was significantly different, 34.5±1.4 vs. 33.7±1.6 weeks, for bevacizumab and laser respectively.¹ Why is this important? If we look at 1 and 2 standard deviations (SD) above the mean, the bevacizumab group infants could have been treated at 35.9 weeks and not recurred until 27.8 weeks after laser (one SD), or 63.7 weeks postmenstrual age, which means 13.7 weeks after the primary endpoint, and hence not be included in the primary endpoint as a failure.¹ For 2 SD, the failure in the bevacizumab group would not have occurred until 72.3 weeks postmenstrual age, 18.3 weeks after the primary outcome. In fact, 47.7% (2 standard deviations) of the bevacizumab group recurrences would have occurred after the primary endpoint.¹ This was not the case for the laser group, where 1 SD above the mean could have been treated at

35.3 weeks and not recurred until 13.1 weeks later, or 48.4 weeks, meaning almost all laser recurrences occurred well within the 54 week primary outcome.¹ Furthermore, the authors did not report on the total number of recurrences requiring treatment at any time point, resulting in an unequal comparison. It does not matter when a patient recurs as much as if the patient recurs, because any recurrence represents a potential for retinal detachment.

While the authors had a reading center to evaluate recurrence, it was not convened until November 21–23, 2009, 20 months after the first patient was enrolled in the trial.¹ According to the methodology and appendix, 6 independent reviewers reached a post hoc consensus as to the outcomes.¹ The trial did not report on the inter- and intra-reader concordance rates.

It is unclear why the authors changed the primary endpoint before “. . . the date on which the data were first analyzed . . .”¹ Regardless, in an unmasked trial, the investigators may be aware of whether any patients in either group were meeting the relatively high bar of recurrence of Stage 3+ ROP in Zone I or II by 54 weeks at the time of the change. Plus disease does not usually recur following regression, although neovascularization does.¹⁰ Therefore, changing the outcome in this unmasked trial midway through the trial, can have the effect of “moving the goalposts.”

We believe that bevacizumab will play a key role in the treatment of ROP, particularly in Zone I ROP. We disagree that bevacizumab can be “rapidly administered at the bedside by any ophthalmologist.”¹ Proper mentored training in intravitreal injection technique in premature infants is essential to avoid lens injury and rhegmatogenous retinal detachment.

On a final note, the joint statement guidelines recommend the following: “Retinal examinations in preterm infants should be performed by an ophthalmologist who has sufficient knowledge and experience to enable accurate identification of the location and sequential retinal changes of ROP.”¹¹ BEAT-ROP reinforces that because of the unusually long time until recurrence,¹ substantially beyond current screening recommendations.¹¹ Laser photocoagulation will succeed or fail within 9 weeks of therapy¹²; in the BEAT-ROP trial, Zone I Stage 3+ ROP recurred up to 7 months after therapy following bevacizumab.¹ The authors issued a word of caution regarding this in the Discussion,¹ which we wish to highlight here. Treatment with bevacizumab is not a one-and-done therapy. ROP can recur late following bevacizumab treatment, and the BEAT-ROP trial did not give us data as to when we might expect to meet the lofty goal of eliminating the angiogenic threat of ROP, or if it happens at all. This has profound implications on the continuity of care of these patients once

they leave the NICU particularly for bevacizumab-treated patients, as it may extend the follow-up period of these patients in outpatient clinics up to 80 weeks postmenstrual age or beyond. In that situation, as the infants get older adequate examination in the office is often not feasible and may require confirmatory examination under anesthesia. All of these factors should be taken into account when deciding how to incorporate BEAT-ROP results into the care of the premature infant.

References

1. Mintz-Hittner HA, Kennedy KA, Chuang AZ. Efficacy of intravitreal bevacizumab for stage 3+ retinopathy of prematurity. *N Engl J Med* 2011;364:603–15.
2. Michels S, Rosenfeld PJ, Puliafito CA, et al. Systemic bevacizumab (Avastin) therapy for neovascular age-related macular degeneration twelve-week results of an uncontrolled open-label clinical study. *Ophthalmology* 2005;112:1035–47.
3. Compennolle V, Brusselmans K, Acker T, et al. Loss of HIF-2 α and inhibition of VEGF impair fetal lung maturation, whereas treatment with VEGF prevents fatal respiratory distress in premature mice. *Nat Med* 2002;8:702–10.
4. Shahar J, Avery RL, Heilweil G, et al. Electrophysiologic and retinal penetration studies following intravitreal injection of bevacizumab (Avastin). *Retina* 2006;26:262–9.
5. Miki K, Miki A, Matsuoka M, et al. Effects of intraocular ranibizumab and bevacizumab in transgenic mice expressing human vascular endothelial growth factor. *Ophthalmology* 2009;116:1748–54.
6. Avery RL, Pearlman J, Pieramici DJ, et al. Intravitreal bevacizumab (Avastin) in the treatment of proliferative diabetic retinopathy. *Ophthalmology* 2006;113:1695.e1–15.
7. Al-Dhibi H, Khan AO. Bilateral response following unilateral intravitreal bevacizumab injection in a child with uveitic cystoid macular edema. *J AAPOS* 2009;13:400–2.
8. Avery RL. Extrapolating anti-vascular endothelial growth factor therapy into pediatric ophthalmology: promise and concern. *J AAPOS* 2009;13:329–31.
9. Hairston RJ, Maguire AM, Vitale S, Green WR. Morphometric analysis of pars plana development in humans. *Retina* 1997;17:135–8.
10. Vinekar A, Trese MT, Capone A Jr. Evolution of retinal detachment in posterior retinopathy of prematurity: impact on treatment approach. *Am J Ophthalmol* 2008;145:548–55.
11. Section on Ophthalmology American Academy of Pediatrics; American Academy of Ophthalmology; American Association for Pediatric Ophthalmology and Strabismus. Screening examination of premature infants for retinopathy of prematurity. *Pediatrics* 2006;117:572–6.
12. Coats DK, Miller AM, Brady McCreery KM, et al. Involution of threshold retinopathy of prematurity after diode laser photocoagulation. *Ophthalmology* 2004;111:1894–8.

Financial Disclosures

Financial Disclosure(s):

DMM (Convene, LLC, equity; Google, Inc., consulting; InSitu Therapeutics, Inc., consulting, equity; Genentech, Ad Board; OcuBell, Inc., consult-

ing, equity; Oraya Therapeutics, consulting, equity; Realm Global, LLC, equity). ABM (Clarity Medical Systems, consulting).