

## CORRESPONDENCE



## Bevacizumab for Retinopathy of Prematurity

**TO THE EDITOR:** The study by Mintz-Hittner et al. (Feb. 17 issue)<sup>1</sup> advances our knowledge about the use of bevacizumab for the treatment of retinopathy of prematurity, but important questions remain about this drug's safety and efficacy. In the absence of functional vision testing or patient safety data, the sweeping endorsement of an experimental new treatment is unwarranted. Lack of protection against investigator bias is a concern. Assessment of the primary outcome (i.e., recurrence of retinopathy of prematurity requiring retreatment) by two ophthalmologists who were aware of the treatment assignments leaves the door open for such bias to influence results. These results were "validated" after retreatment by independent photographic assessments, also without masking of the treatment received. Although Reynolds, in his editorial, states that the independent reading center was similar to those in prior major studies of retinopathy of prematurity,<sup>2</sup> this is not true. In the Cryotherapy for Retinopathy of Prematurity study (CRYO-ROP; ClinicalTrials.gov number, NCT00000133)<sup>3</sup> and the Early Treatment for Retinopathy of Prematurity study (ETROP, NCT00027222),<sup>4</sup> investigators assessing events relevant to the primary outcome were not aware of the treatment assignments. Studies of the dose of bevacizumab, the timing of treatment, vision outcome, and especially safety data are warranted.

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No potential conflict of interest relevant to this letter was reported.

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. Reynolds JD. Bevacizumab for retinopathy of prematurity. *N Engl J Med* 2011;364:677-8.

3. Cryotherapy for Retinopathy of Prematurity Cooperative Group. Multicenter trial of cryotherapy for retinopathy of prematurity: three-month outcome. *Arch Ophthalmol* 1990;108:195-204.

4. Early Treatment for Retinopathy of Prematurity Cooperative Group. Revised indications for the treatment of retinopathy of prematurity: results of the Early Treatment for Retinopathy of Prematurity randomized trial. *Arch Ophthalmol* 2003;121:1684-94.

**TO THE EDITOR:** In response to the article by Mintz-Hittner et al.: we note that bevacizumab (an anti-vascular endothelial growth factor [VEGF] agent) is already being used as first-line or rescue treatment for retinopathy of prematurity in many middle and emerging economies. In these settings, the population of babies with severe disease is very different from that in industrialized countries because more mature babies (gestational age of >31 wk) are also often affected.<sup>1</sup> This phenomenon has been termed the "third epidemic" of retinopathy of prematurity.<sup>2</sup> Angiogenesis is still active in many organs of these babies at the time of treatment of retinopathy of prematurity, yet the potential risks of anti-VEGF

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agents may not be fully explained to parents, and access to medical legal redress is limited. It is imperative that the pharmacodynamics and safety profile of bevacizumab (or alternative agents) in the premature infant with acute retinopathy of prematurity and breakdown of the blood–ocular barrier be better delineated.<sup>3</sup> Randomized clinical trials that are adequately powered to detect adverse events and that have sufficiently long follow-up to assess neurodevelopmental outcomes are urgently needed. Until that time we would advocate that anti-VEGF medications be used only when laser photocoagulation fails and when informed consent is rigorously obtained.

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2. Gilbert C. Retinopathy of prematurity: a global perspective of the epidemics, population of babies at risk and implications for control. *Early Hum Dev* 2008;84:77-82.
3. Nomoto H, Shiraga F, Kuno N, et. Pharmacokinetics of bevacizumab after topical, subconjunctival, and intravitreal administration in rabbits. *Invest Ophthalmol Vis Sci*. 2009;50:4807-13.

**TO THE EDITOR:** The Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity study (BEAT-ROP, NCT00622726) suggests that the intraocular injection of bevacizumab is useful in the treatment of severe retinopathy of prematurity, but unknown systemic and ocular safety issues remain a concern. To establish mortality risk, the authors suggest that a study with 2800 infants is needed; since such a study would clearly be difficult to conduct, systemic safety data will not be immediately available. The issue of systemic safety is still being debated in large trials of anti-VEGF agents for other, more common neovascular eye diseases.<sup>1</sup> Although the investigators in the BEAT-ROP study administered half the dose of bevacizumab that is typically delivered, intravitreally, to adults, the premature infant's body weight is many times lower than an

adult's, and any systemic exposure is disproportionately greater. Systemic VEGF levels are almost fully suppressed 1 month after a single intraocular bevacizumab injection.<sup>2</sup> VEGF contributes to lung development,<sup>3</sup> and it is worrying that in the BEAT-ROP study, mortality with bevacizumab was higher than with laser treatment (6.6% vs. 2.6%), with four of the five deaths among those treated with bevacizumab resulting from low oxygen or respiratory failure. Finally, with respect to ocular safety, VEGF is needed for retinal differentiation and neuronal survival,<sup>4</sup> and the safety effects of bevacizumab are therefore better reflected in long-term visual and functional outcomes than in immediate structural complications.

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Drs. Mitchell and Wong report serving on advisory boards for Allergan, Bayer, Novartis, Pfizer, and Solvay and having received travel, honoraria, and research support from these companies. No other potential conflict of interest relevant to this letter was reported.

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2. Matsuyama K, Ogata N, Matsuoka M, Wada M, Takahashi K, Nishimura T. Plasma levels of vascular endothelial growth factor and pigment epithelium-derived factor before and after intravitreal injection of bevacizumab. *Br J Ophthalmol* 2010;94:1215-8.
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4. Hartnett ME. Studies on the pathogenesis of avascular retina and neovascularization into the vitreous in peripheral severe retinopathy of prematurity (an American Ophthalmological Society thesis). *Trans Am Ophthalmol Soc* 2010;108:96-119.

**TO THE EDITOR:** We are concerned about the strong recommendation made by Reynolds in his editorial regarding the BEAT-ROP study that intravitreal bevacizumab should replace conventional laser therapy for the treatment of severe retinopathy of prematurity. Bevacizumab has been found in the systemic circulation long after intravitreal injection.<sup>1</sup> The historical lesson on anti-angiogenesis drugs in infants was provided by the use of interferon alfa in the treatment of capillary hemangiomas — spastic diplegia or other neuromotor abnormalities developed in almost

10% of the infants so treated.<sup>2</sup> If the rate of neuro-motor disturbance in infants of less than 26 weeks of age is approximately 16 to 28%,<sup>3</sup> the BEAT-ROP study was too small to detect even a 10% increase in incidence of neurologic damage from bevacizumab. Without larger studies that yield robust data on adverse outcomes, the recommendation that bevacizumab should be the treatment of choice would appear to be premature.

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No potential conflict of interest relevant to this letter was reported.

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3. Milligan DWA. Outcomes of children born very preterm in Europe. *Arch Dis Child Fetal Neonatal Ed* 2010;95:F234-F240.

**THE AUTHOR REPLIES:** As Gilbert et al. note, intravitreal bevacizumab injections are already being used to treat retinopathy of prematurity in many developing countries, and additional studies of the pharmacokinetics and safety of intravitreal bevacizumab and the systemic administration of bevacizumab are needed. In industrialized nations, infants with retinopathy of prematurity have poor outcomes, probably because ever smaller infants survive premature birth, and therefore the number of infants with zone I retinopathy of prematurity is increasing.

The data my colleagues and I reported, collected at 6 months after treatment, suggest that intravitreal bevacizumab injections are more effective than laser treatment for zone I retinopathy of prematurity. We did not suggest that this treatment should be considered the standard of care; however, we did state that additional studies should be designed to evaluate the long-term efficacy and safety of intravitreal bevacizumab injections to treat zone I disease and zone II disease and acknowledged the need to determine an appropriate follow-up schedule when using such therapy. We suggested that the evaluation of lower doses would be appropriate.

Regarding ocular efficacy, we cited the only study of human ocular pathology subsequent to intravitreal bevacizumab injection available to us when our article went to press.<sup>1</sup> The results of this study indicated no ocular toxicity. However, we did not mention two rat studies of anti-VEGF therapy in which a neutralizing antibody to VEGF<sup>2</sup> and an inhibitor of VEGF receptor 2 tyrosine kinase<sup>3</sup> were injected intravitreally. Both studies showed that anti-VEGF therapy reduced endothelial-cell migration into the vitreous without interfering with endothelial-cell migration into the retina toward a VEGF gradient. The results of these studies in animals are consistent with the results of our study. They also suggest that the loss of visual field may possibly be reduced by treatment with an anti-VEGF agent.

We realized during the planning stages that a lack of masking would be an issue, as it was in previous multicenter trials of approaches to treat retinopathy of prematurity (the CRYO-ROP and the ETROP studies) that yielded preliminary results (collected at 6 to 9 months after treatment). However, RetCam imaging, which provided objective documentation throughout the study, was a critical part of our study design. This imaging allowed multiple opinions of disease classification and treatment responses. We intend to follow these infants for 5 years (or longer) and to include assessments of neurodevelopmental outcomes, as well as ocular outcomes, by independent, masked examiners.

The decision to submit the article was fueled by concerns of the physicians who participated in this study. We thought that it would be unethical to withhold the data from other physicians who are responsible for the care of patients who present with severe zone I stage 3+ retinopathy of prematurity.

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Since publication of her article, the author reports no further potential conflict of interest.

1. Kong L, Mintz-Hittner HA, Penland RL, Kretzer FL, Chevez-Barrios P. Intravitreal bevacizumab as anti-vascular endothelial growth factor therapy for retinopathy of prematurity: a morphologic study. *Arch Ophthalmol* 2008;126:1161-3.
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duction in endothelial tip cell filopodia corresponds to reduced intravitreal but not intraretinal vascularization in a model of ROP. *Exp Eye Res* 2009;89:718-27.

**THE EDITORIALIST REPLIES:** In my editorial, I noted many areas of concern about the BEAT-ROP study carried out by Mintz-Hittner and colleagues and endorsed the use of bevacizumab to treat retinopathy of prematurity in a limited fashion. I agree that, according to the study design, the investigators were not masked. The study was, however, a prospective, controlled, randomized, multicenter trial with an independent data and safety monitoring board and an independent reading center — all features of previous rigorously conducted trials designed to test approaches to the treatment of retinopathy of prematurity. As such, the BEAT-ROP study was superior to previous studies of case series of infants with retinopathy of prematurity treated with bevacizumab.<sup>1</sup> In the CRYO-ROP study, patients whose eyes showed an anatomically defined level of serious disease (i.e., threshold retinopathy of prematurity) underwent peripheral cryosurgical retinal ablation. Only 7.6% of these treatable eyes had disease in zone I, but those eyes had a very high unfavorable anatomic result. The CRYO-ROP study did not initially provide visual results. The ETROP study reported in 2003, which mainly used laser therapy in place of cryosurgery, showed more favorable results for zone I serious retinopathy of prematurity, but some of that improvement may have been due to methodologic differences in the ways in which zone I retinopathy of prematurity was defined in the two studies. The study by Mintz-Hittner et al. provided compelling evidence of a more efficacious intervention to treat zone I disease, with fewer ocular side effects.

As I noted in my editorial, safety remains a “potentially profound” issue and “continued vigilance will be important.” Concerns about minute circulating levels of bevacizumab and potential exacerbation of periventricular leukomalacia and bronchopulmonary dysplasia are warranted. However, the comparison by Gole and colleagues between multiple, systemic doses of interferon and a single intravitreal dose of bevacizumab that is about 0.25% of the normal systemic adult dose is problematic.

No study is definitive and no protocol is flawless. The CRYO-ROP investigators selected threshold retinopathy of prematurity as the intervention point, which became the standard of care until the ETROP study showed that it is better to treat the disease at an earlier point in the disease spectrum. Although the issue of adverse events is potentially profound, there is little direct supporting evidence of systemic adverse events consequent to the intravitreal injection of bevacizumab. Much more data will be forthcoming, and, as stated in my editorial, “as our experience with bevacizumab grows, its indications and relative contraindications will be refined.” The limited use of bevacizumab for zone I retinopathy of prematurity must include informed consent that is based on a discussion of the known and unknown risks versus the risk of blindness.

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Since publication of his article, the author reports no further potential conflict of interest.

1. Law JC, Recchia EM, Morrison DG, Donahue SP, Estes RL. Intravitreal bevacizumab as adjunctive treatment for retinopathy of prematurity. *J AAPOS* 2010;14:6-10.

## Apixaban in Patients with Atrial Fibrillation

**TO THE EDITOR:** Connolly et al. (March 3 issue) report the results of the AVERROES (Apixaban Versus Acetylsalicylic Acid [ASA] to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment) trial regarding apixaban in patients with atrial fibrillation.<sup>1</sup> Aspirin has been shown to be modestly effective in the primary prevention of ischemic strokes in patients with nonvalvular atrial fibrillation. Historically, a meta-analysis of six major trials comparing aspirin with warfarin showed that warfarin significantly reduced the

rate of ischemic stroke, as compared with aspirin (2.0 vs. 4.3 events per 100 patient-years; hazard ratio, 0.48).<sup>2</sup> It is not surprising that Connolly et al. were able to report a benefit with apixaban relative to aspirin in reducing the risk of ischemic stroke and systemic embolism. These investigators allowed physicians to choose the dose of aspirin administered to the participants. It is also important to note that no information was provided about other medications being taken by the participants that might limit aspirin's effect (e.g., nonsteroidal antiinflammatory drugs [NSAIDs])