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TO THE EDITOR: The study by Mintz-Hittner et al. (Feb. 17 issue) 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, this is not true. In the Cryotherapy for Retinopathy of Prematurity study (CRYO-ROP; ClinicalTrials.gov number, NCT00000133) and the Early Treatment for Retinopathy of Prematurity study (ETROP, NCT0027222), 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.


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. This phenomenon has been termed the “third epidemic” of retinopathy of prematurity. 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. 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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TO THE EDITOR: The Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity study (BEAT-ROP, NCT00622726) suggests that the intravitreal 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. 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 intravascular bevacizumab injection. VEGF contributes to lung development, 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, 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.


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. The historical lesson on antiangiogenesis 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.2 If the rate of neuro-
motor disturbance in infants of less than 26 weeks
of age is approximately 16 to 28%,3 the BEAT-ROP
study was too small to detect even a 10% increase
in incidence of neurologic damage from bevaciz-
umab. 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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ported.

2. Michaud AP, Bauman NM, Burke DK, Manaligod JM, Smith
RJH. Spastic diplegia and other motor disturbances in infants
3. Milligan DWA. Outcomes of children born very preterm in

THE AUTHOR REPIES: 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 na-
tions, infants with retinopathy of prematurity
have poor outcomes, probably because ever small-
er 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, col-
clected at 6 months after treatment, suggest
that intravitreal bevacizumab injections are more ef-
eective than laser treatment for zone I retinopa-
thy of prematurity. We did not suggest that this
treatment should be considered the standard of
care; however, we did state that additional stud-
ies should be designed to evaluate the long-term
efficacy and safety of intravitreal bevacizumab
injections to treat zone I disease and zone II dis-
ease 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.1 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 VEGF2
and an inhibitor of VEGF receptor 2 tyrosine
kinase3 were injected intravitreally. Both studies
showed that anti-VEGF therapy reduced endothe-

delial-cell migration into the vitreous without inter-
ferring 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 re-
sults (collected at 6 to 9 months after treatment).
However, RetCam imaging, which provided ob-
jective documentation throughout the study, was
a critical part of our study design. This imaging
allowed multiple opinions of disease classifica-
tion and treatment responses. We intend to fol-
low these infants for 5 years (or longer) and to
include assessments of neurodevelopmental out-
comes, as well as ocular outcomes, by indepen-
dent, 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 un-
ethical to withhold the data from other physi-
cians who are responsible for the care of patients
who present with severe zone I stage 3+ retinopa-
thy of prematurity.

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

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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.1 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).2 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]) 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.