Dear Editor,

Wood et al. describe a neonatal female born at 28 weeks with a weight of 990 grams who, at 37 weeks postmenstrual age, developed Zone 1, Stage 3 retinopathy of prematurity (ROP) with plus disease in the right eye and Zone 1, Stage 2 ROP with plus disease in the left eye. The right eye underwent intravitreal injection with low-dose bevacizumab (0.0625 mg; IVB) (Avastin; Genentech, South San Francisco, CA), whereas the left eye underwent laser ablative therapy. At 42 weeks, the right eye was vascuarily quiet despite nasal retinal folds, whereas the left eye had a tractional retinal detachment (TRD).

The authors concluded the “atypical” TRD in the left eye was due to a to crossover “crunch” effect from the right IVB. This conclusion is highly unlikely. In macaques weighing between 3 kg to 6 kg (a reasonable surrogate for a 42-week neonate), bevacizumab concentrations in the uninjected contralateral eye were more than 2,500-fold lower than in the injected eye (ie, well below the in vitro or in vivo minimum therapeutie threshold).

The authors also proposed that the reduction in vascular endothelial growth factor from IVB increased the pro-fibrotic effect of transforming growth factor-beta (TGF-β) based on cytokine analysis from adults with proliferative diabetic retinopathy. Such cytokine changes after IVB have not been consistently reported in adults, have not been examined in neonates with ROP, and have not been reported in the uninjected contralateral eye. In contradiction to the authors’ TGF-β hypothesis, the right eye, which received bevacizumab, did not develop a TRD.

A more likely explanation is that the laser ablative therapy itself caused the TRD. In a comprehensive study by Coats et al., 36 eyes of 138 infants who received laser ablative therapy for ROP from a single institution during a period of 4 years developed a TRD, 47% of which occurred within the first 28 days. In comparison, a large 7-year retrospective study across six high-volumeROP centers found 35 neonatal eyes developed a TRD after IVB. Though the total number of intravitreal injections was not reported, given the number sites and duration of the study, the incidence rate of TRDs is likely much less than the 13.7% reported following laser ablative therapy. Anecdotally, at our institution, no TRDs have developed after IVB, whereas progressive TRDs have been observed following laser ablative therapy.

In summary, consistent with the authors’ observations, but contrary to their conclusions, laser ablative therapy appears to have a greater risk of inducing TRDs in ROP than IVB.

Ira Schachar, MD, MSc
Department of Ophthalmology
Stanford University
Stanford, CA

REFERENCES


Ira Schachar, MD, MSc, can be reached at Stanford University School of Medicine, 291 Campus Drive, Stanford, CA 94305; email: ischacha@stanford.edu.

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Reply to Letter to the Editor: Fellow Eye Anti-VEGF ‘Crunch’ Effect in Retinopathy of Prematurity

We very much appreciate the thoughts of the authors of the letter regarding the management of type 1 retinopathy of prematurity (ROP). Although we agree with the authors that fellow-eye anti-vascular endothelial growth factor (VEGF) levels have not been directly measured in human infants, considering the effect on macaque monkeys may maintain less relevance given a fellow-eye anti-VEGF effect has been measured in human adults. The primary feature leading us to consider a fellow-eye anti-VEGF crunch effect is the anatomy of the retinal detachment in the case described: atypical for tractional retinal
detachments, which evolve following laser, yet with anatomic features characteristic of “crunch” detachments, as have been reported pursuant to ROP treatment with anti-VEGF drugs. Asymmetric bilaterality is common in ROP and likely explains the lack of “crunch” seen in the injected eye. Our goal is not to ascribe relative superiority to one ROP treatment option over another, as this outside the scope of this paper, but rather to describe a unique clinical finding in a fellow-eye following anti-VEGF therapy. We thank the authors for their time and consideration of this paper.

Edward H. Wood, MD
Kimberly A. Drenser, MD, PhD
Antonio Capone, MD
Michael T. Trese, MD
William Beaumont Hospital
Associated Retinal Consultants
Royal Oak, MI

REFERENCES


Edward H. Wood, MD, can be reached at Associated Retinal Consultants, William Beaumont Hospital, Neuroscience Center, 3555 W. 13 Mile Road, Suite LL-20, Royal Oak, MI 48073; email: ewood@arcpc.net.

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