

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

Dear Editor,

Wood et al.<sup>1</sup> 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 vascularly 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 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<sup>2</sup> (ie, well below the in vitro or in vivo minimum therapeutic 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- $\beta$ ) based on cytokine analysis from adults with proliferative diabetic retinopathy. Such cytokine changes after IVB have not been consistently reported in adults,<sup>3</sup> have not been examined in neonates with ROP, and have not been reported in the uninjected contralateral eye. In contradiction to the authors’ TGF- $\beta$  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.,<sup>4</sup> 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-volume ROP centers found 35 neonatal eyes developed a TRD after IVB.<sup>5</sup> 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

1. Wood EH, Rao P, Moysidis SN, et al. Fellow eye anti-VEGF ‘crunch’ effect in retinopathy of prematurity. *Ophthalmic Surg Lasers Imaging Retina*. 2018;49(9):e102-e104.
2. Miyake T, Sawada O, Kakinoki M, et al. Pharmacokinetics of bevacizumab and its effect on vascular endothelial growth factor after intravitreal injection of bevacizumab in macaque eyes. *Invest Ophthalmol Vis Sci*. 2010;51(3):1606-1608.
3. Arimura N, Otsuka H, Yamakiri K, et al. Vitreous mediators after intravitreal bevacizumab or triamcinolone acetonide in eyes with proliferative diabetic retinopathy. *Ophthalmology*. 2009;116(5):921-926.
4. Coats DK, Miller AM, Hussein MAW, McCreery KMB, Holz E, Paysse EA. Involution of retinopathy of prematurity after laser treatment: factors associated with development of retinal detachment. *Am J Ophthalmol*. 2005;140(2):214-222.
5. Yonekawa Y, Wu WC, Nitulescu CE, et al. Progressive retinal detachment in infants with retinopathy of prematurity treated with intravitreal bevacizumab or ranibizumab. *Retina*. 2018;38(6):1079-1083.

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

**Disclosure:** Dr. Schachar reports no relevant financial disclosures.

## 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.<sup>1,2</sup> 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.<sup>3</sup> Asymmetric bilateral-ity 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**

1. Bakbak B, Ozturk BT, Gonul S, Yilmaz M, Gedik S. Comparison of the effect of unilateral intravitreal bevacizumab and ranibizumab injection on diabetic macular edema of the fellow eye. *J Ocul Pharmacol Ther.* 2013;29(8):728-732.
2. Hanhart J, Tiosano L, Averbukh E, et al. Fellow eye effect of unilateral intravitreal bevacizumab injection in eyes with diabetic macular edema. *Eye (Lond).* 2014;28(6):646-653.
3. Yonekawa Y, Wu WC, Nitulescu CE, et al. Progressive retinal detachment in infants with retinopathy of prematurity treated with intravitreal bevacizumab or ranibizumab. *Retina.* 2018;38(6):1079-1083.

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**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.

**Disclosures:** The author reports no relevant financial disclosures.

doi: 10.3928/23258160-20190301-01