Re: Lepore et al.: Follow-up to age 4 years of treatment of type 1 retinopathy of prematurity intravitreal bevacizumab injection versus laser: fluorescein angiographic findings (Ophthalmology. 2018;125:218-226)

TO THE EDITOR: We thank the authors for providing follow-up to their original study1 from 2014 (reference 34 from the current report). The original study was undertaken at 9 months of age, and the authors raised concerns that angiographic abnormalities seen in eyes that received anti-vascular endothelial growth factor (VEGF) for retinopathy of prematurity (ROP) may have long-lasting implications for visual function. The key challenge in both the 2014 and this follow-up study is assigning functional value to the structural findings. We had anticipated new information regarding visual outcomes, which we assume could be collected in this 4-year follow-up study, but was not presented. Without visual acuity, contrast sensitivity, or visual field testing, what do these findings mean to the patient? Anti-VEGF treatment has important benefits, including rapid regression of pathologic neovascularization without destruction of retinal tissue and decreased rates of retinal detachment. Suggesting that these advantages should be ignored owing to abnormal intraretinal vascular development seems misguided. Ultimately, visual outcomes, rather than fluorescein angiographic findings, will determine optimal treatment.

In our opinion, these anomalous vascular patterns may be visually equivocal and could ultimately be consistent with excellent visual acuity and visual field. In contrast, retinal detachment, which was only seen in the laser group, is clearly associated with blindness. In addition, chorioretinal atrophy (from laser scars) reflects loss of the retinal pigment epithelium and photoreceptors, and has definite negative implications for visual function. From a functional standpoint, we might also expect to see a high degree of unilateral myopia, and perhaps anisometropic amblyopia, in eyes that received laser treatment.2

To highlight this disconnect between structure and function, anomalous branching patterns are well-documented in other diseases with normal visual acuity. ROP itself, for example, causes abnormal vascular development, yet many adults with spontaneously regressed ROP and good vision also have circumferential and fingerlike vessels. Many of these abnormalities arise from ROP itself, as evidenced by their presence in nearly all eyes before treatment in their study. The vascular shunts may be residual from the original ROP stage 3 ridge, and their persistence may cause the abnormal radial, fingerlike vessels that grow anterior into the avascular retina. This growth does not (usually) occur into ablated retina.

We agree that chronic hyperfluorescence and hypofluorescence reflects residual ischemic retina and we think that serious consideration for treatment should be given, even after 4 years, not because these findings are harmful to vision per se, but to prevent associated late ROP reactivation and retinal detachment. There is evidence that this residual anterior avascular retina should be treated with prophylactic laser around 60 months postmenstrual age.3

The 1 lesion of functional concern is the retinal pigment epithelium pigmentary disruption seen in Figure 8. We have been most interested in the incidence of this visually important event. We have rarely seen this retinal pigment epithelium dropout after laser therapy, but not after anti-VEGF, and have hypothesized transient exudative retinal detachment. This finding warrants further study, but is not unique to anti-VEGF therapy.

In addition to theoretical adverse ocular outcomes, the authors also expressed concerns about the systemic implications of anti-VEGF therapy, citing retrospective studies with numerous confounding factors.4 These studies must be interpreted with caution, particularly when blindness is one of the defining criteria of severe developmental disability, along with sensorineural hearing loss, inability to sit, shunted hydrocephalus, and Bayley scores of >2 standard deviations below the mean.5

Anti-VEGF therapy is used worldwide to treat ROP, and we thank the authors for describing some of the differences in its postoperative condition. Regardless of treatment, ROP is a life-long disease. After reaching stage 3, the retina will never become normal regardless of treatment. We look forward to information regarding visual outcomes in these eyes.

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References

