Dear Editor,

We read with great interest and concern the report by Snyder et al.\(^1\) describing a case of aggressive posterior retinopathy of prematurity (ROP) treated with bevacizumab (Avastin; Genentech, South San Francisco, CA) and found to recur as late as 2.5 years of age. We would be interested to know the frequency of follow-up examinations carried out before this devastating recurrence was noted, and whether any concerning ocular findings were noted at the last examination (e.g., pre-plus at the disk or in the periphery). The authors say that the child was seen by another retinal specialist and sent to pediatric ophthalmology for follow-up after 80 weeks postmenstrual age (PMA); however, no description was given of this follow-up plan. It was also not mentioned whether the child had recurrent infections, breathing difficulties or hypoxia, or other conditions of oxidative stress predisposing to ROP recurrence during this follow-up. Finally, it was not described as to whether 2.5 years was the child’s corrected or uncorrected age;\(^2\) for an infant born at 24 weeks PMA, this makes a big difference.

The above information would be useful in planning a better follow-up schedule for babies who have had similar disease severity treated with bevacizumab. As with screening guidelines for the assessment of ROP development in at-risk infants, the challenge here is to follow-up injected babies closely enough to detect recurrences promptly, but not unnecessarily closely. The authors encouraged prolonged and frequent follow-up, but no one really knows how prolonged and how frequent is appropriate. They also suggested that fluorescein angiography (FA) could be useful in patients where the peripheral retina is difficult to examine. Similar suggestions were made by Toy et al.\(^3\) in their recent study, where a pattern of “vascular arrest” was described in some patients, and prophylactic laser photocoagulation to the remaining avascular retinal periphery was suggested in these cases. However, FA is not available in every institution treating ROP.

The case reported by Snyder et al. is somewhat shocking and raises real concern to clinicians using bevacizumab in ROP while they are perhaps not able to follow-up these patients themselves in the long term. With all of the emerging anti-vascular endothelial growth factor injectable treatments, and augmentation of their usage since the BEAT-ROP study, we believe that it is time a panel of experts evaluates all current knowledge and establishes a set of follow-up and treatment guidelines to assist physicians less experienced with ROP management. This will also help convince parents to adhere to their follow-up, as well as to treatment suggestions.

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Reply to Letter to the Editor: Very Late Reactivation of Retinopathy of Prematurity After Monotherapy With Intravitreal Bevacizumab

We thank the letter writers for their interest in our report.\(^1\) We hope that this case, along with others regarding reactivation after bevacizumab (Avastin; Genentech, South San Francisco, CA) treatment for retinopathy of prematurity (ROP),\(^2-5\) convinces ROP treaters to follow the protocol we and others\(^6\) have suggested to prevent late complications, namely fluorescein angiography (FA)-guided treatment of persistent nonperfused retina. We prefer
the term “reactivation” to emphasize that as long as there is either residual neovascularization or peripheral nonperfusion, the ROP is not cured, but rather persists in a deceptively dormant state, rather than using the term “recurrence,” which implies disappearance or cure and subsequent return. We agree that a consensus statement would be helpful, but unfortunately controversy exists. Some recommend against anti-vascular endothelial growth factor (VEGF) treatment altogether, and some do not believe prophylactic laser is needed. Unfortunately, long-term data may be lacking for several reasons: study endpoints may be before reactivation has occurred, patients can be lost to follow-up, and the periphery is difficult to examine in children old enough to resist. Additionally, infants treated in countries where prophylactic laser has generally not been performed are likely to have had higher birth weights and later gestational ages, so direct comparison regarding need for retreatment with infants born in the United States and other countries where very small neonates survive may not be valid.

We agree that it is uncertain how long frequent, prolonged follow-up is needed, but reason that as anti-VEGF effect wanes, intravitreal VEGF accumulation will be dependent on the amount of ischemic retina that is metabolically active. This may vary among eyes and infants with different degrees of peripheral vascular growth and systemic oxygenation. FA-guided laser ablation seems the ideal solution. We have not seen a recurrence after prophylactic laser.7 Centers without FA capabilities could treat under anesthesia or sedation, based on careful examination attentive to patterns of reactivation. Alternatively, infants could be referred to centers with access to FA. Even after laser (and particularly without it), we suggest stage 3 ROP has a chronic component that is life-long. Therefore, follow-up every 3 months until the child can reliably report visual symptoms and then lifelong follow-up every 6 months thereafter is warranted. It may be that not all eyes with persistent avascular retina need to be treated, but those that progress to advanced detachment have a poor prognosis. There is little downside to laser ablation to residual nonperfused retina, particularly when laser has been the standard of care for many years and ablative treatment of retina ischemia is established and effective in the full range of retinovascular diseases. Post-bevacizumab eyes behave distinctly from those that underwent spontaneously regression that have historically been observed. It should be noted that even after spontaneous regression, some eyes progress to detachment in older children and adults. We have seen many late recurrences (acknowledging referral bias) in older children, many of whom present when the second eye is involved, with the first being inoperable. Lifelong risk of ROP complications is supported by 15-year CRYO ROP data.8

With regard to questions about the patient in this case report, there were no recurrent infections, breathing difficulties, or oxidative stress. No concerning ocular findings were noted prior to detachment, and 2.5 years was the patient’s uncorrected age. The ophthalmologists to whom the family transferred care were not particularly concerned about reactivation of ROP, and follow-up was scheduled every 6 months.

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