

ONLINE FIRST

Reactivation of Retinopathy of Prematurity After Bevacizumab Injection

Jennifer Hu, MD; Michael P. Blair, MD; Michael J. Shapiro, MD; Steven J. Lichtenstein, MD; John M. Galasso, MD, PhD; Rashmi Kapur, MD

Objective: To report late reactivation and progression of retinopathy of prematurity (ROP) after intravitreal bevacizumab monotherapy.

Methods: Retrospective review of 9 patients (17 eyes) with recurrence of ROP after initial treatment with intravitreal bevacizumab monotherapy. Data collected included (1) location and stage of ROP activity, (2) number and timing of treatments, and (3) structural outcomes.

Results: Mean age at treatment-requiring recurrence was 49.3 weeks (SD, 9.1 weeks; minimum, 37 weeks; maximum, 69 weeks) postmenstrual age (PMA). The mean time between initial treatment and treatment-requiring recurrence was 14.4 weeks, with a minimum of 4 and maximum of 35 weeks. Five eyes progressed to retinal detachment (4 eyes stage 5, 1 eye stage 4a). Age at reti-

nal detachment ranged from 49 to 69 weeks PMA with a median of 55 weeks PMA and mean of 58.4 weeks PMA. No eye that received laser treatment for recurrence progressed to retinal detachment.

Conclusions: Although intravitreal bevacizumab treatment is effective in inducing regression of ROP, the effect may be transient. Recurrence can occur later in the course than with conventional laser therapy. Late retinal detachment can occur despite early regression. Long-term favorable structural outcome may require extended observation and retreatment. Laser may be a useful treatment for recurrences.

Arch Ophthalmol. 2012;130(8):1000-1006.

Published online April 9, 2012.

doi:10.1001/archophthalmol.2012.592

RETINOPATHY OF PREMATURITY (ROP) is a retinal vascular developmental disease affecting premature infants. It remains a major cause of blindness despite advances in treatment. Randomized treatment trials initially established peripheral retinal ablation with cryotherapy for threshold disease¹ and subsequently laser photocoagulation for type 1 prethreshold ROP.² The role of vascular endothelial growth factor (VEGF) in the pathophysiology of ROP is well studied,³⁻⁵ and recently, a prospective randomized controlled stratified multicenter trial assessed bevacizumab monotherapy (BEAT-ROP).⁶ It concluded that when considering both zone 1 and posterior zone 2 ROP together, bevacizumab treatment was more effective than peripheral laser ablation. When considering the prospectively stratified subgroups separately, this benefit held for zone 1 ROP eyes but not for posterior zone 2 ROP eyes.

The BEAT-ROP study reported that the interval from initial treatment to treatment-requiring recurrence was longer in the be-

vacizumab group compared with the laser group. This interval was approximately 3 months longer in zone 1 eyes, but the number of eyes with retreatment-requiring recurrences in each group was small.⁶ In our clinical experience, we have observed late reactivation of ROP after bevacizumab treatment⁷ including progression to stage 5 retinal detachment.⁸ In this report, we describe our experience of 17 eyes that received initial intravitreal bevacizumab monotherapy (Avastin) and in which treatment-requiring recurrence occurred.

METHODS

Clinical records were reviewed from a pediatric retina referral practice of 17 eyes of 9 patients who received intravitreal bevacizumab monotherapy as initial treatment for ROP and subsequently required further treatment. Patients who received bevacizumab injection but did not have recurrence were not included in this study. Approval from the institutional review board at the University of Illinois at Chicago was obtained. The injection dose of be-

Author Affiliations: University of Illinois at Chicago (Drs Hu, Blair, and Shapiro) and University of Chicago (Dr Blair), Chicago, Retina Consultants Ltd, Des Plaines (Drs Blair, Shapiro, Galasso, and Kapur), and University of Illinois College of Medicine at Peoria (Dr Lichtenstein).

vacuzumab was a 0.025- to 0.03-mL dose of 0.625 to 0.750 mg. Gestational age, birth weight, age at bevacizumab injection, age at recurrence, age at diagnosis of retinal detachment, and recurrence pattern were recorded.

Recurrence of ROP was defined as arrest of anterior progression of retinal vasculature associated with a new demarcation line, ridge, or extraretinal fibrovascular proliferation (EFP) or leakage on fluorescein angiography, with or without recurrence of plus disease. Extraretinal fibrovascular proliferation was not required for recurrence. *Recurrence* implied reactivation after a period of regression while *persistence*, on the other hand, was defined as lack of adequate regression after treatment. It may be difficult to distinguish recurrence from persistence in a retrospective study. Therefore, we arbitrarily defined ROP to be persistent if the retreatment occurred within 1 month from the previous treatment. Recurrence patterns were categorized by anatomic location as follows: *anterior recurrence* was defined as EFP, ridge, or demarcation line at the location of the second arrest of intrinsic retinal vasculature, after initial anterior progression; *posterior recurrence* was defined as recurrence at least 3 disc diameters posterior to the current area of vascular arrest. The posterior recurrence was documented by serial evaluation in some eyes to be the original EFP if there were persistent residua. In other eyes with more complete regression of initial EFP or transfer of care, this correlation of prior location of EFP could not be verified in this retrospective study. The anterior recurrence was at or near the current junction of vascular and avascular retina, while the posterior recurrence was well within the area of vascularized retina and distinctly more posterior. In eyes with stage 5 ROP, because of prevalence of anterior EFP behind the lens, anterior-posterior landmarks were impossible to locate and recurrence was designated to be anterior, unless prior clinic notes also described posterior recurrence as well.

Retreatment criteria were not standardized. Retreatment was done at the discretion of the treating clinician but usually was done if plus disease returned, with or without EFP, or if EFP returned, with or without plus disease. Statistics calculated included mean, median, and standard deviations.

RetCam (Clarity Medical Systems Inc) photography and angiography were reviewed when available. Since the clinical appearance of the recurrences was different from the proliferations seen in the natural history of ROP described in the International Classification of ROP,⁹ selected case reports and figures are also included.

RESULTS

The **Table** presents gestational age, birth weight, age at initial bevacizumab therapy and at recurrence, treatment for recurrence, recurrence pattern, and age at retinal detachment for 17 study eyes of the 9 patients. At the time of initial treatment, all patients had posterior elevated extraretinal vessels (stage 3) with plus disease (type 1 prethreshold ROP). Gestational age ranged from 23 to 32 weeks with a mean of 25 weeks. Birth weight ranged from 510 to 1843 g with a mean of 731.7 g. Age at initial injection varied from 32 to 35 weeks postmenstrual age (PMA), with a mean of 34.1 weeks PMA, and averaged 8.9 weeks after birth. Mean age at treatment-requiring recurrence was 49.3 weeks PMA with a maximum of 69 weeks, a minimum of 37 weeks PMA, and an SD of 9.1 weeks. The mean time between initial treatment and treatment-requiring recurrence was 14.4 weeks, with a minimum of 4 and maximum of 35 weeks. Two cases, 3 and

9, because of both persistence and recurrence, required repeated injections followed by laser treatment. Five eyes (cases 1, 2, and 8) had recurrence in the form of retinal detachments necessitating surgical repair. Median age at retinal detachment was 55 weeks PMA and mean age was 58.4 weeks PMA, ranging from 49 to 69 weeks PMA. Eight eyes had anterior recurrence only, 2 eyes had posterior recurrence only, and 7 eyes had combined anterior and posterior recurrence patterns.

CASE 3

A former 24-week premature, 530-g neonate received intravitreal injections of bevacizumab at 34 weeks PMA in both eyes for aggressive posterior ROP (APROP) (zone 1, stage 3 ROP) (**Figure 1**). Persistence was noted at 2 weeks postinjection (36 weeks PMA) and bevacizumab injection was repeated in both eyes. Five weeks later, combined anterior and posterior recurrence of vessels was noted, and bevacizumab injection with concurrent laser in both eyes was administered at 41 weeks PMA. The posterior extraretinal vessels appeared quite elevated and similar to APROP, because they were not associated with significant fibrous elements. They appeared similar to established elevated neovascularization seen in diabetic retinopathy. The anterior recurrence appeared with typical stage 3 EFP.¹⁰ Last follow-up at 104 weeks PMA demonstrated attached retinas in both eyes.

CASE 5

A former 24-week premature, 710-g neonate received bevacizumab in both eyes at 32 weeks PMA for APROP (zone 1, atypical stage 3 with plus disease) (**Figure 2**). Recurrence was noted at 5 weeks postinjection or 37 weeks PMA as persistent posterior APROP without significant fibrous elements, anterior recurrence with typical EFP, and a return of plus disease. Laser treatment was administered in both eyes without subsequent progression to retinal detachment, with the last follow-up at 79 weeks PMA. Fundus photographs taken at 58 weeks PMA demonstrate contracture of the posterior cicatrix as well as anterior cicatricial EFP.

CASE 8

A former 25-week premature, 510-g neonate received bevacizumab in both eyes at 34 weeks PMA for zone 1, stage 3 ROP with plus disease (**Figure 3**). The left eye underwent uncomplicated cataract extraction at 48 weeks PMA for cataract presumably related to injection. Recurrence of ROP was noted as stage 5 retinal detachment in the right eye and far anterior stage 4a retinal detachment with a heterotopic macula in the left eye at 35 weeks postinjection or 69 weeks PMA. Initial surgical repair in the left eye was performed with scleral buckle. Subsequently, at 78 weeks PMA, the left eye was noted to have a small, posterior tent-shaped detachment associated with a hyaloid artery remnant as well as persistent anterior detachment, and vitrectomy was performed. The macula in the left eye has remained attached and the peripheral detachment was successfully treated. The right eye has

Table. Clinical Characteristics of Infants and Eyes With Treatment-Requiring Recurrence After Bevacizumab Treatment

Patient No.	GA	Weight, g	Eye	PMA, wk, at Initial Bev	Weeks After Birth at Time of Bev	PMA, wk, at Recurrence	Weeks After Bev at Recurrence	Recurrence Pattern ^a	Treatment for Recurrence	Age at Detachment (PMA, wk)
1	23	567	OS	32	9	49	17	S5: wide, broad fibrous attachment between anterior and posterior ridges	PPV	49
2	23	560	OD	35	12	50	15	S4a at 50 wk PMA, then S5 at 54 wk PMA: anterior and posterior	PPV at 57 wk PMA	50
2			OS	35	12	55	20	S5: anterior and posterior	PPV at 57 wk PMA, then open-sky vitrectomy at 72 wk PMA	55
3	24	530	OD	34	9	41	4	Anterior and posterior recurrence of vessels	Bev for persistence at 36 wk PMA, Bev with concurrent laser treatment at 41 wk PMA for recurrence	NA
3			OS	34	9	41	4	Anterior and posterior recurrence of vessels	Bev for persistence at 36 wk PMA, Bev with concurrent laser treatment at 41 wk PMA for recurrence	NA
4	26	625	OD	34	8	48	14	Anterior only	Laser	NA
4			OS	34	8	48	14	Anterior only	Laser	NA
5	24	710	OD	32	8	37	5	S3: anterior and posterior recurrence, taut posterior fibrosis	Laser	NA
5			OS	32	8	37	5	S3: anterior and posterior recurrence, taut posterior fibrosis	Laser	NA
6	24	640	OD	35	11	51	16	S2-S3: anterior	Laser	NA
6			OS	35	11	51	16	S2-S3: anterior	Laser	NA
7	24	600	OD	35	11	51	16	S2-S3: anterior	Laser	NA
7			OS	35	11	51	16	S2-S3: anterior	Laser	NA
8	25	510	OD	34	9	69	35	S5: anterior	Open-sky vitrectomy at 84 wk PMA	69
8			OS	34	9	69	35	S4a at 69 wk PMA: anterior, posterior recurrence near optic nerve at 78 wk PMA	Scleral buckle, PPV at 78 wk PMA for 2nd recurrence	69
9	32	1843	OD	35	3	42	7	S2: atypical, posterior	Bev for recurrence at 42 wk PMA, then laser treatment for recurrence at 48 wk PMA	NA
9			OS	35	3	48	5	S2: atypical, posterior	Bev for persistence at 38 wk PMA, Bev for recurrence at 42 wk PMA, and laser treatment for recurrence at 48 wk PMA	NA
Mean	25.0	731.7		34.1	8.9	49.3	14.4			58.4
Median	24.0	600.0		34.0	9.0	49.0	15.0			55.0
SD	2.8	421.2		1.1	2.6	9.1	9.5			9.9
Max	32.0	1843.0		35.0	12.0	69.0	35.0			69.0
Min	23.0	510.0		32.0	3.0	37.0	4.0			49.0

Abbreviations: Bev, bevacizumab treatment; GA, gestational age; Max, maximum; Min, minimum; NA, not applicable; PMA, postmenstrual age; PPV, pars plana vitrectomy; S2, stage 2; S3, stage 3; S4a, stage 4a; S5, stage 5.

^aAll eyes had posterior stage 3 ROP at the time of initial treatment.

undergone open-sky vitrectomy and residual detachment remains.

CASE 9

A former 32-week premature, 1843-g neonate received intravitreal bevacizumab in both eyes at 35 weeks PMA for APROP (zone 1 atypical stage 3 with plus disease) (**Figure 4**). Recurrence was noted at 42 weeks PMA in

the right eye and a second injection of bevacizumab was administered. Similarly, persistence in the left eye was noted at 38 weeks PMA for which bevacizumab was again injected. Recurrence in the left eye was noted at 42 weeks PMA, and a third injection was given. Recurrence in both eyes was noted at 48 weeks PMA in an atypical stage 2 pattern with worsening preplus disease. There was no ophthalmoscopically obvious posterior extraretinal fibrovascular proliferation, yet there was posterior leakage on

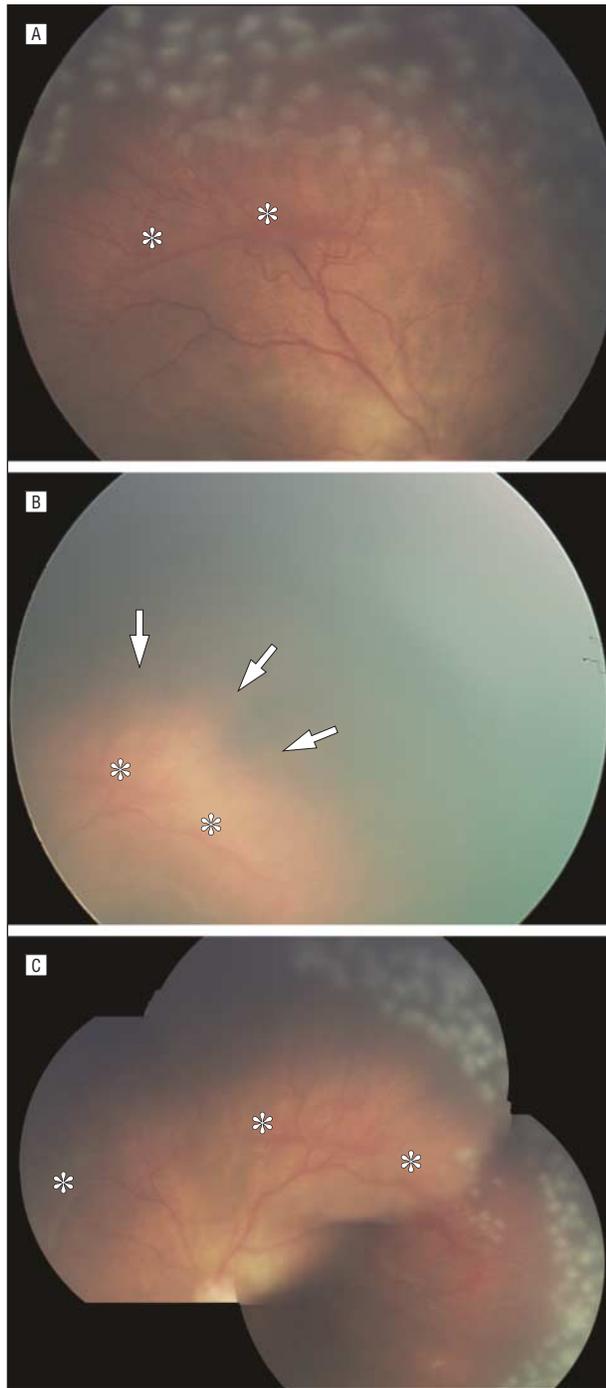


Figure 1. Case 3. A, RetCam (Clarity Medical Systems Inc) 80° color fundus photograph of the right eye immediately after the start of laser treatment demonstrating posterior recurrence (indicated with *) of extraretinal fibrovascular proliferation. The extraretinal vessels are an irregular vascular proliferation not accompanied by opaque or translucent fibrous elements seen in classic retinopathy of prematurity ridge stage 2 or extraretinal fibrovascular proliferation stage 3 nor are they the usual frond or brush border pattern seen in aggressive posterior retinopathy of prematurity. B, RetCam color fundus photograph of the left eye prior to laser treatment demonstrating posterior recurrence (indicated with *) more prominent than anterior recurrence (indicated with arrows). The posterior extraretinal vessels are fine vessels unaccompanied by high-contrast opaque tissue. C, Montage RetCam color fundus photograph of the left eye after anterior laser treatment demonstrating posterior recurrence (indicated with *) of extraretinal fibrovascular proliferation. Laser treatment posterior to the anterior ridge (not visualized in the photograph) was initiated but not completed at the time of the photograph. Dilated vessels helped to direct the examiner's attention posteriorly to the extraretinal vasculature, which is largely devoid of fibrosis.

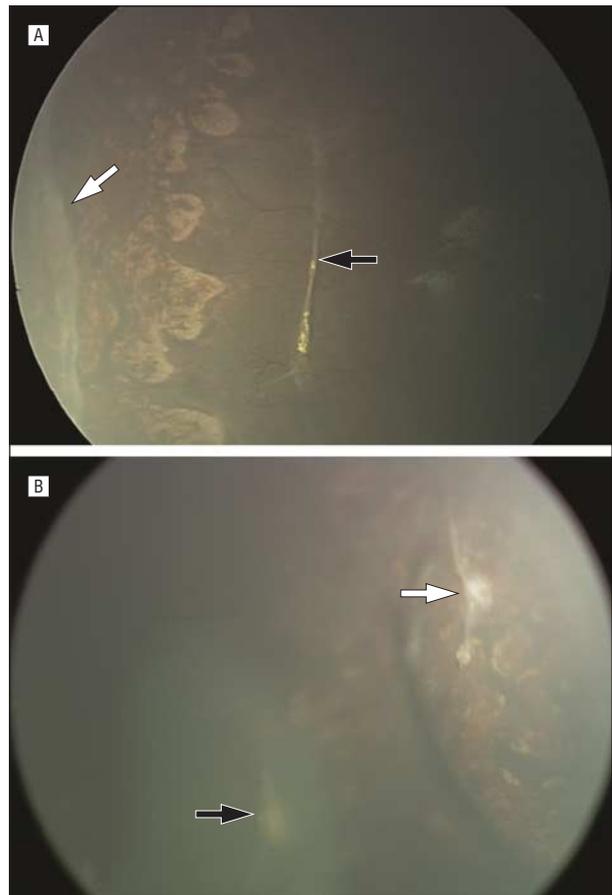


Figure 2. Case 5. A, RetCam (Clarity Medical Systems Inc) color fundus photograph of the right eye demonstrating posterior contracted extraretinal fibrovascular proliferation (black arrow) as well as anterior extraretinal fibrovascular proliferation (white arrow). Laser treatment was applied posterior to the second ridge because of presumed posterior incomplete vascularization in this area. B, Montage RetCam color fundus photograph of the left eye demonstrating posterior extraretinal fibrovascular proliferation (black arrow) as well as anterior extraretinal fibrovascular proliferation (white arrow).

fluorescein angiography. We suspected there were fine extraretinal vessels posteriorly and treatment with laser was performed in both eyes without subsequent progression to retinal detachment, with the last follow-up at 56 weeks PMA.

COMMENT

In this case series, we described 17 eyes of 9 patients with ROP that, despite initial treatment with intravitreal bevacizumab monotherapy, developed progression of disease. All 17 eyes underwent additional treatment, whether with bevacizumab (4 eyes), laser photocoagulation (12 eyes), or surgical retinal detachment repair (5 eyes).

Our study demonstrated that significant recurrences occurred when bevacizumab was used as initial therapy and that this effect occurred later when compared with recurrence after primary laser treatment. This delay in recurrence was reported by the BEAT-ROP study, despite the small number of treatment-requiring recurrences in eyes that received bevacizumab (n=6). That study reported significantly different times to recur-

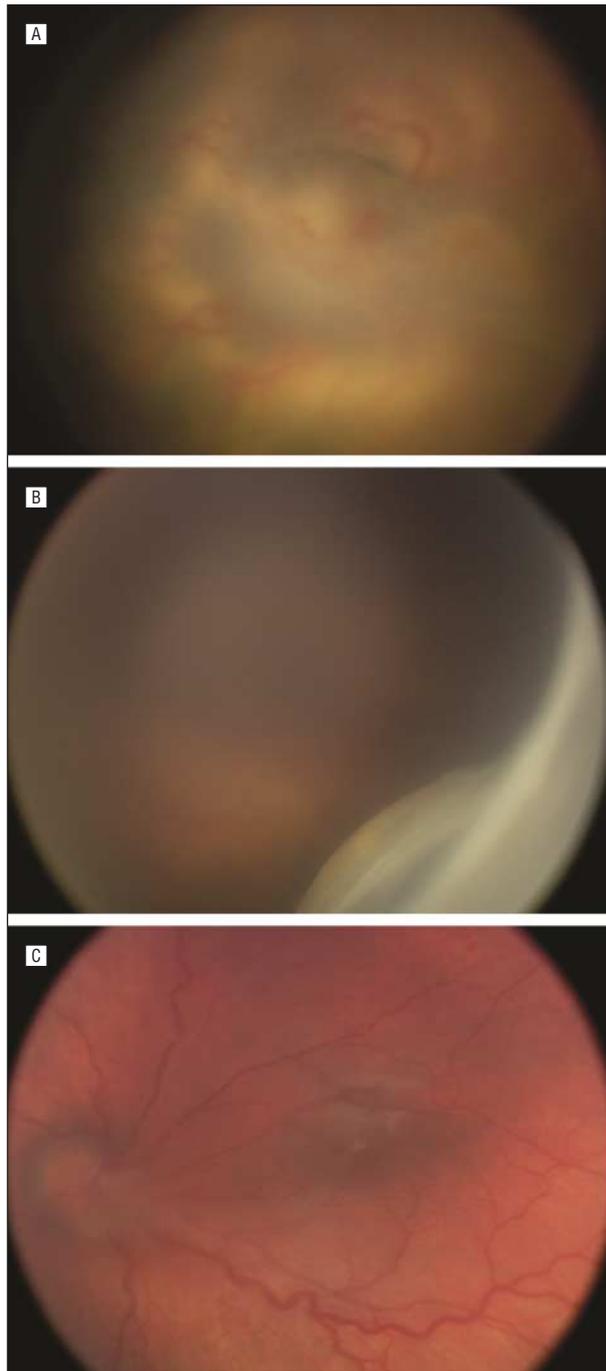


Figure 3. Case 8. A, RetCam (Clarity Medical Systems Inc) color fundus photograph of the right eye demonstrates total retinal detachment (stage 5 retinopathy of prematurity). B, RetCam color fundus photograph of the left eye with scleral depression of the anterior retina shows stage 4a retinopathy of prematurity with a temporal band of fibrous elements at the apex of the detachment. C, Temporal dragging of the vessels of the retina by the tractional elements seen in part B resulted in a narrowed angle between the temporal arcade vessels, residual inferior venous dilation and tortuosity, and a heterotopic macula in the left eye.

rence between the bevacizumab and laser groups.⁶ In eyes with zone 1 disease, the mean (SD) time to recurrence was 6.5 (6.7) weeks after laser treatment but 19.2 (8.6) weeks after bevacizumab treatment. The BEAT-ROP study used 54 weeks PMA as the final end point for assessment of recurrence. Assuming a normal distribution,

97.5% of all recurrences are encompassed after an interval less than 2 SDs and the end point PMA would have to be extended to 72.3 weeks, which is 18.3 weeks after the primary outcome used in BEAT-ROP.¹¹ Thus, the number of later recurrences in that study may have been greater than reported.

In our case series, we also observed that recurrence after bevacizumab treatment can occur late, with a mean (SD) age of recurrence of 49.3 (9.1) weeks PMA. Using 2 SDs, 97.5% of recurrences would be included only by 68 weeks PMA, which is around 3 months after the 54 weeks final examination used in BEAT-ROP. Of the 5 eyes that progressed to retinal detachment, the median age of detachment was 55 weeks PMA (range, 49-69 weeks) with a mean age of 58.4 weeks PMA.

In addition to a change in timing of recurrence, anti-VEGF therapy may alter the pattern of recurrence. We have observed that reactivation of proliferative ROP after bevacizumab treatment may occur posteriorly at or near the original posterior site of extraretinal fibrovascular proliferation rather than more anteriorly at the junction of the vascular and avascular retina. In this study, we characterized recurrence patterns by anatomic location with posterior recurrence occurring at or posterior to the location of the original extraretinal fibrovascular proliferation and anterior describing a more anterior ridge secondary to anterior progression of retinal vasculature. In our cohort of eyes, 47% (8 of 17 eyes) had anterior recurrence only, 12% (2 of 17 eyes) had posterior recurrence only, and 41% (7 of 17 eyes) had combined anterior and posterior recurrence patterns. This posterior recurrence pattern has not been well described previously, and such alterations may delay diagnosis and treatment owing to deviation from standard clinical recognition patterns based on experience after laser treatment. Importantly, these posterior extraretinal vessels may grow with minimal or no fibrous elements, similar to APROP, and may show little color contrast or may be mistaken as hemorrhages, making them difficult to identify. Furthermore, broader vitreoretinal adhesions between both anterior and posterior ridges, as well as altered adhesion strength at the vitreoretinal interface, may lead to higher contractile force and more rapidly developing retinal detachment. Additionally, the lack of laser-induced retinal-retinal pigment epithelium adhesion likely decreases the tendency of the retina to remain attached in the face of contractile EFP and thus may change the timing pattern to detachment.

The optimal treatment for recurrence after bevacizumab treatment is not known, whether using injection or laser. Some recurrence may also be self-limited and not require treatment. Clearly, cases of retinal detachment do not fall in that group. The number of eyes requiring retreatment after bevacizumab in the BEAT-ROP study was small (n=6) and the end point may not be sufficiently long to identify later recurrences, so no firm conclusions can be drawn from that study. We find several trends in our study intriguing. All 4 eyes that received a second injection of bevacizumab for recurrence or persistence ultimately received laser photocoagulation. No eye that received laser treatment for recurrence or persistence required further treatment, and

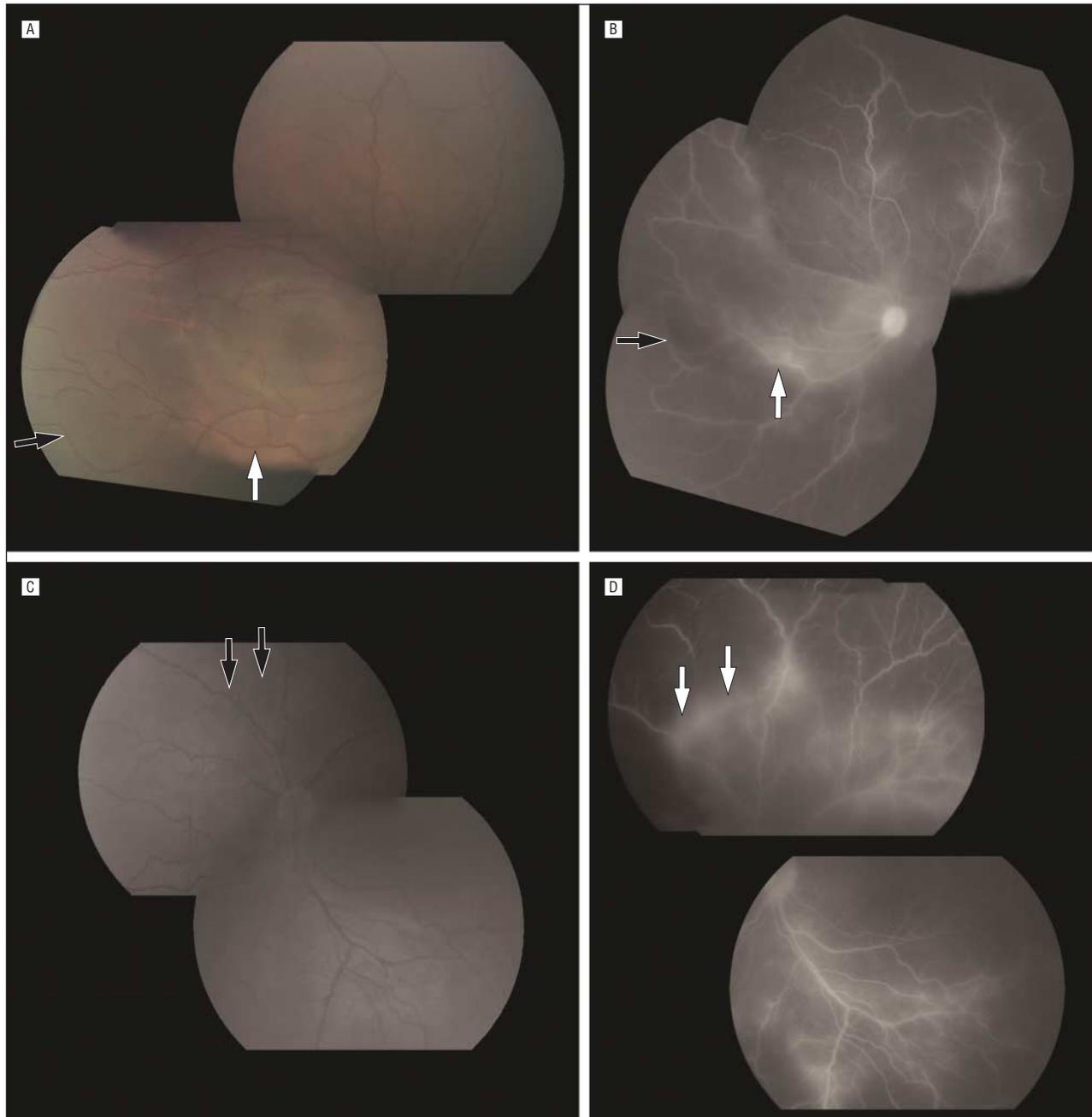


Figure 4. Case 9. A, Montage RetCam (Clarity Medical Systems Inc) color fundus photograph of the right eye demonstrates the posterior pole without evidence of extraretinal fibrovascular proliferation. No extraretinal vessels are seen emanating from the posterior arcade (white arrow). The black arrow indicates an anomalous circumferential vessel for correlation with part B. B, Montage RetCam fluorescein angiography of the right eye demonstrating leakage of posterior pole vasculature. The mechanism for leakage may be that (1) intrinsic retinal vasculature leaks abnormally, (2) there may be fine extraretinal vessels or vascular channel remnants that leak, or (3) tractional forces, presumably from regressed extraretinal fibrovascular proliferation, cause leakage. The white arrow corresponds to the area indicated by the white arrow in part A. The black arrow indicates an anomalous circumferential vessel, corresponding to part A. C, Montage RetCam red-free fundus photograph of the left eye demonstrating retinal vasculature without evidence of extraretinal fibrovascular proliferation. Arrows correlate to the location of arrows in part D. D, Montage RetCam fluorescein angiography of the left eye demonstrating leakage of posterior pole vasculature. Arrows correspond to the location of arrows in part C.

no eye that received laser treatment progressed to retinal detachment. Conversely, none of the 5 eyes that progressed to detachment had laser treatment. Given these findings, it would seem that laser photocoagulation might be preferable for recurrence. Because the BEAT-ROP data demonstrated no significant difference in recurrence in zone 2 eyes, it would seem reasonable to conclude that standard treatment with laser be considered for recur-

rence in zone 2, particularly in infants who are healthy enough for the anesthesia required for laser treatment.

There are several limitations to our study that weaken the strength of the conclusions. First, the number of eyes included is small, and the study is retrospective, without controls. Furthermore, there is very likely referral bias in our study that may significantly increase the number of eyes with recurrence of atypical or severe ROP, in-

cluding development of retinal detachment. Similarly, although many repeated injections have been given by us, we have excellent pediatric anesthesia available that allows the safer use of laser treatment. Therefore, we may have a degree of treatment bias for laser treatment over repeated bevacizumab injection, based on historical treatment patterns. Similar to the infants in BEAT-ROP, these were significantly small infants with posterior disease who required intervention at relatively early ages (the majority were <35 weeks PMA). Behavior of more typical anterior ROP after bevacizumab treatment may or may not be similar.

Bevacizumab alters the natural history of ROP in a manner qualitatively different from laser ablation. Bevacizumab causes transient blockade of VEGF rather than the long-term downregulation induced by laser. Given the biology and the experience in other diseases, it is not surprising that a single dose of VEGF blockade does not effect a permanent reversal in all eyes with ROP. Clearly, the extraretinal neovascularization seen in the posterior recurrences is novel. Although they share the absence of fibrous elements with EFP seen in APROP stage 3, in our cases we found them elevated well into the vitreous and to be less symmetric in the vascular distribution. This requires the examiner not only to study the anterior retina for EFP at the junction of vascularized and avascular retina but also to carefully study the posterior retina with a 20-diopter lens to identify fine persistent and recurrent vessels. We believe the present classification of ROP may not have a language to completely describe posterior recurrences. We speculate that these vessels were persistent in a nonperfused state that became visible with the return of generalized vascular dilation seen in plus disease or are newly proliferated because of the original injury at this site. In APROP, the plus disease and posterior avascular retina combine to raise the possibility of severe disease. Can plus disease provide a reliable clue for ROP recurrence? A prospective examination protocol with collection of long-term data following treatment of bevacizumab may provide guidance for avoidance of blindness from late ROP recurrences. Meanwhile, caution from the physicians and compliance from parents is required to ensure optimal outcomes.

Given the long interval to recurrence in our study, as well as the BEAT-ROP study, we suggest that follow-up for patients with ROP receiving bevacizumab monotherapy must be prolonged and highly vigilant. We consider the definitive end point for ROP treated by bevacizumab monotherapy an unsettled issue. We recommend that until further data on the course of ROP after beva-

cizumab treatment are collected, only with complete vascularization to the ora serrata and no active disease can treatment be considered successful. Many cases may not reach the ora serrata and they will require long-term monitoring. The optimal time and method to intervene for recurrence after bevacizumab treatment is not known. More studies are needed to determine what pattern of anti-VEGF therapy is needed to eliminate hypoxia-induced vascular proliferation. Until then, the community must be aware of the unexpected pattern and potential for unfavorable outcomes associated with late reactivation of ROP after anti-VEGF monotherapy.

Submitted for Publication: December 17, 2011; final revision received February 7, 2012; accepted February 10, 2012.

Published Online: April 9, 2012. doi:10.1001/archophthalmol.2012.592

Correspondence: Michael P. Blair, MD, Department of Ophthalmology, Retina Consultants Ltd, University of Chicago, 2454 E Dempster St, Ste 400, Des Plaines, IL 60016 (michaelblairmd@gmail.com).

Financial Disclosure: None reported.

REFERENCES

1. Cryotherapy for Retinopathy of Prematurity Cooperative Group. Multicenter trial of cryotherapy for retinopathy of prematurity: preliminary results. *Arch Ophthalmol.* 1988;106(4):471-479.
2. Early Treatment for Retinopathy of Prematurity Cooperative Group. Revised indications for the treatment of retinopathy of prematurity: results of the early treatment for retinopathy of prematurity randomized trial. *Arch Ophthalmol.* 2003;121(12):1684-1694.
3. Chen J, Smith LE. Retinopathy of prematurity. *Angiogenesis.* 2007;10(2):133-140.
4. Smith LEH. Pathogenesis of retinopathy of prematurity. *Acta Paediatr Suppl.* 2002;91(437):26-28.
5. Mintz-Hittner HA, Best LM. Antivascular endothelial growth factor for retinopathy of prematurity. *Curr Opin Pediatr.* 2009;21(2):182-187.
6. Mintz-Hittner HA, Kennedy KA, Chuang AZ; BEAT-ROP Cooperative Group. Efficacy of intravitreal bevacizumab for stage 3+ retinopathy of prematurity. *N Engl J Med.* 2011;364(7):603-615.
7. Hoang QV, Kiernan DF, Chau FY, Shapiro MJ, Blair MP. Fluorescein angiography of recurrent retinopathy of prematurity after initial intravitreal bevacizumab treatment. *Arch Ophthalmol.* 2010;128(8):1080-1081.
8. Patel R, Blair MP, Shapiro MJ, Lichtenstein SJ. Significant treatment failure with intravitreal bevacizumab for retinopathy of prematurity. *Arch Ophthalmol.* In press.
9. The Committee for the Classification of Retinopathy of Prematurity. An international classification of retinopathy of prematurity. *Arch Ophthalmol.* 1984;102(8):1130-1134.
10. International Committee for the Classification of Retinopathy of Prematurity. The International Classification of Retinopathy of Prematurity revisited. *Arch Ophthalmol.* 2005;123(7):991-999.
11. Moshfeghi DM, Berrocal AM. Retinopathy of prematurity in the time of bevacizumab: incorporating the BEAT-ROP results into clinical practice. *Ophthalmology.* 2011;118(7):1227-1228.