

Intravitreal Bevacizumab versus Laser Treatment in Type 1 Retinopathy of Prematurity

Report on Fluorescein Angiographic Findings

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Purpose: To compare the structural outcome at 9 months of eyes treated with intravitreal injection of bevacizumab with fellow eyes treated with conventional laser photocoagulation in zone I type 1 retinopathy of prematurity (ROP).

Design: Single randomized controlled trial.

Participants: All inborn babies with type 1 zone I ROP at a single institution were included in the study. One eye was randomized to receive an intravitreal injection of 0.5 mg bevacizumab; the fellow eye received conventional laser photocoagulation.

Methods: Digital fundus photographs and fluorescein angiography (FA) using the RetCam (Clarity Medical Systems Inc., Pleasanton, CA) were performed before treatment and 9 months after treatment.

Main Outcome Measures: Presence of retinal and choroidal abnormalities on FA at 9 months.

Results: Thirteen infants were enrolled; 1 died 3 months after birth. One laser-treated eye progressed to stage 5 retinal detachment. The remaining 23 eyes had favorable structural results at the 9-month follow-up and provided FA results. At 9 months of age, all eyes treated with a bevacizumab injection were noted to have abnormalities at the periphery (large avascular area, abnormal branching, shunt) or the posterior pole (hyperfluorescent lesion, absence of foveal avascular zone). These posterior and peripheral lesions were not observed in the majority of the lasered eyes.

Conclusions: This study documents significant vascular and macular abnormalities of eyes in the bevacizumab group. Long-lasting implications of these abnormalities for visual function of the child need to be studied. *Ophthalmology* 2014;121:2212-2219 © 2014 by the American Academy of Ophthalmology.

Retinopathy of prematurity (ROP) is a disease resulting from delayed and abnormal retinal vessel growth after premature birth. Retinopathy of prematurity manifests itself in 2 phases: The first or the hyperoxic phase occurs when exposure of the preterm infant to the relative hyperoxia of the extrauterine environment leads to disruption of normal vessel growth and downregulation of hypoxia-induced growth factors, in particular vascular endothelial growth factor (VEGF)-A. The decrease in vessel density along with increased oxidative demands from the developing retinal neurons makes retinal tissues hypoxic, signaling the onset of the hypoxic phase II.¹ The hypoxia-induced secretion of angiogenic factors leads to abnormal neovascularization not only at the boundary of vascularized retina but also within the vascularized retina.² The current treatment standard is the ablation of the peripheral avascular retina at ROP severity levels established by the Cryotherapy for ROP study³ and modified by the Early Treatment for Retinopathy of Prematurity (ETROP) study.⁴ Although

some reports suggest that laser photocoagulation does well even in aggressive posterior ROP,^{5,6} it is relatively ineffective in decreasing retinal detachment in type 1 ROP in zone I when compared with zone II eyes. At the 6-year outcome of the ETROP study, more than 30% of zone I type 1 eyes had visual acuity of $\leq 20/200$ and more than 20% had macular folds or retinal detachments. Therefore, more effective treatments are needed for severe ROP in zone I.

In the past decades, it has become clear that synthesis of local VEGF-A plays a key role in pathologic retinal angiogenesis.⁷⁻¹¹ The inhibition of VEGF-A as a therapeutic strategy for ocular neovascularization began in 1996,¹² and the use of first humanized anti-VEGF antibody was proposed by Presta et al¹³ in 1997. Bevacizumab (Avastin; Genentech, South San Francisco, CA), a humanized anti-VEGF antibody derived from antibody A4.6.1,¹⁴ was selected because of its affinity to membrane-bound receptors (VEGF receptor-1 and -2).¹⁵ Bevacizumab blocks

VEGF receptor binding and signaling: Its epitope overlaps (although it is not identical to) the epitopes of VEGF receptor-1 and -2. The drug has been approved by the US Food and Drug Administration for use in humans as a cancer therapeutic since 2004.

In 2007, the first 3 reports of the use of bevacizumab for ROP appeared in the literature,^{16–18} followed by numerous others, including the use of bevacizumab as monotherapy,^{19,20} in combination with laser,^{21,22} or as rescue therapy after failed laser photocoagulation,²³ and in combination or before vitrectomy.²⁴ Although the use of anti-VEGF drugs in eyes with abnormal vasculogenesis has rapidly spread around the world, concern about safety for both adults²⁵ and premature babies has arisen.^{26,27} Adverse ocular effects thus far have been mainly due to fibrotic reaction after intravitreal injection.^{28,29} Many authors urged caution about using an antiangiogenic drug in an infant because of its potential adverse systemic effects in developing neurons and the lung.²⁶ This concern is reinforced by the data from Sato et al³⁰ documenting that bevacizumab “escape(s) from the eye into systemic circulation” and reduces the serum level of VEGF in infants with ROP.

On the basis of the results of a randomized multicenter clinical trial of eyes with stage 3 ROP with plus disease in zone I or posterior zone II, Mintz-Hittner et al³¹ reported a significant reduction of ROP recurrence requiring treatment in zone I eyes compared with eyes treated with conventional laser therapy (6% vs. 42%).³¹ Although this could represent an important improvement in the therapy of severe ROP, concerns about long-term local and systemic adverse effects arose.^{26,27} We report a series of fluorescein angiography (FA) studies in a case series of babies who developed type 1, zone I ROP in both eyes. For each infant, 1 eye was randomly assigned to receive bevacizumab and conventional laser photocoagulation in the fellow eye within 24 hours of diagnosis of type 1 ROP, as defined by ETROP criteria.⁴

Methods

This is a single-center, randomized, controlled trial conducted at the Catholic University in Rome. All babies born in this clinical center who developed type 1 zone I ROP in both eyes were eligible to be included in the study.

Within a maximum interval of 24 hours after diagnosis, all babies underwent general anesthesia for evaluation and treatment. Before treatment, fundus images were obtained using a RetCam II (Clarity Medical Systems Inc., Pleasanton, CA) and video-digital FA was performed using a bolus of 10% fluorescein solution intravenously administered at a dose of 0.1 ml/kg, followed by an isotonic saline flush.³ For treatment, 1 eye was randomly selected (using a random number series) to undergo conventional laser photocoagulation of the peripheral avascular retina; the fellow eye received an intravitreal injection of 0.5 mg bevacizumab in a 0.02 ml balanced salt solution. The eye assigned to conventional laser peripheral ablation was treated first. The FA was examined by the treating physicians before conducting laser photocoagulation to provide more detailed information about the status of the eye and to indicate areas of the retina

that might be treated. The eye randomized to receive bevacizumab was then prepared using 5% povidone/iodine and topical antibiotic, and 0.5 mg (0.02 ml) of bevacizumab was injected intravitreally through the pars plicata. After the injection, intraocular pressure and retinal artery perfusion were checked, and patients received topical tobramycin in both eyes for 3 days.

After treatment, binocular indirect ophthalmoscopy and RetCam imaging were performed every 3 days, and FA was performed every 2 weeks until discharge. After discharge from the neonatal intensive care unit, binocular indirect ophthalmoscopy was performed every 2 weeks until 52 weeks' postmenstrual age and then monthly until 1 year of age. Babies underwent FA at 9 months of age under general anesthesia.

Angiograms were examined retrospectively by 2 experienced ophthalmologists (D.L. and F.M.) for the following characteristics described by Lepore et al.² Abnormalities at the junction of vascular and avascular retina were considered present if at least 1 quadrant of the eye showed irregular arteriolar branching or naked arteriovenous shunts. The same criteria were used to assess the capillary loss within the vascularized retina and the posterior pole. The macula was considered abnormal if any or all of the following were present: (1) absence of foveal avascular zone, (2) presence of hyperfluorescent lesions, and (3) pigment epithelium abnormalities of the macular region. If only large linear choroidal vessels without choriocapillaries were observed in the early FA phases, a linear filling pattern was recorded.

The institutional review board at the Catholic University of the Sacred Heart of Rome approved the study protocol, and the trial was registered with the EudraCT as number 2009-012609-20, protocol number 343/09 April 24 2009. Group differences were examined using the Fisher exact test.

Results

From September 1, 2009, to December 31, 2010, 127 preterm babies with a gestational age (GA) of 32 weeks or less or a birth weight (BW) less than 1500 g were referred for ROP examinations at the Neonatal Intensive Care Unit at the “Agostino Gemelli” University Hospital. Thirteen infants (10.2% of the screened population) had developed type 1 ROP in zone I in both eyes and required treatment, according to ETROP⁴ criteria. These 13 were enrolled in this study. Six eyes (3 babies; mean BW, 693 g; BW range, 615–710 g; mean GA, 25.0 weeks; GA range, 24–27 weeks) were classified as zone I stage 3 with plus disease; 20 eyes (10 babies; mean BW, 705 g; BW range, 450–750 g; mean GA, 25.7 weeks; GA range, 23–29 weeks) were classified as zone I stage 3 without plus. All of these eyes had flat neovascularization typical of severe ROP.

One eye (8.5%) with a stage 3, zone I ROP with plus disease treated with conventional laser progressed to a complete retinal detachment 4 weeks after treatment. A second eye also with stage 3 zone I ROP with plus disease and treated with conventional laser progressed to stage 4a and underwent lens-sparing vitrectomy with a favorable structural outcome. Furthermore, 1 infant died because of pulmonary complications at 3 months of age.

Pretreatment FA scans from the 13 patients were available for evaluation for this report by 2 different ROP experts, along with FA scans from 12 eyes from the bevacizumab-injected eyes and 11 from the laser-treated eyes. The FA results before treatment and 9 months after treatment are presented in [Tables 1 and 2](#).

Table 1. Branching Abnormalities in Bevacizumab versus Laser Groups: Number and Percentage of Eyes with Abnormalities

	Tangles		Naked Shunts	
	Before Treatment	9 Months After Treatment*	Before Treatment	9 Months After Treatment*
Avastin (Genentech, South San Francisco, CA) (n = 12)	12 (100%)	11 (91.6%)	11 (91.6%)	11 (91.6%)
Laser (n = 11)	11 (100%)	3 (27.3%)	9 (81.8%)	2 (18.2%)

* $P < 0.001$.

Vascular Features of the Vascular-Avascular Junction

Before treatment, all eyes in this study showed hyperfluorescence (popcorn abnormalities, focal capillary dilatation, cotton wool, capillary tufts, rosary bead-like arterioles); hypofluorescent lesions (capillary loss, periarteriolar capillary-free zone); and irregular branching starting at various distances from the optic disk (Table 1, Fig 1A, C). A less common feature, observed in 87.0% (20/23 eyes), was a circumferential vessel that ran along the vascular-vascular junction.

Fluorescein angiography 9 months after the treatment showed that the bevacizumab eyes had extensive areas of avascular retina (Fig 1B), whereas the lasered eyes all showed the typical retinochoroidal atrophy expected from the treatment (Fig 1D). In the bevacizumab eyes, the normal dichotomous branching pattern was absent and abnormal tangles were observed in 11 of 12 eyes (Table 1, Fig 2A). All but 1 of the bevacizumab eyes showed a circumferential vessel along the junction between vascular and avascular retina. The so-called naked arteriovenous shunt seems to be a long-lasting characteristic of the eyes injected with bevacizumab (Figs 2B and 3B).

Abnormalities within the Vascularized Retina

As shown in Table 2, a massive loss of retinal capillary bed at the posterior pole or in the periphery within the vascularized retina is a common finding not only, as expected, in the pretreatment FA scans (Fig 4A, C) but also 9 months after treatment in 11 of 12 eyes treated with bevacizumab (Fig 4B). In contrast, just 3 of the 11 eyes treated with conventional laser showed hypofluorescent lesions within the vascularized retina (Fig 4D).

Macular abnormalities (e.g., absence of foveal avascular zone or hyperfluorescent lesions in the posterior pole) were observed before treatment in both groups. These lesions persist in the eyes treated with bevacizumab more frequently than in eyes treated with laser (75.0% vs. 36.4%; $P < 0.05$) (Fig 3E, F and Fig 5).

Choroidal Filling Pattern

Details on choroidal filling pattern are provided in Table 2. Before treatment, the majority of eyes (91.30%, 21/23 eyes) showed a linear choroidal filling pattern (Fig 4A, C). This pattern was still clearly visible in 6 of 12 eyes injected with bevacizumab at 9 months' follow-up (Fig 3D); on the other hand, a lobular pattern, as is commonly observed in premature babies 9 months post-term in our clinical experience, was noted in 8 of 11 eyes (72.73%) treated with laser.

Discussion

The results of this study confirm that there may be serious and lasting ocular structural abnormalities in eyes with severe ROP treated with bevacizumab.³² These abnormalities include both vascular changes, such as branching abnormalities and capillary dropout, and macular changes. Findings such as abnormal choroidal filling are noted in both the bevacizumab and the laser groups and also suggest that abnormalities of blood flow, which we have previously noted in severe ROP eyes before treatment,² may be long lasting.

When considering the results of this study, it is also important to recall that masking of images when assessing treatment effects can be done only for posterior pole views because when assessing the more peripheral changes, laser scars are clearly evident juxtaposed to the peripheral vascular changes. Further, because bevacizumab is found in the serum after intravitreal injection,³⁰ it is reasonable to conclude that some of the features observed in the laser-treated eye were affected by the injection of bevacizumab in the fellow eye. However, both of these circumstances would bias against finding differences between laser- and bevacizumab-treated eyes, but that is not the case.

Table 2. Lesions within Vascularized Retina in Bevacizumab versus Laser Groups: Number and Percentage of Eyes with Abnormalities

	Macular Abnormalities (Absence of Foveolar Avascular Zone or Hyperfluorescent Lesions)		Capillary Bed Loss (Central or Peripheral)		Linear Choroidal Filling Pattern	
	Before Treatment	9 Months After Treatment*	Before Treatment	9 Months After Treatment†	Before Treatment	9 Months After Treatment‡
Avastin (n = 12)	12 (100%)	9 (75.0%)	12 (100%)	11 (91.6%)	11 (91.6%)	6 (50.0%)
Laser (n = 11)	11 (100%)	4 (36.4%)	11 (100%)	3 (27.3%)	9 (81.8%)	3 (27.7%)

* $P < 0.05$.† $P < 0.001$.

‡Not significant.

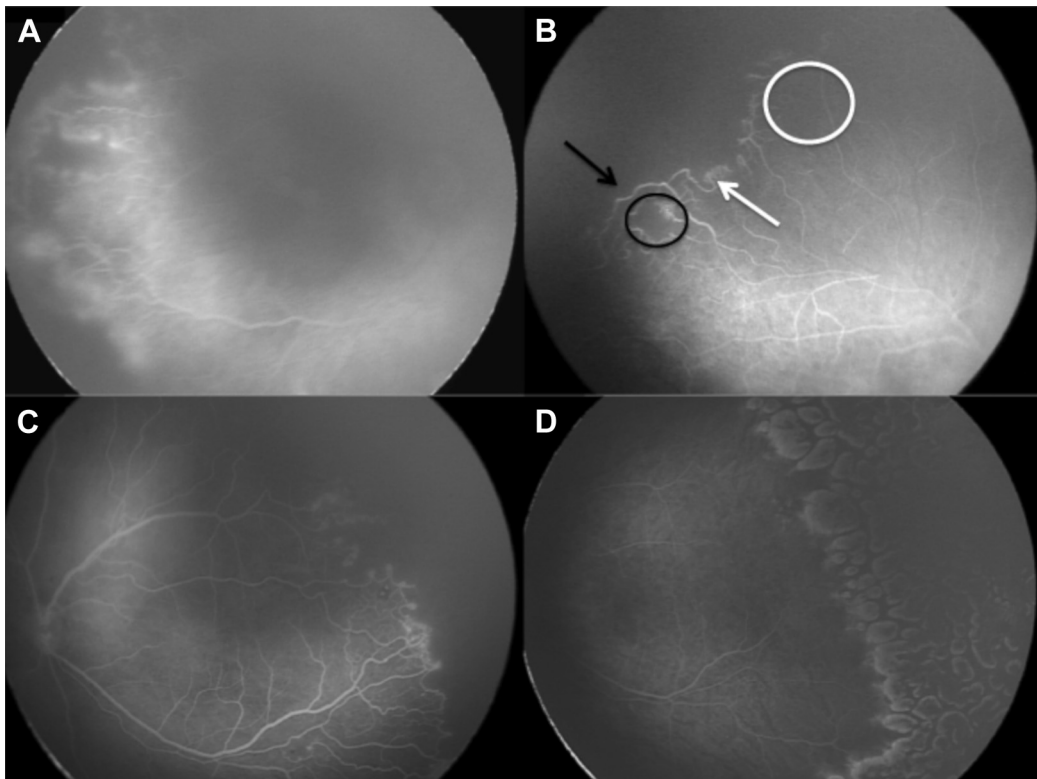


Figure 1. Fluorescein angiographic images before treatment and 9 months after treatment showing the junction between the vascularized and avascular retina in an infant born at 24 weeks' gestational age (**A** and **B**, bevacizumab injected; **C** and **D**, laser treated). There is persistent leakage and irregular branching in both eyes at the time of treatment (**A** and **C**). In the eye injected with bevacizumab at 9 months' follow-up (**B**), there is persistent avascular retina (*black circles*) together with hypofluorescent areas (*white circles*), capillary tufts (*white arrow*), and peripheral shunt at the junction between vascularized and avascular retina. **D**, The chorioretinal scar 9 months after conventional laser treatment is shown.

One of the concerns that has been voiced about the use of anti-VEGF drugs to treat severe acute ROP is that systemic effects may be observed later in life in this vulnerable population.^{26,27} This small case series in which 1 eye was treated with bevacizumab and the fellow eye with laser photocoagulation now raises concerns about the longer-term ocular effects in the use of these drugs. There were not only effects found in macular development in the

bevacizumab group but also more peripheral vascular abnormalities noted in this group at 9 months. Such abnormalities may have long-lasting implications for the visual function of the child. This study also highlights advances in imaging that are transforming our understanding of angiogenesis-related pathogenesis of ROP and that techniques such as FA could play a central role in understanding ROP.

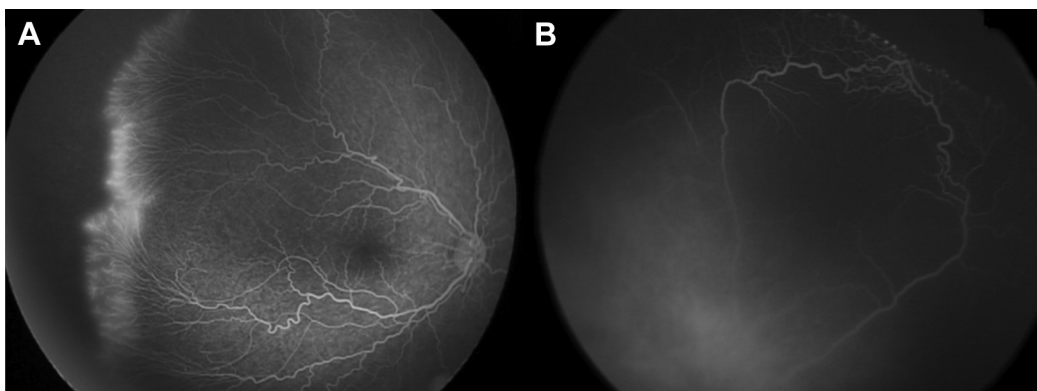


Figure 2. Fluorescein angiograms of 2 different eyes treated with a single injection of bevacizumab. On the left (**A**), irregular retinal branching is present with massive leakage. On the right (**B**), there is a prominent peripheral arteriovenous shunt. Abnormal branching and hypofluorescent areas within the vascularized retina are also evident.

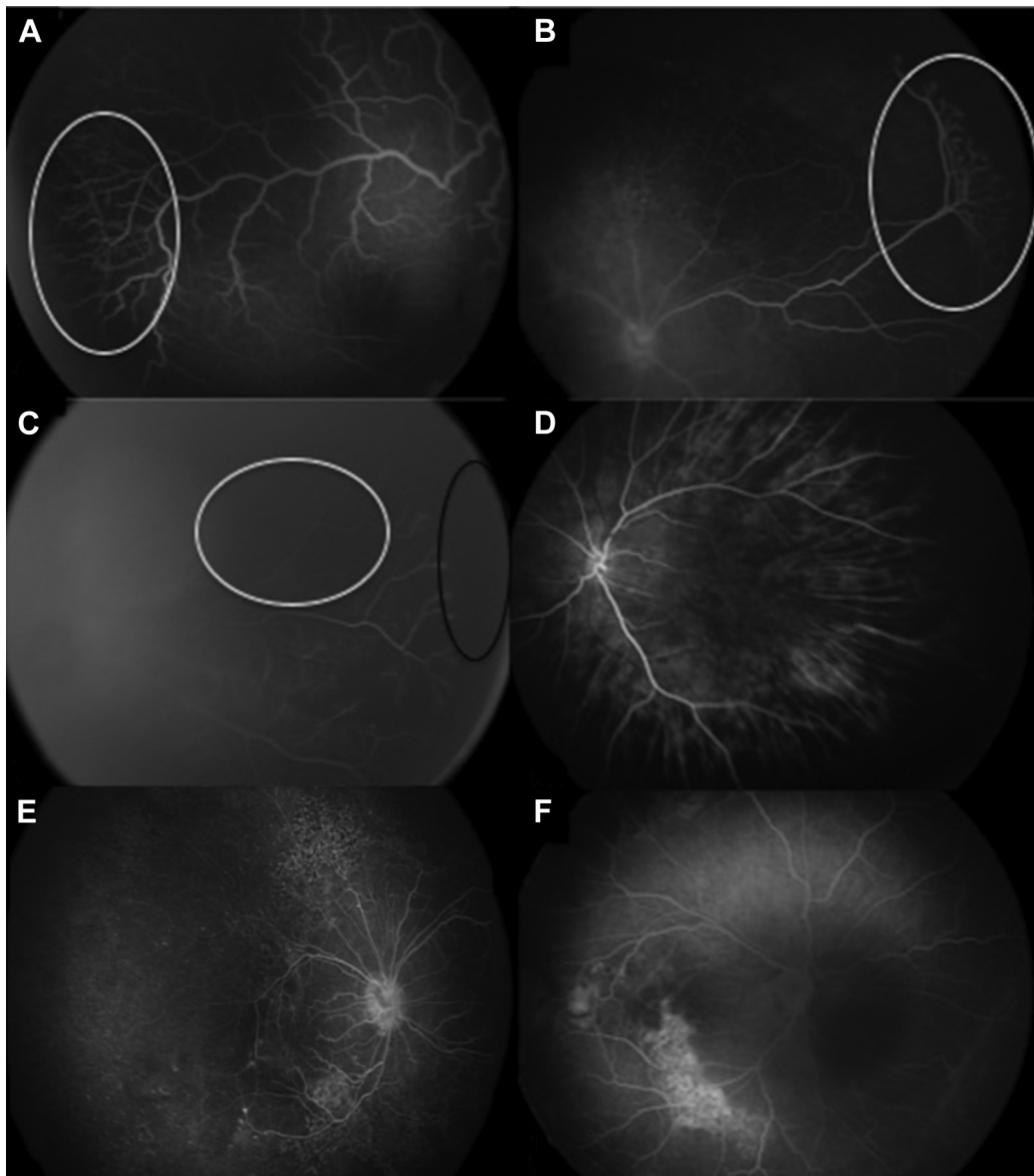


Figure 3. Montage of the features observed in various eyes treated with a single injection of bevacizumab 9 months after treatment: irregular retinal vascular branching (A) and large peripheral shunt at the retinal periphery (B); diffuse absence of retinal capillary network (white circle) in the vascularized retina and persistent peripheral avascular retina (black circle) (C); linear choroidal filling pattern with hypofluorescent areas, possibly related to abnormal choriocapillary perfusion at 26 seconds after injection (D); absence of foveal avascular zone, hypofluorescent and hyperfluorescent lesions, and massive pigmentary dystrophy at the posterior pole with irregular vascular branching and peripheral shunts in the area of junction between vascular and avascular retina (E and F).

In the conventional management of severe ROP using laser photocoagulation, the retina peripheral to the retinopathy is ablated, and there is a low further risk for abnormal angiogenesis. On the other hand, after bevacizumab treatment, there were large avascular areas peripheral to the location of acute-phase retinopathy. Are these areas likely to require further treatment or are they likely to lead to retinal tears or holes? The fact that abnormal arteriolar branching was noted in bevacizumab-treated eyes likely indicates continued abnormal angiogenesis, and the implications of this in the long term are unknown. It may be that the ocular effects noted in bevacizumab-treated eyes in this series

would not be observed if a different dose of bevacizumab had been chosen, a different anti-VEGF drug had been used, or the vehicle or methods of delivery of the drug had been different.

The ROP status of the eyes in this study is not identical to the eyes described in Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity (BEAT ROP) study because all eyes in BEAT ROP were diagnosed with plus disease. Still, the eyes in this study fulfilled the ETROP criteria for treatment as type 1 ROP eyes, and the long-term ocular results of their treatment are relevant to the care of premature infants today.

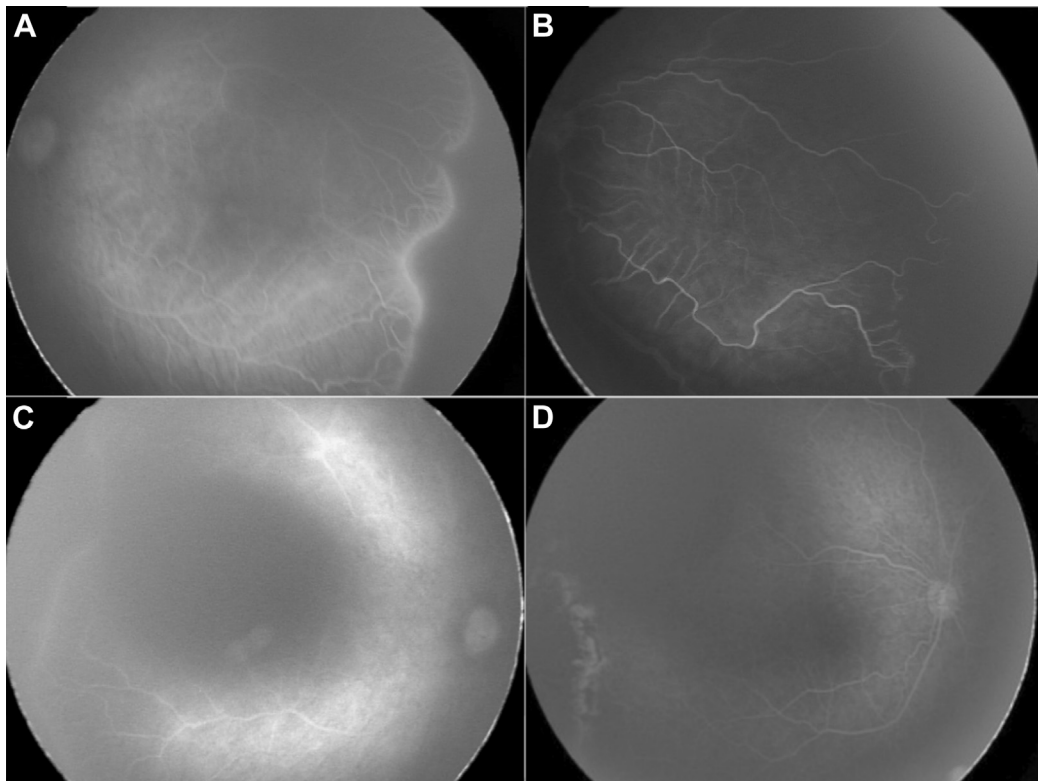


Figure 4. Fluorescein angiographic images of the posterior pole retina in an infant born at 25 weeks' gestational age, before treatment, and 9 months after treatment (A and B, bevacizumab injected; C and D, laser treated). Both eyes at the time of treatment (A and C) show absence of foveal avascular zone (FAZ) and hypofluorescent areas. The absence of FAZ, hypofluorescent areas, and retinal vascular abnormalities persist at 9 months in the posterior pole of the eye treated with bevacizumab injection (B). The FAZ is clearly evident in the retina treated with conventional laser.

The current standard of peripheral retinal ablation does have untoward effects, including at least some loss of visual field in eyes that respond to the treatment, and the field defects may be more dramatic in eyes with very posterior disease. It is yet uncertain what the effect on visual field extent will be after the use of anti-VEGF agents.

In conclusion, there is a need for a masked randomized trial to investigate the use of anti-VEGF drugs for ROP, as well as a registry to record the long-term findings of infants who are treated. While waiting for further information on the important issue of systemic and ocular effects of the use of anti-VEGF drugs in type 1 ROP in zone I, we should err

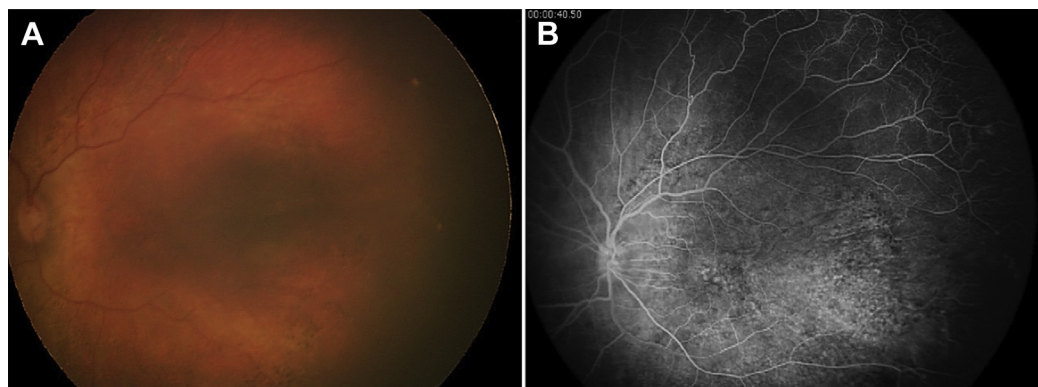


Figure 5. Color fundus image at 9 months of an eye treated with a single injection of bevacizumab (A), showing pigmentary abnormalities at the posterior pole. In the corresponding fluorescein angiogram at 40 seconds after injection (B), posterior pole anomalies, peripheral irregular branching, and retinal capillary hypoperfusion are even more evident.

on the side of caution until we understand the implications of these findings on the visual system and the overall development of the child.

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Footnotes and Financial Disclosures

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Abbreviations and Acronyms:

BW = birth weight; **ETROP** = Early Treatment for Retinopathy of Prematurity; **FA** = fluorescein angiography; **FAZ** = foveal avascular zone; **GA** = gestational age; **ROP** = retinopathy of prematurity; **VEGF** = vascular endothelial growth factor.

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