

An Evidence-Based Meta-analysis of Vascular Endothelial Growth Factor Inhibition in Pediatric Retinal Diseases: Part 1. Retinopathy of Prematurity

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ABSTRACT

Recently there has been interest in the novel, off-label use of anti-vascular endothelial growth factor (anti-VEGF) agents for various stages of retinopathy of prematurity (ROP). The authors report on the quality and depth of new evidence published from 2009 to 2011 concerning the treatment of retinopathy of prematurity (ROP) with bevacizumab (Avastin; Genentech Inc., South San Francisco, CA) as either primary or adjunctive treatment for ROP. There is significant variability in the evidence, quality, and design of the studies available in the literature. There has been a trend in the scientific literature of the past 2 years toward larger, multi-center, randomized studies investigating the role of bevacizumab in the treatment of ROP. More recent evidence suggests that monotherapy with intravitreal bevacizumab may be a viable first-line treatment for select cases of zone I ROP and possibly for posterior zone II disease. Adjunctive treatment with bevacizumab may enhance outcomes in patients treated with laser photocoagulation or pars plana vitrectomy. However, there are significant concerns regarding its long-term safety profile. Further prospective studies are warranted to more fully determine the role of anti-VEGF therapy in this disease. [*J Pediatr Ophthalmol Strabismus* 2012;49:332-340.]

INTRODUCTION

Retinopathy of prematurity (ROP) is a pathologic condition in neonates that results from a multiplicity of factors, including an imbalance in oxygen levels, low birth weight, and structural immaturity of the developing retina.¹⁻³ Its pathogenesis is mediated by several factors, most notably vascular endothelial growth factor (VEGF), insulin growth factors, and erythropoietin, which are upregulated in response to retinal non-perfusion.⁴ This in turn promotes neovascularization, which may be complicated by the development of macular drag, vitreous hemorrhage, and retinal detachment.^{5,6} ROP remains a major cause of childhood blindness in industrialized nations, whereas its incidence is on the rise in developing nations.³

TREATMENT: PROVEN AND NEW

The standard of treatment for the past two decades has been peripheral retinal ablation using either laser or cryotherapy,⁷ which has proven successful in preventing neovascular growth, vitreous hemorrhage, retinal detachment, and permanent blindness. However, conventional laser peripheral retinal ablation can also produce unwanted side ef-

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Originally submitted January 11, 2012. Accepted for publication June 13, 2012. Posted online August 28, 2012.

The authors have no financial or proprietary interest in the materials presented herein.

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doi: 10.3928/01913913-20120821-03

TABLE 1
**Quality of Evidence Based on the Grades of Recommendation,
 Assessment, Development, and Evaluation Working Group**

Underlying Methodology	Quality Rating
Randomized trials or double-upgraded observational studies	High
Downgraded randomized trials or upgraded observational studies	Moderate
Double downgraded randomized trials or observational studies	Low
Triple-downgraded randomized trials or downgraded observational studies or case series/ case reports	Very low

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fects, such as permanent and often significant central and/or peripheral visual loss, macular traction or drag, and myopia.^{8,9} In addition, an increasing number of low birth weight infants are surviving in the United States and worldwide, which has given rise to a new epidemic and has stimulated interest in more efficacious and cost-effective treatments for this devastating condition.²

In 2004, the U.S. Food and Drug Administration approved the use of bevacizumab (Avastin; Genentech Inc., South San Francisco, CA) for treatment of metastatic colon cancer. Bevacizumab was the first commercially available angiogenesis inhibitor, and is a monoclonal antibody that works by binding VEGF-A through two antigen binding sites.¹⁰ Since then, it has gained popularity with ophthalmologists for its off-label use as an anti-neovascular agent when injected intravitreally for treatment of age-related macular degeneration, proliferative diabetic retinopathy, clinically significant macular edema, branch and central retinal vein occlusion, neovascular glaucoma, and retinopathy of prematurity.¹¹⁻¹⁴

In the developing eye, VEGF has a neuroprotective effect and plays a key role in retinal neural cell survival, especially in the setting of retinal ischemic conditions such as ROP.¹⁵ VEGF also stimulates angiogenesis and vasodilation via upregulation of nitric oxide and mediates fibrinolytic processes.¹⁶ Blockade of these normal physiologic pathways has raised concerns about the deleterious effects of anti-VEGF therapy (hypertension and thromboembolic events).¹⁷

Although the function of VEGF in the pathogenesis of ROP is well documented,^{18,19} the role of anti-VEGF agents in the treatment of ROP has been more controversial and hampered by a lack of dem-

onstrated evidence.²⁰ Until recently, there have been only limited reports concerning the use of bevacizumab in the treatment of ROP, most of them of low scientific value because of the non-randomized, retrospective, and variable study designs.²¹ Given the off-label use of the drug, there is no clearly established standard of care, nor are there significant data on the proper dosing, frequency, or timing of this drug in this disease.

An increase in the quality and quantity of data available over the past 2 years has allowed for this current analysis, which highlights the most recent research efforts and clinical evidence in the treatment of ROP with intravitreal bevacizumab as either monotherapy or adjunctive therapy.

ANALYSIS AND GRADE SYSTEM

The three main scientific databases of Ovid, PubMed, and Cochrane were searched for articles published between January 1, 2009, and February 1, 2012, using the following terms: retinopathy of prematurity, bevacizumab, Avastin, ranibizumab, Lucentis, pegaptanib, Macugen, anti-VEGF, and angiogenesis inhibitors. Each term was used first as medical subject heading and then as title/abstract keyword. The relevant searches were then corroborated using the AND/OR option to obtain the final list.

Search results were reviewed independently by two reviewers (MM and KC) and were further examined and included in the study if they investigated the use of bevacizumab for ROP in a case report, case series, or randomized control trials. All molecular studies, animal studies, conference proceedings not published in peer-reviewed journals, and non-English language articles were excluded from this review.

The evidence from the studies reviewed was rat-

ed using the GRADE method,²² developed by the Grades of Recommendation, Assessment, Development and Evaluation Working Group and adopted by the Cochrane Collaboration for reviews (Table 1). This method evaluates several factors (methodology used, dose-response gradient, likelihood of bias, and limitations, imprecision, and consistency of design) to provide an objective measure of the quality of the scientific evidence offered. A rating is created, with the ultimate goal of aiding the reader in the evidence-based clinical decision-making process.

LITERATURE REVIEW AND ANALYSIS

A total of 10 articles representing more than 135 eyes of 145 infants met the study criteria and were included for review. They consist of two case reports, six case series (two prospective, four retrospective), one retrospective case-control study, and one prospective, randomized clinical trial.

The five most significant studies are reviewed in detail in the body of the article, whereas the remaining five articles are summarized in Table 2 only.

In the most comprehensive multi-center study to date (prospective, controlled, randomized, and stratified), Mintz-Hittner et al. assessed the role of monotherapy with intravitreal bevacizumab (0.625 mg/0.025 mL) versus laser photocoagulation in the treatment of both zone I and zone II (posterior) stage 3 ROP with plus disease. Although treatment is required for zone I any stage ROP with plus disease, zone I stage 3 ROP without plus disease, and zone II stage 2 or 3 with plus disease, this study specifically looked at patients with zone I and posterior zone II stage 3 with plus disease, finding a significant treatment outcome for bevacizumab in zone I stage 3 with plus disease ($P = .003$), but not zone II ($P = .27$).⁹

Significantly, in patients with zone I disease, 13 eyes treated with laser needed pars plana vitrectomy versus none in the bevacizumab group, and 2 eyes treated with laser progressed to retinal detachment. There was also a significant difference in macular drag (16 vs 1). In posterior zone II ROP, 2 eyes treated with bevacizumab required vitrectomy, whereas none treated with laser required it. Additionally, 2 eyes treated with bevacizumab progressed to retinal detachment.⁹ Six eyes (2 of 62 eyes in infants with zone I ROP and 4 of 78 eyes in infants with zone II posterior ROP) treated with bevacizumab monotherapy had recurrence of disease after a mean of

16.0 ± 4.6 weeks, compared to 6.2 ± 5.7 weeks for 32 eyes after laser treatment.⁹

There were seven deaths before 54 weeks postmenstrual age: three with zone I disease and four with zone II disease. Five were treated with bevacizumab (four died of respiratory causes) and two with laser (one of whom died of respiratory causes), but this difference was not statistically significant. In addition, 4 of 40 eyes in the zone II group randomized to laser treatment had complications that are typically rare: three eyes developed lenticular opacity and one eye developed corneal opacity, all of which required surgical intervention.⁹

Given the quality of the research design, lack of confounding factors and treatment bias, and corroboration of treatment decisions by a reading committee, the evidence for the use of bevacizumab for select cases of ROP as demonstrated by Mintz-Hittner et al. in this study would be rated as high. Still, there are several concerns with both the design and side effect profile of this particular study. Although initially the primary outcome was determined to be the lack of recurrence of stage 3 with plus disease before 54 weeks postmenstrual age, this outcome was changed to “ROP recurrence needing treatment before 54 weeks premenstrual age” before initial data analysis. The disease may have recurred after the end of the follow-up period in the study, given that anti-VEGF agents might produce an inhibitory effect on acute disease, with recurrences possible at later stages of retinal development.²³ Although there was reading center validation of recurrence and need for retreatment, these decisions were made based on uncropped photographs, which allows for the introduction of reader bias. Additionally, although the study was not powered to evaluate safety (2,800 infants would be required to establish statistically significant systemic side effects), the study reported a twofold higher mortality rate in the bevacizumab arm compared to laser (6.6% vs 2.6%), with 4 of 5 deaths occurring secondary to respiratory failure. The potentially significant local and systemic side effects of intravitreal bevacizumab will be discussed in the following section.

In their retrospective case series, Law et al. examined the outcomes of 13 eyes (7 infants) treated with injections of 0.75 mg/0.03 mL of intravitreal bevacizumab. Eight eyes had no prior treatment, whereas 5 had received prior laser peripheral retinal ablation. Indications for treatment included iris ru-

TABLE 2

Master Table Comparing Treatment Modalities and Outcomes in Several Peer-Reviewed Publications

Author	No. of Eyes	No. of Patients	Agent	BW (g)	Mean GA (wk)	Zone	Stage Before Injection	Dose (mg)	Initial Regression	Additional/ Adjunctive Tx	Favorable Outcome ^a	Follow-up
Mintz-Hittner et al. ⁹	68	31	Bevacizumab	615.2	24.3	I (62 eyes)	3 (+)	0.625	(Y) 29/31	None	Yes	Up to 54 wks PMA
	78	39	Bevacizumab	689.2	24.5	II (78 eyes)	3 (+)		(Y) 37/39	None	Yes	
Law et al. ²⁴	10	5	Bevacizumab			I (1 eye)	3		(Y) 1/1	LP	Yes	
	10	5	Bevacizumab			I (1 eye)	3		(N) 1/1	LP, PPV	NS	
	10	5	Bevacizumab	NS (700 for whole study)	NS (25 for whole study)	II (2 eyes)	3	0.75	(Y) 2/2	None	Yes	NS (9 mos for whole study)
	10	5	Bevacizumab			II (6 eyes)	3		(Y) 4/6	LP, PPV	NS	
	1	1	Bevacizumab			II (1 eye)	4A		(N) 1/1	LP, PPV	NS	
	2	1	Bevacizumab			II (2 eyes)	2		(Y) 2/2	LP	Yes	
Lee et al. ²⁵	2	1	Bevacizumab	555	24.1	I (2 eyes)	3		(Y) 2/2	LP	Yes	
	10	5	Bevacizumab	902	26.2	II (10 eyes)	3	0.50	(Y) 10/10	LP	Yes	2 mos
	4	2	Bevacizumab	845.3	24.4	III (4 eyes)	3		(Y) 4/4	LP	Yes	
Spandau et al. ²⁶	4	2	Bevacizumab	570	23	I, Post. II (4 eyes)	3 (+)	0.40	(Y) 4/4	None	Yes	Mean 53 wks PMA (range: 39–93 wks)
	10	5	Bevacizumab	615.6	24.4	I, Post. II (10 eyes)	3 (+)	0.625	(Y) 6/10	LP, CRY	Yes	
Wu et al. ²⁷	41	23	Bevacizumab	845	25.7	I (9 eyes)	3		(Y) 37/41	None	Yes	8.4 mos
	41	23	Bevacizumab	845	25.7	II (32 eyes)	3		(Y) 37/41	LP	Yes	8.4 mos
	2	1	Bevacizumab	1,435	29	I (2 eyes)	4A	0.625	(N) 4/6	LP	Yes	6 mos
	2	1	Bevacizumab	1,148	28	I (2 eyes)	5		(N) 2/2	LP, PPV	No	12 mos
	4	2	Bevacizumab	2,285	26.5	II (4 eyes)	4A		(N) 4/6	LP, PPV	Yes	7.5 mos
Dorta et al. ⁵¹	12	7	Bevacizumab	846.6	25.6	I (9 eyes)	Type 1		(Y) 12/12	None	Yes	NS
	12	7	Bevacizumab	846.6	25.6	II (3 eyes)	Type I		(Y) 12/12	None	Yes	
Jang et al. ⁵³	2	1	Ranibizumab	1,690	32	I (2 eyes)	3 (+)	0.30	(Y) 2/2	LP, PPV	Yes	4 mos
Hoang et al. ²³	2	1	Bevacizumab	675	26	II (2 eyes)	3 (+)	0.75	(Y) 2/2	LP	Yes	2 mos
Kychental et al. ⁵⁵	11	8	Bevacizumab	950	25.7	I (5 eyes)	4		(Y) 11/11	LP, PPV	Yes	8.5 mos
	11	8	Bevacizumab	950	25.7	II (6 eyes)	4		(Y) 11/11	LP, PPV	Yes	
Nazari et al. ⁵⁶	4	2	Bevacizumab	950	55.5	I (4 eyes)	Prethreshold with VH	0.625	(Y) 4/4	LP	Yes	6.75 mos
	10	6	Bevacizumab	1,080	50.5	II (10 eyes)			(Y) 10/10	LP	Yes	9.8 mos

BW = birth weight; GA = gestational age; Tx = treatment; PMA = postmenstrual age; NS = not specified; LP = laser photocoagulation; PPV = pars plana vitrectomy; post = posterior; CRY = cryotherapy; VH = vitreous hemorrhage.

^aFavorable outcome was regression of the disease as described in each report and unfavorable outcome was retinal detachment or worsening of the condition.

beosis with poor dilation, vitreous hemorrhage, and/or vitreoretinal traction despite complete laser treatment. Injection was used as adjunctive treatment in all cases, with resultant marked regression of fibrovascular activity and increased pupillary dilation in 9 eyes, whereas 4 eyes progressed to tractional retinal detachment. No ophthalmic or systemic side effects were reported during the 2 to 17 months of follow-up. The authors concluded that intravitreal bevacizumab can be used as adjunctive treatment because of its powerful inhibition of fibrovascular proliferation, but recommended prompt vitrectomy surgery after treatment to prevent retinal detachment.²⁴ The study design (non-randomized, retrospective case series) and the small number of patients translate into low quality evidence according to the GRADE method.

Lee et al.²⁵ investigated 30 eyes of 15 infants in their retrospective chart review (case series) study. Eight patients (16 eyes) received 0.5 mg/0.02 mL of intravitreal bevacizumab in addition to laser treatment, whereas 7 patients (14 eyes) received only laser therapy. All eyes were diagnosed as having moderate-to-severe stage 3 ROP. Patients receiving both laser and bevacizumab therapy had a more rapid, statistically significant improvement (resolution of plus disease, regression of fibrovascular membranes, and development of peripheral retinal vessels) than those receiving only laser treatment. No ocular or systemic complications were reported during the follow-up (at least 8 weeks, or until peripheral retinal vascularization over the scars was reported) in patients treated with bevacizumab. Despite the statistically significant results, the quality of the evidence and recommendation for this study remains low, given the retrospective chart review design, the relatively small number of patients (case series), and the limited follow-up interval.

In their retrospective chart review study, Spandau et al.²⁶ examined 16 eyes of 8 patients with aggressive posterior ROP who were treated with laser ablation alone or laser ablation and intravitreal bevacizumab (0.4 and 0.625 mg). Of 4 patients receiving laser ablation as the initial treatment, three patients (6 eyes) were treated with intravitreal bevacizumab as salvage treatment because of the lack of regression of ROP. All but one eye (which developed macular dragging) had good anatomical outcomes. The remaining 4 patients (8 eyes) were treated with first-line intravitreal bevacizumab: four eyes regressed after a single injection and the other

four experienced initial ROP regression but required a second injection and then laser ablation because of outgrowth of vessels in zone II. All eyes receiving intravitreal bevacizumab as a first-line therapy ultimately had favorable anatomical outcomes. There were no systemic side effects reported by the authors. Although the study makes a case for using bevacizumab as first-line treatment for aggressive zone I ROP, its non-randomized, retrospective study design and the limited number of patients enrolled translate into low quality evidence according to the GRADE method.

In their multicenter, retrospective case series, Wu et al.²⁷ studied 49 eyes of 27 patients: 41 eyes (23 patients) with stage 3 ROP (9 eyes in zone 1 and 32 eyes in zone 2), 6 eyes (3 patients) with stage 4A ROP, and 2 eyes (1 patient) with stage 5 ROP, with a mean follow-up of 6 months. Thirty-six eyes with stage 3 ROP received intravitreal bevacizumab (0.625 mg/0.025 mL) as the primary treatment, with 32 eyes showing ROP regression. Four eyes required additional laser treatment because of lack of response 2 to 3 weeks after bevacizumab treatment. Two eyes of patients with stage 4 ROP regressed after bevacizumab injection and 4 eyes regressed after bevacizumab injection followed by subsequent vitrectomy. Two eyes with stage 5 ROP showed decreased vascular tortuosity after injection of bevacizumab, but the retina failed to reattach after multiple surgeries. All eyes treated with bevacizumab showed regression of plus disease and vasculosa lentis, although in advanced ROP with retinal detachment, the benefits of bevacizumab were less evident than in stage 3 ROP (including zone I ROP), which revealed best results. Major complications included vitreous or pre-retinal hemorrhage in 4 eyes and vascular sheathing, which regressed. No systemic complications were noted.

The study reports that bevacizumab injection could work as either primary or salvage treatment after previously failed laser treatment.²⁷ Despite the large number of patients and the relatively long follow-up interval, this study is limited by its retrospective nature, lack of a control group, and other confounding factors, which gives it a moderate quality rating based on the GRADE method.

The use of anti-VEGF agents in the treatment of ROP has been steadily gaining scientific attention during the past decade. There is a trend in the literature toward larger and more numerous case series

investigating the role of bevacizumab as both monotherapy and adjunctive therapy in the treatment of ROP. However, according to the GRADE method, the level of evidence continues to remain low, with only one prospective randomized study in the literature to date that would be considered high quality.

DISCUSSION

Based on the articles reviewed in this study, there is growing consensus that we have entered the era of anti-VEGF use in ROP. The literature provides increasing evidence of the positive effects of bevacizumab on the control of neovascularization in select cases of active ROP, with a significant impact on plus disease and iris engorgement. Although treatment of carefully selected cases of ROP with intravitreal anti-VEGF agents may be appropriate, there are several considerations that must be evaluated prior to its administration. These include both systemic and local safety issues, dosing considerations, timing of administration, and its use as either a primary treatment option or as an adjuvant or rescue therapy.

Because of its widespread use and cost-effectiveness, bevacizumab was the drug of the choice in nine of the articles reviewed, with only one case report describing the use of same-class anti-VEGF agent ranibizumab (Lucentis; Genentech, Inc.). Research has shown important pharmacokinetic differences between these two drugs. Specifically, the serum elimination half-life of bevacizumab has been reported to be approximately 20 days, whereas that of ranibizumab has been reported to be approximately 2 hours. Bevacizumab is a full-length antibody, with its Fc domain binding specifically to the Fc portion on endothelial cells, which could explain its extended systemic clearance time interval. Ranibizumab is a smaller molecule, allowing for more rapid clearance from circulation,²⁸ which could offer a theoretical advantage with respect to its safety profile.

Experience with neovascular conditions has historically shown that anti-VEGF agents are well tolerated locally,²⁹ and animal models have not revealed long-term ocular side effects.³⁰ After intravitreal administration, bevacizumab enters the general circulation, where it is detected for weeks to months, and also reaches the fellow eye in potentially therapeutic concentrations,³¹ where it inhibits retinal and choroidal neovascularization.³² In adults, no decrease in systemic VEGF was found in patients treated with

ranibizumab, whereas those treated with bevacizumab experienced a significant drop in systemic VEGF levels (from 190 to 110 pg/mL).^{28,33-36}

There is evidence to suggest that the use of intravitreal anti-VEGF agents for exudative age-related macular degeneration in adults may lead to an increased rate of hospitalization and systemic side effects such as myocardial infarction or stroke.^{28,37,38} There is also recent evidence of increased treatment-related mortality (primarily from hemorrhage) in patients with cancer who are treated with intravenous bevacizumab compared to those receiving standard chemotherapy alone.³⁹

Although these data are specifically derived from adults, it may be possible to extrapolate these concepts to infants. In the pediatric population, the serum concentration of bevacizumab is highest 2 weeks after intravitreal injection and it correlates negatively with serum VEGF levels, which drop from 1,628 to 269 pg/mL after injection of 0.5 mg of bevacizumab.⁴⁰ Therefore, there is further concern regarding the long-term effects of VEGF inhibition on a newborn's developing organs, particularly in the areas of alveolar development and lung maturation,^{41,42} due to the relatively small plasma volume of this population.⁴³ Future research efforts should investigate whether same-class agents, including ranibizumab and the recently released aflibercept (Eylea; Regeneron Inc., Tarrytown, NY), have different efficacies and side effects when used in infants with ROP, as well as whether different doses of the same drug are required to control stages of different severity.

No ophthalmic or systemic side effects were reported in the articles reviewed, but this may not be a true lack of systemic toxicity. The relatively short follow-up period in all of the reviewed articles would need to be extended considerably in the pediatric population. Although technically challenging due to the paucity of cases and the large number of subjects required (approximately 2,800),⁹ future larger-scale projects would be needed to evaluate any statistically significant and long-term side effects.

The most commonly used dose of bevacizumab for off-label treatment of neovascular age-related macular degeneration in adults is 1.25 mg/0.05 mL.¹³ The appropriate dosing for intravitreal injection in ROP is still under debate. In the studies we reviewed, the most common dosage used was half of the adult dose, 0.625 mg/0.025 mL (range: 0.5 to 0.75 mg). Even so, because postmortem infant eye

volumes have been shown to be less than one-third of those in adults,³ there is increasing agreement that this dose may be at least one order of magnitude greater than what is required to have a positive effect on ROP.²⁸ Because higher doses could potentially interfere with normal retinal vasculogenesis, the smallest, most efficacious dose should be sought. Animal research involving aflibercept confirmed that the lowest doses administered successfully blocked progressive neovascularization and caused regression of existing neovascularization without appreciably affecting vasculogenesis, whereas higher doses inhibited normal vascularization.⁴⁴ Therefore, dosage represents an important variable in the management of ROP that deserves further study.

Patients with ROP demonstrate a biphasic pathologic neovascularization.^{18,45} In phase I (occurring between birth and approximately 32 weeks postmenstrual age), there is suppression of VEGF by relative hyperoxia. In phase II, the hypoxia-induced rise in VEGF levels leads to pathological vessel growth at approximately 34 weeks. If angiogenesis is interrupted too early, the retina may develop more slowly or poorly, given the VEGF requirement for normal retinal vasculogenesis.^{46,47} This is of concern not only for the development of retinal vasculature, but also with respect to the timing of anti-VEGF administration.

In infants treated with intravitreal bevacizumab as early as 32 weeks postmenstrual age, the growth of retinal vessels was often slower than that seen in premature infants who received no treatment.⁴⁸ If anti-VEGF treatment is given too late, there is concern for exacerbation of the disease, resulting in profound scarring, fibrosis, and retinal detachment.^{45,49} This is analogous to the contraction of membranes and development of tractional retinal detachments seen in adults with advanced proliferative ischemic retinopathies receiving intravitreal bevacizumab.⁵⁰ The implication is that anti-VEGF therapy should be administered during phase II of the neovascular ROP process, typically approximately 34 weeks. Results of our review, specifically those from Lee et al., who demonstrated that anti-VEGF use did not prevent peripheral vasculogenesis at a gestational age of 34 weeks and 6 days while inhibiting plus disease, offer support for this hypothesis.

Debate also exists as to whether bevacizumab should be administered as monotherapy or as adjunctive therapy. Monotherapy appears to be a feasi-

ble treatment option in sick infants and in eyes with poor posterior pole visibility secondary to persistent fetal vasculature, vitreous hemorrhage, or media opacity.^{23,51} There appears to be a role for bevacizumab monotherapy in the treatment of aggressive posterior ROP (zone I and posterior zone II), where laser ablation may induce visually threatening structural changes (foveal damage or macular dragging).⁹ Of note, there is evidence^{9,26} that the disease may recur after an average of 16 weeks in eyes that had initially achieved complete regression after bevacizumab treatment, compared to an average of 6 weeks after laser treatment. This has implications for establishing a proper follow-up period, which has been suggested to be at least 10 weeks longer in the bevacizumab group than in the laser group.²⁶

Intravitreal bevacizumab can also be used as an adjunctive treatment to laser ablation or vitrectomy. To date, laser ablation remains the standard of care for ROP.⁶ Nevertheless, it has been shown that regression of plus disease and development of peripheral normal retinal vasculature occurred significantly more rapidly in patients who received both laser ablation and bevacizumab compared to those treated with laser ablation only.²⁵ In eyes receiving combination therapy, there is concern for a potential increase in the side effect profile of bevacizumab, which can theoretically enter the systemic circulation more easily due to the laser-induced breakdown of the blood-ocular barrier.⁵² Furthermore, in eyes with or at risk of detachment from advanced posterior ROP, intravitreal bevacizumab may lead to tissue contraction, increasing the risk of unfavorable outcomes.⁵³ However, because of the improved view to the fundus and regression of the vascular component of the fibrovascular membrane,⁵⁴ such eyes may benefit from adjunctive therapy with bevacizumab before vitrectomy is performed.⁵⁵

The use of bevacizumab in the treatment of ROP during the past few years marks the beginning of an important paradigm shift in the way this devastating condition is managed. The most comprehensive study to date⁹ offers sound clinical evidence for the usefulness of VEGF blockade in the eye with ROP and, more important, establishes the platform for future studies. Such efforts would ideally be controlled, randomized, and powered for statistical significance, and would include long-term data on the ocular and systemic safety profile of intravitreal VEGF use in the treatment of ROP.

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The correct answer to *What's Your Diagnosis?* is infantile nephropathic cystinosis.

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