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Chronic Vascular Arrest as a Predictor of Bevacizumab Treatment Failure in Retinopathy of Prematurity

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Purpose: To describe a pattern of retinopathy of prematurity (ROP) disease regression and chronic vascular arrest after intravitreal bevacizumab treatment that is not observed after peripheral laser ablation.

Design: Single-institution retrospective cohort study.

Participants: Consecutive sample of 58 eyes in 30 patients treated for type 1 ROP.

Methods: Initial treatment with either a single intravitreal injection of bevacizumab in off-label use (n = 33 eyes) or peripheral laser ablation (n = 25 eyes) as part of standard clinical care. There was bias in recommending off-label bevacizumab for smaller infants with type 1 ROP.

Main Outcome and Measures: Reactivation or persistence of ROP, as determined by clinical examination, fundus photography, and fluorescein angiography.

Results: All eyes treated initially with bevacizumab demonstrated irregular progression of the leading vascular edge in a stereotyped pattern, suggestive of scalloped regression. Recurrence, based on angiographic demonstration of leakage, or chronic vascular arrest, confirmed based on angiographic demonstration of peripheral ischemia, was noted in 30 eyes (91%) in the bevacizumab group, at a median interval of 14.9 weeks after injection (corrected gestational age, 49.3 weeks). Univariate logistic regression indicated that the need for rescue treatment was associated with decreased birth weight (odds ratio [OR], −0.007; $P = 0.04$) and age of initial treatment (OR, −0.35; $P = 0.05$), but not gender, race, or gestational age. Multivariate logistic regression indicated that only decreased birth weight (OR, −0.018; $P = 0.04$) was associated with need for rescue treatment.

Conclusions: Treating ROP with intravitreal bevacizumab results in a characteristic scalloped regression pattern that is highly associated with treatment using biologic anti−vascular endothelial growth factor agents. The presence of this pattern in conjunction with chronic vascular arrest and peripheral retinal ischemia persisting beyond standard screening timelines has significant implications for the management of ROP. Fluorescein angiography is important in assessing vascular maturation in these infants. *Ophthalmology 2016;■:1−10 © 2016 by the American Academy of Ophthalmology.*

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Retinopathy of prematurity (ROP) is a disorder of retinal vascular development in premature infants that is characterized by pathologic neovascularization with potentially blinding sequelae, including retinal traction and detachment. Retinopathy of prematurity remains a major cause of childhood visual morbidity, with an estimated worldwide annual incidence of 184 700, resulting in approximately 20 000 new cases of severe visual impairment yearly.[1] The major risk factors for ROP developing are premature birth and low birth weight.[2] Several molecular signaling pathways play a role in the pathogenesis of ROP, including vascular endothelial growth factor (VEGF), erythropoietin, insulin-like growth factor-1, and omega-3 fatty acids.[3]

The pathologic neovascularization characteristic of ROP has 2 phases. Phase 1, occurring during postmenstrual age 22 through 30 weeks, consists of oxygen-induced arrest of normal vascular development, spindle-cell damage and gap junction formation, and obliteration of immature retinal vessels, leading to peripheral retinal avascularity.[3−5] In phase 2, occurring during postmenstrual age 31 through 44 weeks, the retina differentiates and becomes more metabolically active, leading to hypoxia-mediated vasoproliferation in the peripheral areas of ischemia.[3−6] Abnormal levels of VEGF (low in phase 1, high in phase 2) have been implicated in the molecular pathogenesis of ROP.[7]

Intravitreal administration of bevacizumab, a humanized monoclonal antibody against VEGF-A, during phase 2 of ROP, has demonstrated efficacy in causing regression of pathologic neovascularization and promoting progression of putatively normal retinal vascular development through continued canalization of spindle-cell vessel precursors.[8−15] Several studies have reported on the reactivation of ROP

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after intravitreal bevacizumab treatment,[8,13,16–18] characterized as either persistence or recurrence of pathologic neovascularization. Recurrence after treatment with anti-VEGF agents tends to occur later than with conventional ablative therapy.[8,13]

In this article, we report on a characteristic pattern of regression of pathologic neovascularization and chronic vascular arrest associated with intravitreal bevacizumab treatment in ROP that is distinct from findings after peripheral laser ablation. We also discuss potential prognostic and management implications with regard to chronic vascular arrest in these infants.

Methods

Patient Inclusion

This was a retrospective, institutional cohort study of 30 patients treated for type 1 ROP disease (including Early Treatment of Retinopathy of Prematurity high-risk prethreshold, threshold, or aggressive posterior retinopathy of prematurity) by a single surgeon (D.M.M.) between January 2013 and June 2015. The protocol was approved by the Stanford University Institutional Review Board, complied with the requirements of the Health Insurance Portability and Accountability Act, and adhered to the tenets of the Declaration of Helsinki.

As part of standard clinical care, premature infants meeting Joint Statement Screening Guidelines criteria[19] were screened routinely for ROP by binocular indirect ophthalmoscopy. Based on confirmation of findings meeting type 1 ROP criteria and the patient's overall health, the patient's caregivers were offered intravitreal bevacizumab in an off-label use versus traditional laser photocoagulation. There was bias in recommending off-label bevacizumab for smaller infants with type 1 ROP.

Off-Label Bevacizumab Intravitreal Injection Technique and Management

For patients being treated with bevacizumab, a reduced adult dose (0.625 mg in 0.025 ml) of intravitreal bevacizumab was administered at bedside in each eye, using the following technique: sterile gloves, insertion of a lid speculum, instillation of topical povidone–iodine, demarcation 0.5 to 1 mm posterior to the limbus in the inferonasal or inferotemporal quadrants, injection of bevacizumab using a sterile tuberculin syringe with a sterile 30-gauge 0.5-inch needle, removal of the needle with simultaneous occlusion of the sclerotomy site using a sterile cotton-tipped applicator, instillation of topical moxifloxacin, and removal of the speculum. If the other eye was to be treated, all new equipment was used. After injection, patients underwent binocular indirect ophthalmoscopy to assess for lens clarity, retinal breaks, retinal detachment, optic nerve perfusion and spontaneous pulsations, and hemorrhage. Patients were followed up at 24 to 48 hours and then weekly to every other week with dilated ophthalmoscopic examinations until either recurrence or full vascular maturation was noted. Beginning around 50 weeks' postmenstrual age, or when babies were too large to examine safely in the outpatient clinic setting, infants underwent an examination under anesthesia with photography and fluorescein angiography (FA) using the RetCam3 (Clarity Medical Systems, Pleasanton, CA) to assess whether continued evaluation or perhaps treatment were necessary.

We used the following definitions for patterns seen on FA after intravitreal bevacizumab injection: (1) scalloped regression manifesting as an intercalating pattern of vascular loops at the termination of the retinal vasculature, distinct from either immature retinal vasculature, which has no apparent border, and stage 1 ROP, which has a clear, smooth linear demarcation between avascular and vascularized retina; (2) anterior ischemic non-vascularized retina; (3) vascular arrest, defined as failure of the retinal vasculature to grow into zone III, defined as within 2 disc diameters of the ora serrata; and (4) ROP reactivation, manifesting as disease recurrence in stage of disease, plus disease, or neovascularization at the vascular–avascular interface or region of prior extraretinal fibrovascular proliferation.

We performed diode laser photocoagulation (per the protocol below) in the following situations: (1) continued ROP activity (any stage, pre-plus disease, or plus disease), (2) chronic vascular arrest confirmed on FA, and (3) active leakage at the border of the vascular termination or posterior to this area. The rationale for laser photocoagulation was to shut down any continuing VEGF drive. This served 2 purposes: (1) to eliminate the risk of primary retinal detachment from ROP reactivation and (2) to terminate the acute-phase screening of ROP 9 weeks after laser treatment, based on findings by Coats et al.[20]

Traditional Diode Laser Photocoagulation

All caregivers of infants receiving diode laser photocoagulation were informed that the major risks were as follows: decreased peripheral vision, decreased night vision, high myopia, anterior segment ischemia, cataract, phthisis, iris synechiae with irregular pupils, and acute or late angle-closure glaucoma, in addition to the usual risks. All diode laser photocoagulation was performed under general anesthesia in the operating room. Before treatment, binocular indirect ophthalmoscopy with 360° scleral depression was performed to assess and document the disease extent and severity in each eye. This was followed by fundus photography. The laser parameters were as follows: power range, 100 to 300 mW; duration, 150 to 200 ms; and interval, 100 to 200 ms. Laser was applied in a nearly confluent pattern as follows: 1 row anterior to the vascular termination/ridge, 1 row posterior to the ora serrata, and filling in between with 0.25- and 0.5-spot width separation in all locations, except nasal and temporal over the ciliary artery and nerve, where 1- to 1.5-spot width separation was employed to avoid unnecessary damage to the underlying ciliary artery and nerve in an attempt to minimize the possibility of anterior segment ischemia. After laser treatment, binocular indirect ophthalmoscopy with 360° scleral depression was performed to assess and document the absence of skip areas, inadvertent treatment of vascularized retina, new hemorrhage, or retinal break or detachment, or both. This was followed by fundus photography to document these findings. Patients were initiated on postoperative topical prednisolone acetate 1%, atropine 1%, and moxifloxacin 0.5%. Initial assessment was 1 week after diode laser photocoagulation and continued for 9 weeks, when acute-phase screening for ROP was terminated. Patients were scheduled with pediatric ophthalmology 4 to 6 weeks after termination of acute-phase screening for ROP to assess for amblyopia, refractive error, and strabismus.

Data Analysis

Given the small sample size and data that were not normally distributed, continuous variables were summarized as median with range. The Mann–Whitney *U* test was used to compare continuous data between the 2 groups. Chi-square and Fisher exact tests were used to compare categorical data. Logistic regression analyses were performed to assess the impact of various patient and treatment factors (birth weight, gestational age, age of initial treatment, gender, and race) on ROP disease reactivation requiring rescue