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Follow-up to Age 4 Years of Treatment of Type 1 Retinopathy of Prematurity Intravitreal Bevacizumab Injection versus Laser: Fluorescein Angiographic Findings

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Purpose: To compare structural outcome at age 4 years of eyes treated with intravitreal injection of bevacizumab with fellow eyes treated with conventional laser photoablation in type 1 retinopathy of prematurity (ROP).

Design: Single, randomized, controlled trial.

Participants: All inborn babies with type 1 zone 1 ROP at the Neonatal Intensive Care Unit of the Catholic University, Rome, from September 1, 2009, to March 31, 2012.

Methods: In 21 infants (42 eyes), 1 eye was randomized to receive an intravitreal injection of 0.5 mg bevacizumab; the fellow eye underwent conventional laser photoablation. Digital retinal imaging and fluorescein angiography (FA) were performed at an average of 4 years after treatment in follow-up after these studies performed at treatment and 9 months.

Main Outcome Measures: Fluorescein angiograms were examined by 2 experts to document retinal and choroidal findings.

Results: Among the 20 bevacizumab-treated eyes available at 4 years of age, all showed abnormalities at the periphery (avascular area, vessel leakage, shunts, abnormal vessel branching, and tangles) or the posterior pole (hyperfluorescent lesions, absence of foveal avascular zone). These lesions were not observed in the majority of the lasered eyes. Among the 19 laser-treated eyes, leakage was noted in 1 eye, shunts and tangles were noted in 3 eyes, and macular abnormalities were noted in 3 eyes.

Conclusions: Fluorescein angiography has shown potentially serious and long-term ocular effects that are present more commonly after treatment with bevacizumab for acute-phase ROP than after laser. *Ophthalmology 2017;■:1–9 © 2017 by the American Academy of Ophthalmology*

Based largely on the results of 2 large randomized clinical trials conducted over the last 30 years,[1,2] ablation of the peripheral avascular retina is the current standard treatment for retinopathy of prematurity (ROP).[3–5] However, treatment outcomes from severe retinopathy in zone I need to be improved. For example, zone I stage 3 with or without plus disease eyes treated in the Early Treatment for Retinopathy of Prematurity (ETROP) trial had a 30.4% likelihood of developing unfavorable visual acuity outcome (worse or equal to 20/200) on long-term follow-up at 6 years.[1] As survival of very low–birth-weight infants increased, zone I ROP requiring treatment has become more frequent and other modalities of treatment are being considered.[6] Studies of experimental models for ROP have clearly demonstrated a rationale for the use of anti–vascular endothelial growth factor (VEGF) drugs to prevent progression of serious ROP.[4,7]

Since 2007, a number of reports have appeared on the use of intravitreal bevacizumab (IVB) in ROP requiring treatment as monotherapy,[8–10] in combination with laser,[11–13] or as a rescue treatment in combination or before vitrectomy.[14]

The multicenter clinical trial Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity study reported a significant reduction of zone I ROP recurrence with a single intravitreal injection of approximately half the adult dose (0.625 mg of bevacizumab in 25 μl of balanced saline solution) compared with conventional laser therapy (6% vs. 42%).[15,16] After this report, there has been a series with small numbers of subjects or case reports on the use of anti-VEGF drugs, mainly bevacizumab.[17,18] Wallace et al,[19] on behalf of the Pediatric Eye Disease Investigational Group, recently demonstrated that a dose of bevacizumab as low as 0.031 mg was effective in the treatment of type 1 ROP. Reports of ranibizumab monotherapy also documented successful treatment of severe ROP using doses between 0.2 mg and 0.3 mg.[20] This drug was selected largely on the basis of the finding that the drug has a shorter duration of systemic exposure compared with bevacizumab.[21–23]

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There are several advantages of the use of anti-VEGF drugs in eyes with high-risk ROP characteristics: easy and quick injection under topical anesthesia, rapid diminution of retinal vascular dilatation and tortuosity, and the possibility of preservation of visual field and lower degrees of myopia in the long run.[24] These considerations, combined with some practical considerations, such as laser equipment and well-trained ophthalmologists, may not be readily available in some regions, and the relatively low cost of bevacizumab led to the rapid proliferation of the use of anti-VEGF for ROP treatment in many countries.

Although use of these drugs could represent an important improvement in the therapy of severe ROP, concerns arose about short- and long-term local and systemic adverse effects.[25,26] Drug safety, both for adults[16] and for premature infants, needs to be a primary concern. For example, a Canadian Neonatal Network report from Morin et al[27] on developmental outcomes in a nonrandomized cohort of infants who had received intravitreal injections of bevacizumab compared with a cohort who underwent treatment with laser photocoagulation alone documented a 3.1-times higher risk of severe neurodevelopmental disabilities at 18 months in the 27 IVB infants versus the 98 laser-treated infants. In addition, Lien et al[28] recently reported an observational study of 61 infants treated with IVB alone, laser alone, or both. They found that infants treated with bevacizumab and laser had a 5.3-times higher risk of severe psychomotor delays than the laser alone group. Although neither of these studies is a randomized trial, they do add urgency, in agreement with many other investigators, to the need to understand adverse systemic effects of the use of an antiangiogenic in developing neurons, lungs, and other systems of a premature infant.[25,29,30]

Thus far, adverse ocular effects have been mainly due to fibrotic reaction after intravitreal injection.[31–33] In 2014, we reported a series of fluorescein angiography (FA) studies in a case series of infants who developed type 1, zone I ROP in both eyes. For each infant, 1 eye was randomly assigned to receive bevacizumab in 1 eye and conventional laser photocoagulation in the fellow eye within 24 hours of diagnosis of type 1 ROP. In this case series, IVB-treated eyes had significant residual vascular and macular abnormalities compared with laser-treated eyes on FA 9 months after treatment.[34] The purpose of the current report is to present further follow-up results of FA studies,[34–36] along with digital retinal images, of the entire study population (13 from the original report and an additional 8 enrolled from January 1, 2011, to March 31, 2012) 4 years after treatment.

Methods

This is a single-center, randomized, controlled trial conducted at the Catholic University in Rome. All inborn infants with type 1 zone 1 ROP, as defined by ETROP criteria,[1] were enrolled in the study after informed consent was obtained from the parent or guardian.

Within a maximum interval of 24 hours after diagnosis of type 1, zone I ROP, all infants underwent general anesthesia for evaluation and treatment.[37] For each infant, 1 eye was randomly assigned, using a random number series, to undergo conventional laser photoablation of the peripheral avascular retina while the fellow eye received an intravitreal injection of 0.5 mg bevacizumab in a 0.02-ml balanced salt solution. Before treatment, digital retinal images were obtained using the RetCam imaging system (Clarity Medical Systems, Pleasanton, CA) and then video-digital FA, used as a part of the screening protocol for zone I ROP, 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.[34,38] The eye assigned to conventional laser was treated first, and the FA was examined by the treating physician before 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 fellow eye 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 for 3 days.

After treatment, binocular indirect ophthalmoscopy (BIO) and digital RetCam imaging were performed every 3 days along with FA every 2 weeks until discharge. After discharge from the neonatal intensive care unit, BIO was performed every 2 weeks until 52 weeks postmenstrual age and then monthly until 1 year of age. Infants underwent FA at 4 years of age under general anesthesia.

Angiograms were examined retrospectively by 2 experienced individuals (DL, FM) for the following characteristics as described by Lepore et al.[38] Branching abnormalities were considered present if at least 1 quadrant of the eye showed the presence of tangles and shunts. The same criteria were used to assess the capillary loss within the vascularized retina and the posterior pole. Absence of foveal avascular zone and/or the presence of hyperfluorescent lesions and/or pigmented epithelium dystrophy were considered as macular abnormalities. If only large linear choroidal vessels without choriocapillaries were observed in the early FA phases, linear filling pattern was reported.

The Institutional Review Board at the Catholic University of the Sacred Heart of Rome approved the study protocol, and the trial was registered at the EudraCT 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 March 31, 2012, 21 inborn preterm infants who underwent ROP examinations using BIO in the neonatal intensive care unit at the Agostino Gemelli University Hospital developed type 1, zone I ROP in 1 or both eyes and required treatment, according to ETROP[1] criteria. Eight eyes (4 infants; mean birth weight 697 g, range, 615.0–755.0 g; mean gestational age 25.3 weeks, range, 22.7–29.3 weeks) were classified as zone I stage 3 with plus disease; 34 eyes (17 infants; mean birth weight 667 g, range, 380–960 g; mean gestational age 25.6 weeks, range, 22.7–29.3 weeks) were classified as zone I stage 3 without plus.

One eye treated with conventional laser progressed to a complete retinal detachment within 4 weeks after treatment. In addition, 1 infant died of pulmonary complications at 3 months of age.

Therefore, FA images of 20 eyes in the bevacizumab-injected group and 19 in the laser-treated group were available for evaluation by 2 different ROP experts. The FA results before treatment and at 9 months post-treatment have been reported, and included in this report are images from the same group of patients at age 4 years (mean post-conceptional age [PCA], 248 weeks; range, 233–275 weeks PCA).