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Foveal Development in Infants Treated with Bevacizumab or Laser Photocoagulation for Retinopathy of Prematurity

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Purpose: To characterize and quantify early foveal development in preterm infants and to compare this development between eyes treated with intravitreal bevacizumab or laser photocoagulation (LPC) and untreated eyes.

Design: Observational case series.

Participants: One hundred thirty-one preterm infants undergoing retinopathy of prematurity (ROP) screenings.

Methods: Handheld OCT imaging was performed longitudinally on all patients. Thickness measurements of the inner and outer retinal layers were obtained at the foveal center and the nasal and temporal foveal rims. Comparisons between treated and untreated eyes were adjusted for age and other confounding variables.

Main Outcome Measures: Weekly change in inner and outer retinal thickness and presence of inner retinal layers, ellipsoid zone (EZ), and cystoid macular changes (CMCs).

Results: Outer retinal thickness at the foveal center increased by 3.1 μm/week in untreated eyes and 7.2 μm/week in bevacizumab-treated eyes ($P = 0.038$). Eyes treated with LPC had a lower probability of having all inner retinal layers present at the foveal center (odds ratio, 0.04; $P = 0.001$) and a lower probability of having the EZ present at the foveal center (odds ratio, 0.07; $P = 0.024$) compared with untreated eyes. Cystoid macular changes were found in 53% of patients and 22% of imaging sessions. The age-adjusted incidence of CMCs was not correlated with bevacizumab or LPC treatment.

Conclusions: Intravitreal bevacizumab therapy for ROP is associated with more rapid outer retinal thickening at the foveal center, whereas LPC is associated with earlier extrusion of the inner retinal layers and delayed development of the EZ at the foveal center. Long-term follow-up is needed to determine the visual significance of these findings. *Ophthalmology 2017;■:1–9 © 2017 by the American Academy of Ophthalmology*

Retinopathy of prematurity (ROP) is a potentially blinding neurovascular disorder that primarily affects infants born very prematurely with low birthweights. Management of ROP involves carefully timed fundus examinations of at-risk infants based on screening guidelines[1] and treatment with laser photocoagulation (LPC) for certain high-risk findings.[2]

More recently, intravitreal anti–vascular endothelial growth factor (VEGF) therapy has been demonstrated to be as effective as conventional laser treatment for stage 3+ ROP, with lower recurrence rates for zone I disease.[3] However, late recurrences, sometimes leading to retinal detachment, have been described after anti-VEGF therapy.[4–6] Anti-VEGF therapy offers the advantage of preserving the function of the peripheral retina, which is necessarily ablated with LPC. Anti-VEGF therapy also has been shown to result in a lower incidence of high myopia compared with laser treatment.[7–9] Concerns have been raised regarding the potential for adverse systemic effects resulting from intravitreal anti-VEGF therapy in infancy because VEGF plays an important role in many physiologic processes.[10] Similarly, there is a need to evaluate the effect of anti-VEGF therapy on the developing retina, especially the fovea.

Spectral-domain (SD) OCT imaging of infants is a new field that has expanded our understanding of the developing retina through longitudinal, in vivo analysis of the foveal microstructure. Before the last decade, analysis of foveal development was dependent on postmortem histologic studies.[11–13] The advent of mobile SD OCT instruments with handheld probes increased the ease of imaging infants, even without the use of sedation.[14,15] Maldonado et al[16] performed handheld SD OCT imaging on preterm infants from 31 to 41 weeks postmenstrual age (PMA), which helped to establish a timeline of human foveal development during this dynamic period. This timeline later was corroborated and expanded by imaging infants beyond 41 weeks PMA with handheld OCT.[17,18] The fovea before full-term birth has an immature appearance with a shallow foveal pit, persistent inner retinal layers at the foveal center, thin outer retinal layers, and absent photoreceptor subcelluar elements, such as the ellipsoid zone (EZ)

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and interdigitation zone. The inner and outer foveal layers develop along different time frames, with the inner layers maturing around the time of full-term birth and the outer layers reaching maturity within the first few years after birth.[19]

Handheld OCT also has led to the discovery of cystoid macular changes (CMCs) in infants, which resemble retinoschisis or cystoid macular edema, but tend to resolve spontaneously.[20] Cystoid macular changes were found to resolve as early as 36 weeks PMA,[21] and Vinekar et al[22] found that CMCs resolved in all infants by 52 weeks PMA. Cystoid macular changes have been found in healthy full-term infants as well.[23,24] Cystoid macular changes have been hypothesized to be a manifestation of increasing levels of VEGF, decreasing levels of insulin-like growth factor 1, increased intracapillary hydrostatic pressure related to plus disease, or mechanical traction.[21,25–27] The effect of anti-VEGF therapy or LPC on CMCs currently is unknown.

Although our understanding of foveal development has increased since the advent of handheld OCT, the effect of intravitreal anti-VEGF therapy or LPC on this process remains unclear. Laser photocoagulation has been shown to be associated with a higher incidence of foveal abnormalities and worse visual acuity compared with patients with ROP who regress spontaneously.[28] It is not clear if this is because of the treatment itself or other factors associated with more severe ROP.

This study evaluated the inner and outer foveal anatomic characteristics longitudinally in infants undergoing ROP screening examinations using handheld SD OCT. The purpose was to provide information on the timing and characteristics of foveal development and CMCs in this population, including any potential effects related to intravitreal bevacizumab or LPC therapy.

Methods

Participants

This study protocol was approved by the institutional review boards at the Medical College of Wisconsin and Children's Hospital of Wisconsin and was conducted in accordance with the tenets of the Declaration of Helsinki. All information in this study complies with the Health Insurance Portability and Accountability Act. The parents or legal guardians of all infants undergoing ROP screening examinations at Children's Hospital of Wisconsin and Aurora Sinai Medical Center, Milwaukee, Wisconsin, were asked to participate in this imaging study. Infants were enrolled if the parents or legal guardians gave written consent after the nature and possible consequences of the study were explained. Birth weight, gestational age at birth (determined by a neonatologist), gender, and PMA at each imaging session were collected for each participant.

Eyes were dilated with cyclopentolate 0.2% plus phenylephrine hydrochloride 2.5% (Cyclomydril; Alcon, Inc., Fort Worth, TX). Clinical examinations were performed by a pediatric ophthalmologist (D.M.C.) who documented ROP zone (I–III) and stage (1–5) and the presence or absence of plus disease, according to the International Classification of Retinopathy of Prematurity. All eyes with type 1 ROP were treated with bevacizumab or LPC at the discretion of the clinician. In general, eyes with zone I or posterior zone II disease were treated with intravitreal bevacizumab, whereas eyes in which the fibrovascular ridge was located more anteriorly were treated with LPC. Any recurrence of ROP after bevacizumab treatment was always treated with LPC. Eyes treated with LPC were given tobramycin 0.3% plus dexamethasone 0.1% ophthalmic ointment 4 times daily and cyclopentolate 0.2% plus phenylephrine hydrochloride 2.5% 3 times daily in the treated eye(s) for 14 days after the procedure. Eyes injected with bevacizumab underwent antiseptic preparation of the ocular surface with povidone–iodine 5% before injection and were given moxifloxacin hydrochloride 0.5% 4 times daily in the treated eye(s) for 1 week after the injection.

Optical Coherence Tomography

Optical coherence tomography imaging was performed using 2 handheld probe SD OCT systems (Envisu C2300 and R2310; Bioptigen, Inc., Durham, NC). Images were acquired between August 2012 and March 2017 during routine ROP screening examinations in the neonatal intensive care unit, the timing of which was based on established screening guidelines[1] and clinician judgement. Imaging was always performed after clinical examination. A lid speculum was used to keep the eye open during imaging, and artificial tears were used to lubricate the corneal surface. Imaging was performed on both eyes whenever possible. The SD OCT imaging parameters provided by Maldonado et al[29] were used to optimize image quality. The nominal scan size was 8×8 mm or 12×12 mm, and scan density was 160 to 200 B-scans at 1000 A-scans/B-scan. B-scans were oriented at 0° (horizontally).

Individual B-scans that captured the foveal center, nasal foveal rim, temporal foveal rim, or a combination thereof were selected manually from each volume scan. The foveal center was defined as the location at which the foveal pit is deepest. The B-scan within a volume scan with the deepest foveal pit and in which adjacent B-scans showed a shallower pit was presumed to be the foveal center. In very rare cases in which the foveal pit was completely absent in the fovea, the foveal center was defined as the apex of the central bulge of the outer nuclear layer, which was present in most participants. The foveal rim was defined as the location within the fovea or parafovea at which the internal limiting membrane has 0 slope with respect to the retinal pigment epithelium.[30] Measurements of the retinal anatomic features were obtained manually using ImageJ software (National Institutes of Health, Bethesda, MD; provided in the public domain at http://imagej.nih.gov/ij/). To minimize measurement error caused by off-axis scan acquisition, the images were converted to the true anatomic aspect ratio based on axial length before all measurements.[31,32] Axial length was estimated using an age-based linear model.[29]

Measurements were obtained manually using longitudinal reflectivity profiles, which sampled an area of the retina 100-μm wide (Fig 1). The border between adjacent layers on an OCT image was defined as the location on the longitudinal reflectivity profile where the magnitude of reflectivity was midway between the peak reflectivity of the hyperreflective layer and the trough reflectivity of the hyporeflective layer. Measurements of retinal thickness were obtained from the inner border of the internal limiting membrane to the inner border of the retinal pigment epithelium–Bruch's membrane complex at the foveal center, nasal foveal rim, and temporal foveal rim. The inner border of the outer plexiform layer was defined as the border between the inner and outer retina, akin to the definition of Lee et al.[18] The outer plexiform layer was included as part of the outer retina to avoid inconsistent measurements that would result from the directional reflectance of the Henle fiber layer, which is located