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Papilledema Outcomes from the Optical Coherence Tomography Substudy of the Idiopathic Intracranial Hypertension Treatment Trial

*The Optical Coherence Tomography Substudy Committee and the NORDIC Idiopathic Intracranial Hypertension Study Group**

Purpose: To assess treatment efficacy using spectral-domain (SD) optical coherence tomography (OCT) measurements of papilledema in the Idiopathic Intracranial Hypertension Treatment Trial (IIHTT), which evaluated the effects of acetazolamide and weight management and of placebo and weight management in eyes with mild visual loss.

Design: Randomized double-masked control clinical trial of acetazolamide plus weight management compared with placebo plus weight management in subjects with mild visual field loss and previously untreated idiopathic intracranial hypertension (IIH).

Participants: Eighty-nine (43 acetazolamide treated, 46 placebo treated) of 165 subjects meeting IIHTT entry criteria.

Methods: Subjects underwent perimetry, papilledema grading (Frisén method), high- and low-contrast visual acuity, and SD OCT imaging at study entry and 3 and 6 months. Study eye results (worse perimetric mean deviation [PMD]) were used for most analyses.

Main Outcome Measures: Retinal nerve fiber layer (RNFL) thickness, total retinal thickness (TRT), optic nerve (ONH) volume, and retinal ganglion cell layer (RGCL) measurements derived using 3-dimensional segmentation.

Results: Study entry OCT values were similar in both treatment groups. At 6 months, the acetazolamide group had greater reduction than the placebo group for RNFL thickness (175 μm vs. 89 μm; $P = 0.001$), TRT (220 μm vs. 113 μm; $P = 0.001$), and ONH volume (4.9 mm^3 vs. 2.1 mm^3; $P = 0.001$). The RNFL thickness ($P = 0.01$), TRT ($P = 0.003$), and ONH volume ($P = 0.002$) measurements also showed smaller increases in subjects who lost 6% or more of study entry weight. The acetazolamide (3.6 μm) and placebo (2.1 μm) groups showed minor RGCL thinning ($P = 0.06$). The RNFL thickness, TRT, and ONH volume measurements showed moderate correlations ($r = 0.48–0.59$; $P \leq 0.0001$) with Frisén grade. The 14 eyes with RGCL thickness less than the fifth percentile of controls had worse PMD ($P = 0.001$) than study eyes with RGCL in the fifth percentile or more.

Conclusions: In IIH, acetazolamide and weight loss effectively improve RNFL thickness, TRT, and ONH volume swelling measurements resulting from papilledema. In contrast to the strong correlation at baseline, OCT measures at 6 months show only moderate correlations with papilledema grade. *Ophthalmology 2015;■:1–7 © 2015 by the American Academy of Ophthalmology.*

*Supplemental material is available at www.aaojournal.org.

Spectral-domain (SD) optical coherence tomography (OCT) has provided high-quality data collected from multiple clinical sites from patients naïve to treatment for papilledema resulting from idiopathic intracranial hypertension (IIH) who have mild vision loss at entry into the Idiopathic Intracranial Hypertension Treatment Trial (IIHTT).[1,2] Optical coherence tomography reliably and reproducibly demonstrates alterations in the optic nerve head (ONH) and retinal layers (RNFLs) in patients with IIH. At baseline, we measured the average peripapillary RNFL thickness, average peripapillary total retina thickness (TRT), ONH volume, and the retinal ganglion cell layer (RGCL) plus inner plexiform layer (IPL) thickness in the macular region. The RNFL thickness, TRT, and ONH volume also correlated strongly with Frisén papilledema grade.[3] Prior studies of eyes with significant ONH swelling showed that 2-dimensional (2-D) segmentation analysis failures are common when using the proprietary OCT algorithms for measuring the effects of swelling in the peripapillary retina via RNFL thickness with SD OCT (Mandel G, et al. IOVS 2010;51:ARVO E-Abstract 555) and TRT with time-domain OCT.[4] For eyes studied in the IIHTT, the

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proprietary 2-D segmentation algorithm (Zeiss Meditec [ZM] method) used in the commercial OCT device displayed noteworthy failure rates in the measurement of average RNFL thickness (10%), TRT (16%), and RGCL plus IPL thickness (20%). The 3-dimensional (3-D) segmentation algorithm from the University of Iowa engineering group[5] was less prone to failure, with rates of 2.4%, 2.4%, and 0.8%, respectively for the same OCT parameters.

The IIHTT showed that acetazolamide significantly improved perimetric mean deviation (PMD), cerebrospinal fluid (CSF) pressure, quality-of-life measures, and papilledema grade in subjects with mild visual field loss in patients newly diagnosed with IIH.[2] The accepted objective method for evaluating papilledema and monitoring the alterations in the ONH, the Frisén scale, is an ordinal grading based on descriptive features.[6] Spectral-domain OCT provides continuous variable measurements that demonstrate the structural changes in the optic nerve and retina because of papilledema and measures the effects of intracranial hypertension and its treatment.

We report the results of OCT measures for the 6-month investigational phase of the IIHTT by treatment group. We investigated: (1) whether the 3 OCT measures reflecting swelling—RNFL thickness, TRT, and ONH volume—are improved significantly with acetazolamide compared with placebo or with weight loss (see "Methods" for definition) compared with no weight loss; (2) whether these 3 OCT measures change to the same degree from baseline in study eyes at the study outcome time point of 6 months; (3) whether strong interocular correlations for these 3 OCT measures are maintained at 6 months; (4) whether the amount of swelling found with these 3 OCT measures are correlated strongly with the Frisén grade at 6 months; and (5) whether the RGCL plus IPL thins significantly over 6 months and whether RGCL plus IPL thinning correlates with vision performance at 6 months.

Methods

Details of the IIHTT study design and entry criteria are published.[7] Patients with IIH who were naïve to treatment with a PMD of −2.00 to −7.00 dB using the Swedish interactive threshold algorithm standard 24-2 test pattern on the Humphrey Field Analyzer II perimeter (Carl Zeiss Meditec, Inc, Dublin, CA) in the eye with the worse PMD (designated the study eye) were enrolled. All subjects signed consent and the study was performed under institutional review board approval and in accordance with the Declaration of Helsinki. The trial is registered at ClinicalTrials.gov (identifier, NCT01003639).

Standardized fundus photographs, Frisén grading of photographs at the photographic reading center[8] and by clinical examination by site investigators, high- and low-contrast (2.5%) visual acuity, threshold 24-2 perimetry, and SD OCT imaging using the Cirrus 4000 SD OCT device (with version 6.01 software; Carl Zeiss Meditec, Inc) were performed in each eye at each visit. Study sites followed a study-specific protocol for image collection by certified technicians, digitally transferred the collected data, and had quality control and analyses by the OCT reading center. The availability of the specific study OCT limited the substudy to subjects at 24 sites.

The image acquisition protocol required 2 optic disc regions centered on the optic disc and 2 macular region volume scans centered on the fovea. The OCT data were uploaded to the NORDIC imaging center site via a secure upload web client. In addition to certifying site equipment and technicians, the OCT reading center maintained quality control on all OCT data collected.[1]

We used optic disc region volume image data to calculate the peripapillary circumference average RNFL thickness and TRT with the ZM (2-D) method and 3-D segmentation method. The ONH volume was calculated using 3-D analysis of segmented optic disc volume scans.[5] Three-dimensional layer segmentation was performed on the ONH-centered scans, and from each ONH-centered volume, the total retinal volume (i.e., the volume between the internal limiting membrane and the retinal pigment epithelium reference surface) was computed. The RNFL thickness and TRT were computed using a radius of 1.73 mm around the center of the ONH.

Using the Macula Cube volumetric images, TRT of sectors and the average thickness of the RGCL plus IPL complex were measured using the ZM and 3-D segmentation methods. The ZM method finds the distance between the outer boundary of the RNFL and the outer boundary of the IPL to report the combined thickness of the RGCL plus IPL, while excluding the RNFL.[9]

For 3-D segmentation analysis, 11 intraretinal surfaces of each macula-centered volumetric scan were segmented first using the graph-theoretic approach developed at the University of Iowa.[5] The (1) internal limiting membrane, (2) interface between the RNFL and the RGCL, (3) interface between the IPL and the inner nuclear layer, and (4) posterior surface of the retinal pigment epithelial layer surfaces were retained to enable computation of the fovea center and RGCL plus IPL thickness. For each A-scan location, the RGCL plus IPL thickness was defined as the distance between the second surface and the third surface.

Statistical Analyses

For 3-D segmentation RGCL plus IPL thickness, age-matched controls (derived by 3-D segmentation of the set of normative scans provided by Carl Zeiss Meditec, Inc) were used to determine the average RGCL as a percentile of the controls. Descriptive statistics were used to summarize each SD OCT measure based on the first measurement of the study eye (the eye with worse PMD). The first SD OCT measures from both eyes were compared using Pearson correlation coefficients to describe the interocular relationship of these measures (each comparison was for the same measure and method of analysis performed in both eyes).

The RGCL plus IPL value calculated by 3-D segmentation was defined as thinned if the study eye RGCL plus IPL value was less than the fifth percentile of the 3-D segmentation RGCL value derived from age-matched Zeiss normative scans. We used *t* tests to compare this group with study subjects with RGCL plus IPL thickness values in the fifth percentile or more of controls.

The IIH clinical characteristics, collected at 6 months under the IIHTT protocol, were compared with the 6-month OCT findings. Frisén grade of papilledema was determined from digital photographs evaluated by the photographic reading center and also by clinical examination (not by photographic review at the site) performed by the principle investigator at each site. Specific IIH clinical features that were correlated with the OCT findings included amount of weight change, body mass index (BMI), and CSF opening pressure in millimeters of oxygen at 6 months. The best-corrected visual acuity (reported as number of letters correctly identified) for high-contrast (100%) and low-contrast (2.5%) charts and PMD (reported in decibels) on automated threshold visual field testing were correlated with the OCT findings. All OCT data were evaluated and compared for treatment group assignment (acetazolamide plus weight management [acetazolamide-treated group] and placebo plus weight management [placebo-treated group]) and