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Papilledema Outcomes from the OCT Substudy of the Idiopathic Intracranial Hypertension Treatment Trial

The OCT Sub-Study Committee and the NORDIC Idiopathic Intracranial Hypertension Study Group

Abstract

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

Design—Randomized double-masked control clinical trial of acetazolamide (ACZ) plus weight management compared with placebo plus weight management in previously untreated III in subjects withmild visual field loss.

Subjects—Eighty-nine (43 ACZ, 46 placebo treated) of 165 subject meeting entry criteria for the IIHTT.

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

Main Outcome Measures—Retinal nerve fiber layer (RNFL), total retinal thickness (TRT), optic nerve volume (ONHV), and retinal ganglion cell layer (GCL) measurements were derived using 3-D segmentation.

Results—Study entry OCT values were similar in both treatment groups. At 6 months, the ACZ group had greater reduction than the placebo group for RNFL (175 μm vs 89 μm, p=0.001), TRT (220 μm vs 113 μm, p=0.001), and ONHV (4.9 mm^3 vs 2.1 mm^3, p=0.001). The RNFL (p=0.01), TRT (p=0.003), and ONHV (p=0.002) also showed less swelling in subjects who lost ≥ 6% of study entry weight. GCL thinning was minor in ACZ (3.6 μm) and placebo (2.1 μm, p =0.06) groups. The RNFL, TRT, and ONHV showed moderate correlations (r=0.48-0.59, p≤0.0001) with Frisén grade. The 14 eyes with GCL thickness <5^{th} percentile of controls had worse PMD (p=0.001) than study eyes with GCL ≥ 5^{th} percentile.

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Conclusions—RNFL, TRT, and ONH volume measurements of swelling due to papilledema in IIH are effectively improved with ACZ and weight loss. In contrast to the strong correlation at baseline, OCT measures at 6 months show only moderate correlations with papilledema grade.

Keywords

papilledema; intracranial hypertension; optical coherence tomography; OCT

Introduction

Spectral domain optical coherence tomography (SD-OCT) provided high quality data collected from multiple clinical sites from patients naïve to treatment with papilledema due to idiopathic intracranial hypertension (IIH), with mild vision loss, at entry into the IIH treatment trial (IIHTT).[1,2] OCT imaging reliably and reproducibly demonstrates alterations in the optic nerve head (ONH) and retinal layers in patients with IIH. At baseline, we measured the average peripapillary retina nerve fiber layer thickness (RNFL), average total peripapillary retina thickness (TRT), ONH volume, and the ganglion cell plus inner plexiform layer thickness (GCL+IPL) in the macula region. The RNFL, TRT and ONH volume also strongly correlated with Frisén papilledema grade.[3] Prior studies of eyes with significant ONH swelling showed that 2-D segmentation analysis failures are common when using the proprietary OCT algorithms for measuring the effects of swelling in the peripapillary retina via the RNFL thickness with SD-OCT (Mandel G, et al. IOVS 2010;51:ARVO-EAbstract 555) and TRT with time-domain OCT.[4] For eyes studied in the IIHTT, the proprietary two dimensional (2-D) segmentation algorithm (Zeiss Meditec [ZM] method) used in the commercial OCT device displayed noteworthy failure rates in the measurement of average RNFL (10%), TRT (16%) and GCL+IPL thickness (20%). The three dimensional (3D) segmentation (3-D method) 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 the acetazolamide (ACZ) 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 new patients with IIH.[2] The accepted objective method for evaluating papilledema and monitoring the alterations in the optic nerve head, the Frisén scale, is an ordinal grading based on descriptive features.[6] SD-OCT provides continuous variable measurements which demonstrate the structural changes in the optic nerve and retina due to papilledema and measures the effects of intracranial hypertension and its treatment.

We report the results of OCT measures for the six month investigational phase of the IIHTT by treatment group. We investigated: 1. Whether the three OCT measures reflecting swelling; RNFL, TRT, and ONH volume, are significantly improved with ACZ compared with placebo or with weight loss (see methods for definition) compared with no weight loss; 2. Whether these three OCT measures change to the same degree from baseline in study eyes at the study outcome time point of six months; 3. Whether strong interocular correlations for these three OCT measures are maintained at six months; 4. Whether the

amount of swelling found with these three OCT measures are strongly correlated with the Frisén grade at six months; 5. Whether the GCL+IPL significantly thins over six months and whether GCL+IPL thinning correlates with the vision performance at six months.

Methods

Details of the IIHTT study design and entry criteria are published.[7] IIH patients naïve to treatment with a perimetric mean deviation (PMD) of −2.00 dB to −7.00 dB using the SITA standard 24-2 test pattern on the Humphrey Field Analyzer II perimeter (Zeiss Meditec, Inc, Dublin, CA) in the eye with the worst PMD ('study eye') were enrolled. All subjects signed consent and the study was performed under institutional review board approval and in accordance with the Helsinki Declaration. Standardized fundus photographs, Frisén grading of photos at the photographic reading center[8] and by clinical examination by site investigators, high and low (2.5%) contrast visual acuity, threshold 24-2 perimetry, and SD-OCT imaging, using the Cirrus 4000 SD-OCT (with 6.01 software, Carl Zeiss Meditec, Inc, Dublin, CA), were performed ineach 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 (OCTRC). The availability of the specific study OCT limited the sub-study to study subjects at 24 sites.

The image acquisition protocol required two optic disc region centered on the optic disc and two macular region volume scans centered on the fovea. 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 OCTRC maintained quality control on all OCT data collected.[1]

We used optic disc region volume image data to calculate the peripapillary circumference average RNFL and TRT with the Zeiss-Meditec, Inc (ZM, 2-D method) and 3-D segmentation methods. ONH volume was calculated utilizing3D analysis of segmented optic disc volume scans.[5] 3-D 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 optic nerve head.

Using the Macula Cube volumetric images, total retina thickness of sectors and the average thickness of the ganglion cell and inner plexiform layer complex (GCL+IPL) 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 GCL+IPL, while excluding the RNFL.[9]

For 3D-Segmentation analysis, eleven intra-retinal surfaces of each macula-centered volumetric scan were first segmented using the graph-theoretic approach developed at the University of Iowa.[5] The (1) the internal limiting membrane, (2) the interface between the RNFL and the GCL, (3) the interface between the IPL and the inner nuclear layer, and (4) the posterior surface of the retinal pigment epithelial layer surfaces were retained to enable

computation of the fovea center and GCL+IPL thickness. For each A-scan location, the GCL +IPL thickness was defined as the distance between the second surface and the third surface.

Analyses

For 3D-segmentation GCL+IPL thickness, age-matched controls (derived by 3D-segmentation of the set of normative scans provided by Carl Zeiss Meditec, Inc.) were used to determine the average GCL 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 GCL+IPL value calculated by 3D-segmentation was defined as thinned if the 'study eye' GCL+IPL value was < 5^{th} percentile of the 3D-segmentation GCL value derived from age-matched Zeiss normative scans. T-tests were used to compare this group to study subjects with GCL+IPL thickness values ≥ 5^{th} percentile of controls.

IIH clinical characteristics, collected at six months under the IIHTT protocol, were compared to the six 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 photo 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 weight change, body mass index (BMI), and the cerebrospinal fluid (CSF) opening pressure in mm H_2O at six months. The best corrected visual acuity (reported as number of letters correctly identified) for high (100%) and low (2.5%) contrast charts, and perimetric mean deviation (PMD, reported in decibels, dB) on automated threshold visual field testing were correlated with the OCT findings. All OCT data were evaluated compared for treatment group assignment [ACZ-plus weight management (ACZ-treated) and placebo-plus weight management (placebo-treated)] and whether the planned weight loss target (defined as 6% of the weight at study entry) was reached at six months (weight loss or no weight loss).

We also analyzed the OCT data for IIHTT treatment failures. Treatment failure was defined when a participant with baseline PMD up to −3.5 dB had visual function worsen by more than 2 dB PMD from baseline in either eye, or when a participant with baseline PMD between − 3.5 dB and −7 dB had visual function worsen by more than 3 dB PMD from baseline in either eye. An adjudication committee, using all available clinical information, confirmed that the worsening was due to progression of IIH.[7] We explored whether these eyes had baseline OCT features predictive of failure or subsequent OCT features that correlated with visual field worsening.

Mean responses for each OCT variable and interocular correlations were computed using repeated measures analysis of covariance models that included treatment group as the factor of interest with adjustment for site and the baseline value of the outcome. Months three and six were treated as categorical variables. The interactions between treatment group (ACZ or

placebo) and month and between baseline value of the outcome and month were also included in the models. Treatment effects were the group differences (ACZ-placebo) in adjusted mean response. Weight change effects were reported as the group differences (loss-no change) in adjusted mean response. The covariance structure of the R matrix was specified as direct product compound symmetry.

Results

Eighty-nine (43 ACZ, 46 placebo treated) of 165 enrolled IIHTT subjects were included in the OCT substudy. At study entry, all the OCT measures reflecting swelling associated with papilledema, RNFL, TRT, and ONH volume were similar in study eyes of both treatment groups (Figures 1, 2, 3; all baseline data previously reported[1]). Over six months, all three OCT measures were reduced in study eyes in both treatment groups, with significant changes seen by three months (Figures 1, 2, 3). The changes from baseline at six months for ONH volume, and the RNFL and TRT measured by both methods for study eyes showed strong correlation with the fellow non-study eye and for non-study eyes that met criteria for study entry (Table 1). GCL+IPL thickness was minimally reduced at six months. The correlations were strong for 3-D segmentation derived GCL thickness but not for values derived from the ZM method (Table 1, see discussion).

At six months, the ACZ-treated study eyes had the 3-D segmentation derived mean RNFL (174 μm ±, p=0.001), TRT (218 μm ±, p=0.001), and ONH volume (4.9 mm^3 ±, p=0.001) that were less than eyes in the placebo group eyes (93 μm ± , 121 μm ±, 2.4 mm^3 ±, respectively, Figures 1, 2, 3). Similar results were seen in non-study eyes (data not shown). The mean reduction in the RNFL, TRT, and ONH volume compared with study entry was significantly greater in the ACZ-treated study eyes (Table 2). The RNFL (p=0.01), TRT (p=0.003), and ONH volume (p=0.002) showed greater reduction in subjects that lost weight compared with those that had minor or no weight loss (Table 3). The reduction of OCT measurements associated with weight loss was seen in either treatment group. The differences for RNFL, TRT, ONH volume and GCL+IPL between weight groups for ACZ and placebo treatment groups was similar (Table 3).

At six months, the RNFL thickness, TRT, and ONH volume showed significant moderate correlations (r=0.41–0.53, $p \leq 0.0001$ with Frisén grade determined by both clinical exam and photographic reading center evaluations (Table 4). Comparing the *change* in RNFL thickness, TRT and ONH volume with a *change* in Frisén grade, determined by clinical exam and reading center photos, showed slightly stronger correlations (Table 4). There were no correlations (data not shown) for any of the OCT measures compared with high or low contrast visual acuity, PMD, CSF opening pressure, or the BMI (data not shown).

At six months, GCL thickness values derived by 3-segmentation and ZM methods were minimally reduced for both treatment groups (Figure 4, Tables 1 and 2). GCL thickness (by 3D-segmentation) less than the normal fifth percentile, which was found in 9 study eyes (7%) at study entry, 14 study eyes (36%) at three months and in 14 study eyes (50%) at six months. The PMD (p = 0.001) was significantly worse in eyes with $<5^{th}$ percentile GCL at six months; but high contrast visual acuity (p = 0.56), and low (p = 0.12) contrast visual

acuity were not significantly different at six months (Table 5). The PMD and high and low contrast acuity were not significantly different between eyes grouped by GCL thickness at three months (Table 5). The 10 study eyes with RNFL < 5th percentile (83 μm) at six months did not have worse PMD or high or low contrast visual acuity (data not shown).

At six months, 19 eyes had RNFL < the normal ZM fifth percentile thickness (83 μm), eight of which also had 3D-segmentation GCL values < the normal ZM fifth percentile thickness. These 19 eyes did not have significantly worse PMD, high contrast visual acuity or low contrast visual acuity than eyes without RNFL thinning (data not shown).

Six of the seven eyes that met criteria for treatment failure had OCT data collected. Only one of six eyes that had visual field loss leading to treatment failure had GCL+IPL thickness (65.4 μm) that was below the fifth percentile at study entry and this case failed at one month. No other eyes had major GCL reduction prior to or at the same time of treatment failure. None of the treatment failure eyes developed RNFL thinning below the control fifth percentile at the time of failure. OCT data collection was not consistent after treatment failure.

Discussion

Our results, collected in the first longitudinal prospective study and treatment trial of IIH patients utilizing SD-OCT to monitor the effects of papilledema, showed that ACZ-plus weight management was effective in reducing swelling of RNFL, TRT and ONH volume in study and non-study eyes at six months in the IIHTT. These OCT measures were also reduced in the placebo-plus weight management group. Eyes of subjects with at least 6% of baseline body weight reduction (IIHTT planned target) showed significantly less swelling of OCT measures as well, regardless of the treatment group. Thinning or atrophy of the macula region retinal ganglion cell layer was negligible in most study and non-study eyes. RNFL and TRT thickness and ONH volume measurement had similar sensitivity for following the effects of papilledema and the change with treatment. This differs from prior reports of Scott[10] and Vartin[11] suggesting the TRT was superior to RNFL for monitoring papilledema. Our use of 3D-segmentation probably increased the reliability as well as the ability to actually measure the swelling when severe.

There was no overall correlation with the average RNFL or GCL thickness and visual performance at six months. However, even when excluding the treatment failure eyes (six eyes in the OCT cohort), loss or thinning of the GCL below the control fifth percentile at six months, was significantly correlated with mild, but definitely, worse PMD. Also, eyes with RNFL thinning did not demonstrate significantly worse visual performance than eyes with continued RNFL swelling or normal thickness. In IIH where continued papilledema can obscure OCT demonstration of RNFL thinning or atrophy, GCL thickness measurement with 3-D segmentation, in contrast to 2-D methods[1], evaluation is a reliable structural biomarker of neuronal loss. We cannot explain why the GCL thickness was minimally reduced at six months in the ACZ treatment group. This is difficult to reconcile given the better visual field PMD at six months in both treatment groups that was significantly better in the entire IIHTT cohort ACZ-treated eyes as reported in the primary outcome paper.[2] It

may be that the baseline GCL+IPL slight increase in thickness in the ACZ group (see Figure 4) was due to retinal edema or some other etiology of retinal swelling that resolved. Never-the- less, the amount of GCL thinning at six months was nominal compared with GCL thinning due to other optic neuropathies (Wang J- K, et al. IOVS2014; 515: ARVO E-Abstract 5780-B0116). Additionally, we believe the lack of interocular correlation for change of GCL for the ZM method (2D-segmentation) was due to the algorithm failure causing artificially low baseline values at baseline.[1]

We were not surprised to see a weaker correlation than was seen at baseline[3] between the OCT measures of peripapillary retina and ONH swelling and Frisén grade at six months. Given that 52% of placebo and 75% of ACZ treated eyes were either grade 0 or 1, we would anticipate a floor effect as the continuous variable RNFL, TRT and ONH volume values became less swollen. Additionally, OCT and Frisén grading assess different pathophysiological aspects of papilledema. The Frisén grade is based on descriptive inspection of numerous features which are grouped into set stages. Determining progression or regression of edema can be obscured by gliosis, ischemia, and dilated venules. In contrast, the OCT evaluated with 3-D segmentation provides continuous reliable measures that appear to reflect the effects of intra- and extra-cellular edema and axonal loss and thinning across all degrees of swelling. Frisén grade changes over time or in response to therapy can show large changes,[12] but judging grade changes when modest amounts of swelling are present is difficult.

The absolute values or change of from baseline for RNFL, TRT, ONH volume or GCL+IPL at six months did not change with the clinical features relevant to IIH, which included high or low contrast visual acuity, PMD, CSF opening pressure, or the BMI at six months. This is similar to Skau[13] who showed the CSF pressure did not correlate with the OCT in 20 patients followed for less than a month and approximately five years. Our results differed with reports from Skau[13] and Rebolleda,[14] which showed OCT swelling frequently resolves over months. In contrast, IIHTT eyes showed persistent, albeit reduced, OCT measured peripapillary and ONH swelling in many eyes during the uniform six month follow up.

The benefits of ACZ and weight loss on OCT swelling reduction could not be easily separated given that ACZ had effect on weight outcome. Although IIHTT subjects who achieved the weight loss goal of at least 6% of the presentation weight at six months had reduced swelling by OCT, there was no direct correlation with BMI decrease and a reduction in swelling of the RNFL or TRT. This is similar to a prior report that followed patients for three months,[15] suggesting that small amounts of weight loss has limited benefit in IIH. However, at least one report using retrospective data suggested small amounts of weight loss could reduce IIH associated findings.[16]

OCT assessments of swelling due to papilledema in IIH are improved with ACZ-plus-weight management and placebo-plus weight management. In contrast to the strong correlation at baseline, six month RNFL, TRT, and ONH volume show only moderate correlations with papilledema grade. Treated IIH with mild vision loss is associated with minimal GCL+IPL thinning in most eyes. OCT is a useful procedure to follow the

consequences of papilledema due to intracranial hypertension and measure the effects of therapy.

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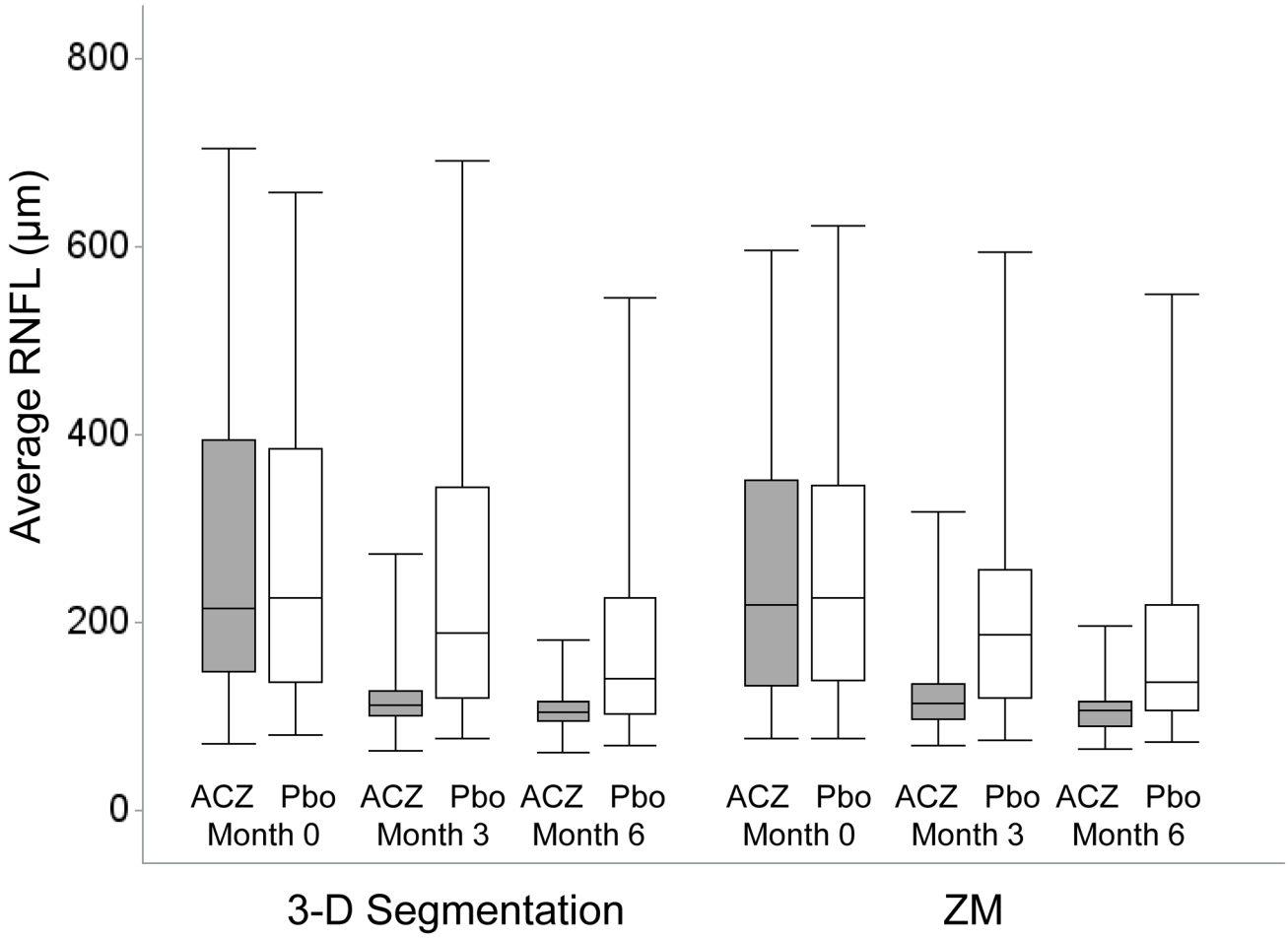

Figure 1.

Boxplots showing average RNFL thickness at study enrollment (Month 0), Month 3, and Month 6, divided by treatment group. ACZ (solid) and placebo (hashed) boxes for each time point for 3D-segmentation (left grouping) and Zeiss-Meditec (ZM, right grouping) algorithm. derived data. The difference from baseline to Month 6 values is significant for both groups using both methods ($P<0.001$ for ACZ and $P=0.001$ for placebo).

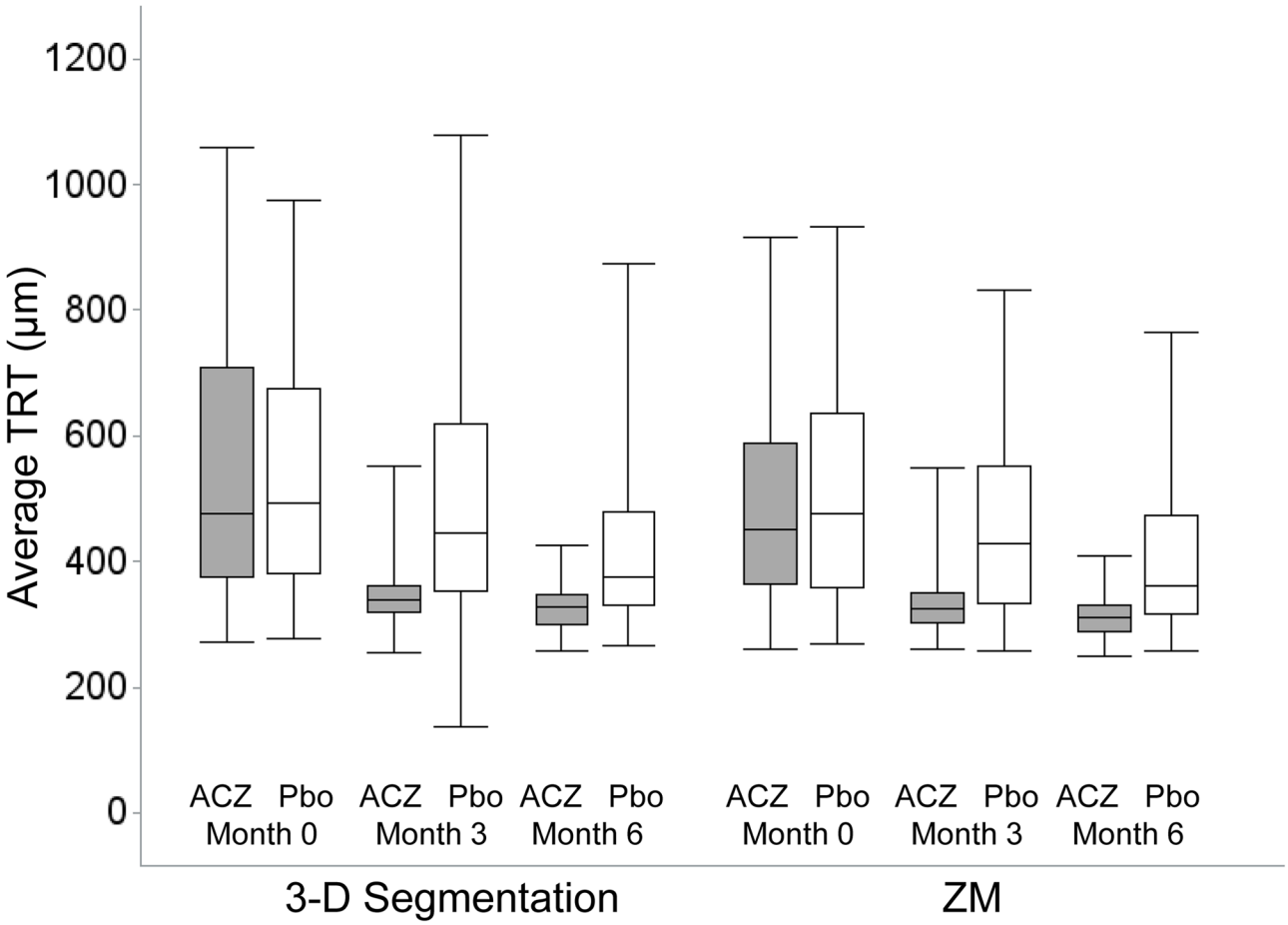

Figure 2.

Boxplots showing average TRT thickness at study enrollment (Month 0), Month 3, and Month 6, divided by treatment group. ACZ (solid) and placebo (hashed) boxes for each time point for 3D-segmentation (left grouping) and Zeiss-Meditec (ZM, right grouping) algorithm. derived data. The difference from baseline to Month 6 values is significant for both groups using both methods ($P<0.001$).

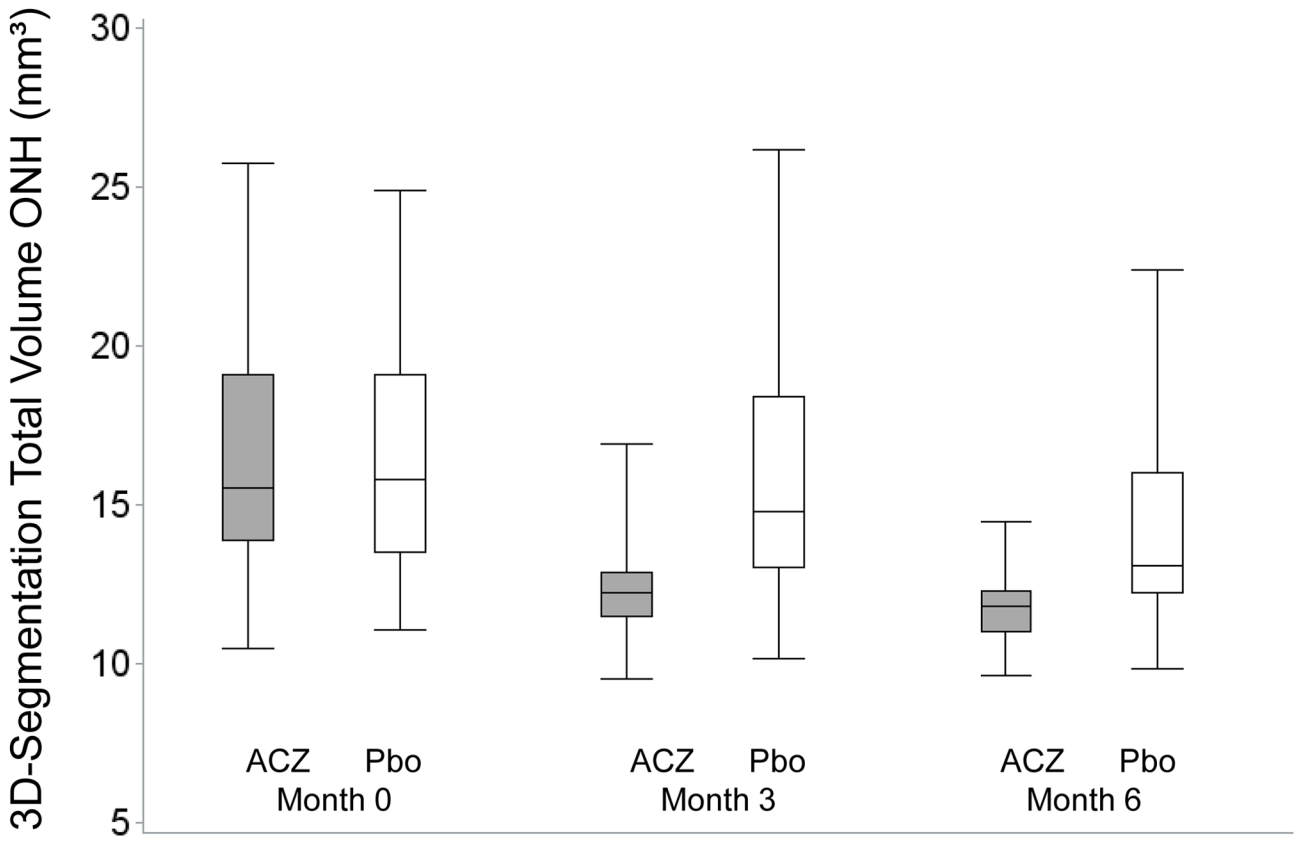

Figure 3.

Boxplots showing average ONH volume at study enrollment (Month 0), Month 3, and Month 6, divided by treatment group. ACZ (solid) and placebo (hashed) boxes for each time point for 3D-segmentation algorithm. derived data. The difference from baseline to Month 6 values is significant for both groups (P<0.001).

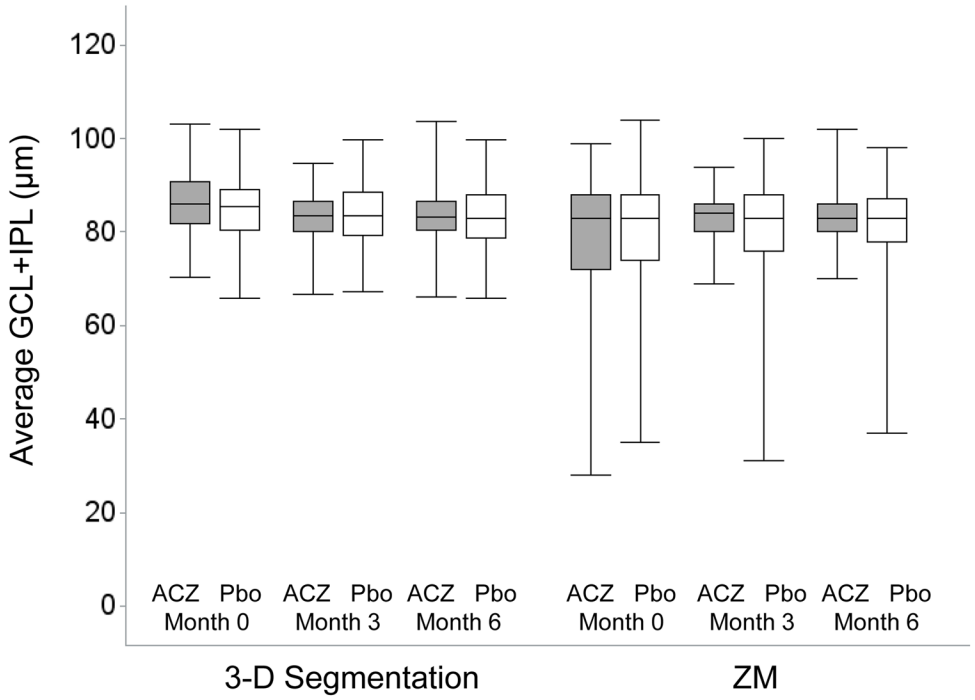

Figure 4.

Boxplots showing average GCL+IPL thickness at study enrollment (Month 0), Month 3, and Month 6, divided by treatment group. ACZ (solid) and placebo (hashed) boxes for each time point for 3D-segmentation (left grouping) and Zeiss-Meditec (ZM, right grouping) algorithm. derived data. The difference from baseline to Month 6 values is significant for both groups using 3D-segmentation ($P<0.001$ for ACZ and $P=0.01$ for placebo) and significant for ACZ ($P=0.03$) but not for placebo ($P=0.09$) for the ZM method. Note the differences were miniscule.

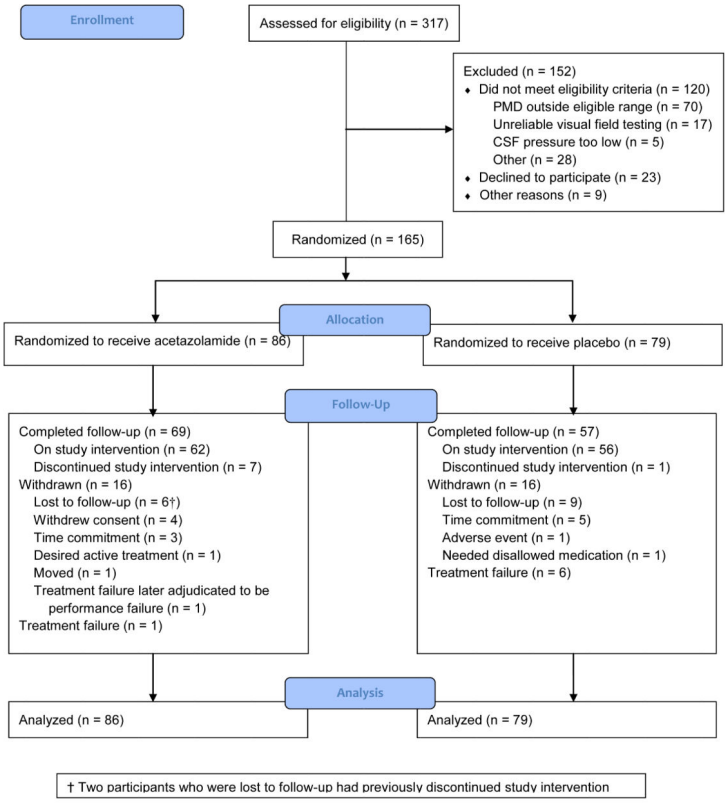

Figure 5.
Participant disposition–CONSORT diagram.

Table 1

OCT Change at Six Months from Baseline Interocular Correlations between Study Eyes and Non-Study Eyes

Label	Correlation between Study Eyes and All Non-Study Eyes	Correlation between Study Eyes and Eligible Non-Study Eyes
3D-Segmentation method		
Total Volume ONH (mm^3)	0.92	0.92
Average RNFL (μm)	0.86	0.86
Average TRT (μm)	0.86	0.86
Average GCL+IPL (μm)	0.72	0.78
ZM methods		
Average RNFL (μm)	0.80	0.81
Average TRT (Circle) (μm)	0.81	0.79
Average GCL+IPL (μm)	0.32	0.10

Eligible non-study eyes defined as fellow eye with baseline PMD worse than -2.0 dB.

Table 2

Treatment Effects on OCT Outcomes in Study Eyes at Month Six

Label	Treatment Group	Adjusted Mean (SE) Change from Baseline	Treatment Effect	95% CI	p-value
3D-Segmentation Method Derived Measures					
Total Volume ONH (mm^3)	Acetazolamide Placebo	−4.9 (0.3) −2.1 (0.3)	−2.8	−3.7, −1.8	<0.001
Average RNFL (μm)	Acetazolamide Placebo	−174.7 (11.8) −88.6 (12.5)	−86.1	−119.8, −52.4	<0.001
Average TRT (μm)	Acetazolamide Placebo	−220.1 (14.8) −113.4 (15.6)	−106.7	−149.0, −64.5	<0.001
Average GCL+IPL (μm)	Acetazolamide Placebo	−3.6 (0.6) −2.1 (0.6)	−1.5	−3.1, 0.08	0.06
ZM Method Derived Measures					
Average RNFL (μm)	Acetazolamide Placebo	−144.6 (10.8) −75.2 (11.7)	−69.4	−100.7, −38.2	<0.001
Average TRT (μm)	Acetazolamide Placebo	−182.4 (13.0) −95.2 (14.0)	−87.2	−124.6, −49.8	<0.001
Average GCL+IPL (μm)	Acetazolamide Placebo	6.3 (1.3) 5.2 (1.4)	1.1	−2.7, 4.9	0.57

Treatment effects are the group differences (acetazolamide-placebo) in adjusted mean response.

Table 3

Weight Change Effects on OCT Outcomes in Study Eyes at Month Six

Label	Weight Change Group	Adjusted Mean (SE) Change from Baseline	Weight Change Effect	95% CI	p-value
3D-Segmentation Method Derived Measures					
Total Volume ONH (mm^3)	Loss No Change	−4.2 (0.4) −2.4 (0.4)	−1.8	−2.8, −0.7	0.002
Average RNFL (μm)	Loss No Change	−153.3 (14.2) −96.4 (13.5)	−56.9	−96.4, −17.4	0.01
Average TRT (μm)	Loss No Change	−197.8 (17.5) −119.5 (16.6)	−78.3	−127.0, −29.7	0.002
Average GCL+IPL (μm)	Loss No Change	−3.4 (0.5) −2.0 (0.5)	−1.4	−2.8, −0.001	0.05
ZM Algorithm Derived Measures					
Average RNFL (μm)	Loss No Change	−125.2 (13.1) −73.5 (12.6)	−51.7	−88.5, −15.0	0.01
Average TRT (μm)	Loss No Change	−165.3 (15.8) −97.5 (15.0)	−67.8	−112.2, −23.4	0.003
Average GCL+IPL (μm)	Loss No Change	6.2 (1.5) 5.7 (1.4)	0.5	−3.8, 4.8	0.83

Weight change effects are the group differences (loss-no change) in adjusted mean response.

Table 4

Spearman correlations between month 6 measures and changes for OCT and Frisén grades for study eyes

OCT Values	Frisén Grade Clinical Exam	Frisén Grade Photos	*Change* in OCT Values	Change Frisén Grade Clinical Exam	Change Frisén Grade Photos
3-D Segmentation method					
ONHV	0.50 P < 0.0001	0.53 P < 0.0001	Change ONHV	0.63 P < 0.0001	0.67 P< 0.0001
RNFL	0.41 P < 0.0004	0.47 P < 0.0001	Change RNFL	0.57 P < 0.0001	0.54 P < 0.0001
TRT	0.41 P = 0.0003	0.44 P = 0.0001	Change TRT	0.58 P < 0.0001	0.60 P < 0.0001
ZM method					
RNFL	0.50 P < 0.0001	0.55 P < 0.0001	Change RNFL	0.64 P < 0.0001	0.69 P < 0.0001
TRT	0.52 P < 0.0001	0.53 P < 0.0001	Change TRT	0.62 P < 0.0001	0.67 P < 0.0001

Table 5

Vision performance in study eyes at three and six months divided by GCL thickness thinning

	PMD MD db, sd	High Contrast Visual Acuity Number Identified	Low Contrast Visual Acuity Number Identified
GCL < 5th percentile 3 months	−2.55 ± 1.82	57.4 ± 4.8	24.6 ± 9.5
GCL ≥ 5th percentile 3 months	−2.48 ± 1.26	58.4 ± 5.1	28.9 ± 9.9
GCL < 5th percentile 6 months	−3.53 ± 1.94	57.7 ± 6.0	24.5 ± 8.2
GCL ≥ 5th percentile 6 months	−2.04 ± 1.37	58.6 ± 5.3	28.7 ± 9.2