The Longitudinal Idiopathic Intracranial Hypertension Trial: Outcomes From Months 6–12

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• PURPOSE: To determine whether the beneficial effects of acetazolamide (ACZ) in improving vision at 6 months continues to month 12 in participants of the Idiopathic Intracranial Hypertension Treatment Trial (IIHTT).
• DESIGN: Nonrandomized clinical study.
• METHODS: In the IIHTT, subjects were randomly assigned to placebo-plus-diet or maximally tolerated dosage of acetazolamide-plus-diet. At 6 months subjects transitioned from study drug to ACZ. This resulted in the following groups: (1) ACZ to ACZ; n = 34; (2) placebo to ACZ; n = 35; (3) ACZ to no treatment; n = 16; and (4) placebo to no treatment; n = 11. Ninety-six IIHTT subjects had evaluations at 6 and 12 months. Our main outcome measure was change from month 6 to month 12 in visual field mean deviation (MD) with secondary measures being change in papilledema grade, ETDRS scores, and quality-of-life (QoL) measures.
• RESULTS: The ACZ to ACZ group improved 0.35 dB, $P = .05$; placebo subjects with no ACZ improved 0.81 dB MD, $P = .07$ at 12 months. The other groups improved 0.35–0.46 dB MD. Mean improvements in papilledema grade occurred most markedly in the group that exchanged placebo for ACZ (0.91 units, $P < .001$). QoL and headache disability scores showed significant improvements in the placebo group with added ACZ.
• CONCLUSION: Improvements in MD continued from month 6 to month 12 of the IIHTT in all treatment groups, most marked in the placebo group tapered off study drug. Adding ACZ to the placebo group significantly improved papilledema grade, headache, and QoL measures. (Am J Ophthalmol 2017;176:102–107. © 2017 Elsevier Inc. All rights reserved.)

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IDIOPATHIC INTRACRANIAL HYPERTENSION (IIH) IS A DISorder primarily of young overweight women characterized by increased intracranial pressure with its associated signs and symptoms in an alert and oriented patient. Neuroimaging and cerebrospinal fluid (CSF) analysis are normal except for raised intracranial pressure and neuroradiologic findings of intracranial hypertension. Also, no secondary cause of intracranial hypertension is apparent. These features comprise the modified Dandy criteria for IIH used for entry to the Idiopathic Intracranial Hypertension Treatment Trial (IIHTT).[1]

The IIHTT is a multicenter, double-blind, randomized, placebo-controlled study of acetazolamide in participants with mild visual loss (perimetric mean deviation of −2 dB to −7 dB). All participants received a lifestyle modification program that included weight reduction with a low-sodium diet. The trial showed acetazolamide significantly improved visual field function, papilledema grade, CSF pressure, and quality-of-life (QoL) measures at 6 months.[2]

At the 6-month visit of the IIHTT, subjects transitioned from study drug to acetazolamide (open label) with the same increasing dosage schedule as the acetazolamide group at the start of the trial. However, subjects with a papilledema grade of less than 1 were tapered off study drug unless they had persisting headaches, pulse-synchronous tinnitus, or a perimetric mean deviation (MD) that failed to improve. Here, we report the outcomes of 96 subjects followed longitudinally, the Longitudinal Idiopathic Intracranial Hypertension Trial (LIIHT) that completed the month 6 to month 12 interventions.

METHODS

THE STUDY (CLINICALTRIALS.GOV IDENTIFIER: NCT01003639) was approved by the Institutional Review Board at each site and individual written informed consent was obtained.

Participants aged 18–60 were eligible if they met the modified Dandy criteria and had reproducible mild visual loss (−2 dB to −7 dB MD). Participants needed to have bilateral papilledema, have an elevated CSF opening pressure, be untreated with regard to IIH, and have no secondary cause of increased intracranial pressure present; other entry criteria are found in prior publications.[2,3]

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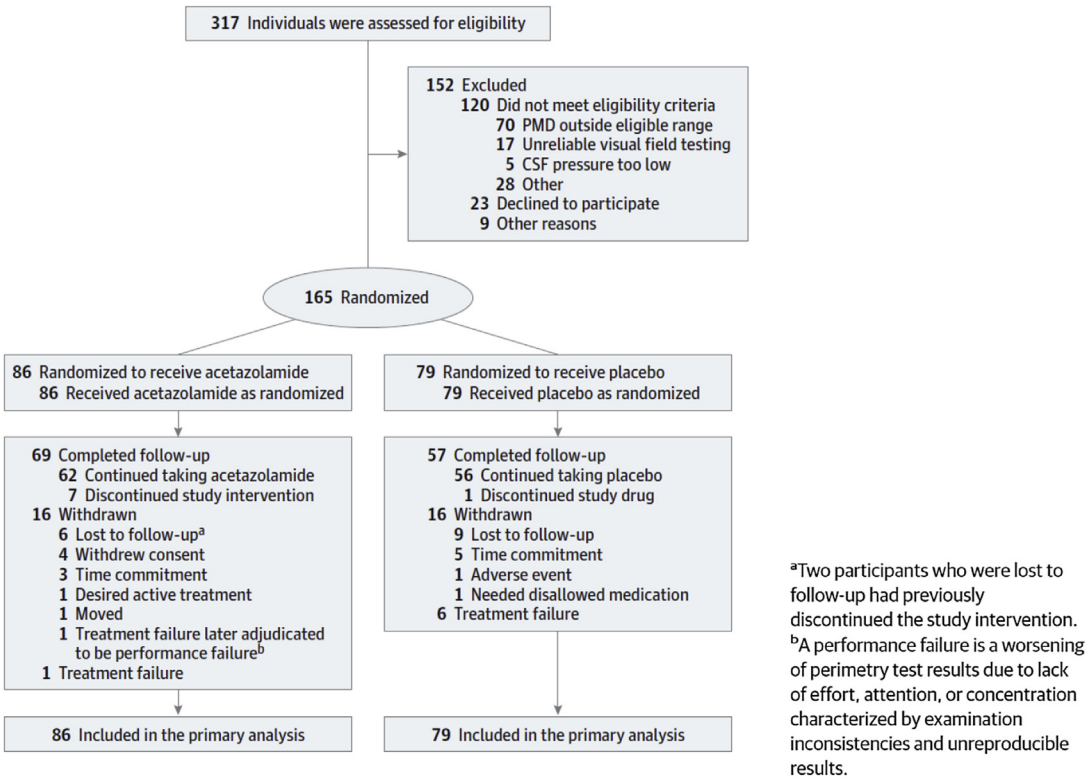

FIGURE. Participant disposition and flow through the trial (CONSORT diagram).

Participants were enrolled at 38 sites in North America from March 2010 to November 2012, with the 12-month follow-up ending in December 2013. They were all offered a supervised diet and lifestyle modification program through the New York Obesity Nutrition Research Center. Also, they were randomly assigned to receive either acetazolamide (ACZ) or matching placebo.

The study drug was ACZ (250 mg) or matching placebo tablets. The initial dosage of study drug was 4 tablets daily in 2 divided doses followed by dosage increases of 1 tablet every week up to a maximum dosage of 4 grams daily for those receiving ACZ. The dosage escalation was stopped if the participant's papilledema grade (Frisén scale)[4,5] became <1 in both eyes and the MD improved to equal to or better than −1 dB in each eye, unless the presence of other symptoms like headache or pulse-synchronous tinnitus suggested that the dosage escalation continue. Participants who were unable to tolerate the study drug could gradually decrease the dosage to a minimum of one-half tablet daily. Participants who discontinued study drug continued to be followed, if willing, for the 12-month duration.

Our CONSORT diagram is found in Figure.

We were interested in the effects on our primary and secondary outcomes from adding ACZ treatment to the subjects in the placebo group. Therefore, at the 6-month visit, to reduce bias, subjects were not told which study drug they had been taking. They were all "transitioned" to ACZ (open label) with the same increasing dosage schedule as at the onset of the IIHTT. However, subjects with a papilledema grade of <1 (based on the Site Investigator examination) were tapered off ACZ unless they had persisting headaches or pulse-synchronous tinnitus or an MD that failed to improve. If so, they were placed on ACZ regardless of the low papilledema grade. Also, they were not tapered off ACZ if they refused to go off. Beginning the day following the 6-month visit, on days 1–6, subjects exchanged 2 tablets of study drug with 2 tablets of ACZ (250 mg/tablet) twice daily. Beginning on day 7, subjects increased the dosage by 1 pill every week until the maximum dosage for that patient was reached or side effects prohibited increasing the dosage further. Thus, subjects who were able to tolerate the maximum dosage of 16 tablets per day (4 g ACZ) reached the maximum dosage of ACZ 84 days after the 6-month visit.

Participants had visits at screening, baseline, and 1, 2, 3, 4.5, 6, 9, and 12 months and then yearly after baseline. At the month 6 and 12 visits, participants had automated perimetry in both eyes using Humphrey Field Analyzer SITA Standard program 24-2. The testing was performed by a technician certified by the Visual Field Reading Center. The papilledema grade (Frisén scale)[4,5] was documented by a team of 3 experienced neuro-ophthalmologist study investigators using fundus photographs; values range from 0 (normal) to 5 (severe papilledema). A best-corrected

TABLE 1. Mean Deviation Change Over 6 Months of the Longitudinal Idiopathic Intracranial Hypertension Trial, by Group

Group	MD[a]	SD[a]	MD Improvement	*P* Value
ACZ to open-label ACZ	−2.34	1.64		
	−1.99	1.47	0.35	.05
PLB to open-label ACZ	−2.44	1.61		
	−2.03	1.06	0.41	.10
ACZ tapered off ACZ	−2.32	1.27		
	−1.86	1.91	0.46	.30
PLB to no ACZ	−1.57	1.59		
	−0.76	1.33	0.81	.07

ACZ = acetazolamide; MD = mean deviation; PLB = placebo.
[a]The first mean deviation value (and standard deviation) is at 6 months and the second value is at 12 months. Mean deviation values are in decibels.

TABLE 2. Frisén Papilledema Grade Change Over Month 6 to Month 12 of the Longitudinal Idiopathic Intracranial Hypertension Trial, by Group

Group	Frisén Grade[a]	SD[a]	Frisén Grade Improvement	*P* Value
ACZ to open-label ACZ	0.50	0.66		
	0.38	0.60	0.12	.10
PLB to open-label ACZ	1.61	1.37		
	0.70	0.73	0.91	<.001
ACZ tapered off ACZ	0.47	0.52		
	0.47	0.74	0.0	.99
PLB to no ACZ	0.73	0.47		
	0.27	0.47	0.46	.02

ACZ = acetazolamide; PLB = placebo.
[a]The first Frisén grade value (and standard deviation) is at 6 months and the second value is at 12 months.

visual acuity using trial lenses mounted in spectacles was measured using ETDRS charts. The eye designated as the study eye, defined at the time of randomization, was the eye with the worse MD; this eye was used for all analyses. Vision-related QoL was assessed using the NEI VFQ-25 and its 10-item neuro-ophthalmic supplement[6,7]; a 4- to 6-point change in NEI VFQ-25 scores represents a clinically meaningful change.[8] Generic health-related QoL was assessed with the SF-36.[9] QoL scores range from 0 to 100, with higher scores indicating better QoL. The HIT-6 Inventory[10] was used to assess headache impact; scores range from 13 to 78, with higher scores indicating worse headache severity. Here we analyze the changes from month 6 to 12.

There were 4 groups identified based on the treatment at IIHTT entry and after 6 months: Group 1, ACZ to ACZ, n = 34; Group 2, placebo to ACZ, n = 35; Group 3, ACZ to no treatment, n = 16; and Group 4, placebo to no treatment, n = 11. For each of these 4 groups, results are reported as mean and standard deviation (SD) of each outcome by visit (ie, month 6 and month 12) along with the associated change in outcome and *P* value. Paired *t* tests were used to compare mean values between month 6 and month 12 separately for each group. *P* values < .05 were considered statistically significant. Mediation analyses were performed to determine if ACZ's effect on weight change is mediating its effects on the clinical outcomes.

RESULTS

A TOTAL OF 96 SUBJECTS HAD SITE EVALUATIONS AT BOTH 6 months and 1 year and met criteria for study entry. Their mean (SD) age was 29.9 (7.9) years, and 98% were female. Their body mass index at the month 6 visit was 37.9 (8.9) kg/m^2. Supplemental Table 1 (Supplemental Material available at AJO.com) shows the baseline IIHTT characteristics comparing subjects in study vs not in study at 12 months. The table shows no significant differences in demographic, neuro-ophthalmologic, or vision- and general health–related QoL characteristics between those that were enrolled in the study at baseline and those that dropped out (all *P* > .05). Those initially randomized to placebo and in study (n = 46) were slightly older than those randomized to placebo and not in study (n = 33) (mean 31.7 vs 27.5 years, *P* = .01); however, the other characteristics were similar between these 2 groups as well as comparing those initially randomized to ACZ. Thirty-four subjects met criteria for possible treatment failure (worsening of either eye of 2 or 3 dB of MD depending on initial mean deviation). During the second 6 months of the trial none of the subjects' visual field worsening was confirmed on repeat testing; that is, there were no subjects that met criteria for treatment failure as defined by study protocol.[3] These subjects were classified by the study Adjudication Committee as "performance failures" and not true worsening of IIH.[11]

Our results can be found in Tables 1–8 and Supplemental Tables 2 and 3 (Supplemental Material available at AJO.com). The ACZ to ACZ group improved 0.35 dB, *P* = .05; and placebo subjects that improved to the point that they could stop medication at 6 months (Group 4) continued their improvement by 0.81 dB, *P* = .07 at 12 months (Table 1). The other 2 groups improved 0.41 and 0.46 dB MD, but neither change reached significance. ETDRS acuity scores also improved in Group 4 (placebo to no ACZ), but the other groups had minimal worsening of their ETDRS acuity (Supplemental Table 2).

Mean improvements in papilledema grade also occurred in all groups, but most markedly in the group that

TABLE 3. Quality-of-Life Measures Showing Short Form-36 Physical Component Scores by Group at 6 and 12 Months

Group	SF-36 Score[a]	SD[a]	SF Improvement	*P* Value
ACZ to open-label ACZ	51.7	7.51		
	52.28	8.08	0.58	.67
PLB to open-label ACZ	49.51	8.69		
	51.56	8.48	2.05	.05
ACZ tapered off ACZ	52.38	5.76		
	53.51	8.60	1.13	.53
PLB to no ACZ	55.26	4.66		
	57.11	3.71	1.85	.26

ACZ = acetazolamide; PLB = placebo; SF = short form.
[a]The first SF-36 score (and standard deviation) is at 6 months and the second is at 12 months.

TABLE 4. Quality-of-Life Measures Showing Short Form-36 Mental Component Scores by Group at 6 and 12 Months

Group	SF-36 Score	SD[a]	SF Improvement	*P* Value
ACZ to open-label ACZ	50.82	6.71		
	50.92	8.04	0.1	.95
PLB to open-label ACZ	45.04	11.97		
	49.42	10.08	4.38	.03
ACZ tapered off ACZ	51.16	5.83		
	51.21	8.27	0.06	.98
PLB to no ACZ	53.48	5.70		
	50.13	12.67	−3.35	.33

ACZ = acetazolamide; PLB = placebo; SF = short form.
[a]The first SF-36 score (and standard deviation) is at 6 months and the second is at 12 months.

exchanged placebo for ACZ (0.91 Frisén grade units, $P < .001$; Table 3). The other groups either did not change (group that tapered off ACZ) or improved 0.46 Frisén scale units.

With regard to QoL scores, there was improvement in most groups, but the only significant improvement was in the group that transitioned from placebo to ACZ. The placebo group that did not receive ACZ actually had mild worsening in the SF-36 mental components scores, but this change was not significant. Headache disability scores (HIT-6 total score) also improved in all groups except the placebo group that did not transition to ACZ (Group 4). In contrast, the largest and most significant improvement in headache disability was in the group that transitioned from placebo to ACZ ($P = .01$).

Weight change occurred in those transitioning from placebo to ACZ, who lost about 6 pounds ($P = .02$), while those tapered off ACZ gained about 7 pounds ($P = .03$). The other 2 groups continued to lose weight, with the least amount of the weight loss in the group that continued ACZ throughout the 12-month period. Mediation analysis showed that acetazolamides effect on PMD was not mediated by its effect on weight change.

DISCUSSION

IMPROVEMENTS IN VISUAL FIELD FUNCTION IN IIHTT PARticipants continued from month 6 to month 12 of the IIHTT regardless of their original treatment group. The only group where this improvement reached significance was in the subjects who continued on ACZ, which was also the largest group in the observational study (35% of LIIHT subjects). However, the effect of visual field MD improvement that was most marked in magnitude, with borderline significance, was in the 12% of LIIHT subjects that were never treated with ACZ. This was an unexpected finding but was supported by the related improvement in visual acuity scores. Interestingly, this group continued to lose weight (5 pounds per subject on average) which may be, in part, responsible for their improvement. This supports one of the current hypotheses for successful therapy: having had an excellent response to the lifestyle management/weight loss program is beneficial for IIH subjects for at least 1 year. Alternatively, it is possible that for this group, their IIH was a self-limited disease and they improved spontaneously.

It should be noted that the IIHTT cohort of subjects with mild visual loss did not have a large range in which to improve, especially in the ACZ group after 6 months of regimented therapy. This is reflected in the small improvements present in the 2 groups that took ACZ for the first 6 months. While we were not surprised to find that the group comprising the placebo-plus diet that did not receive ACZ continued to improve, we cannot explain why there was not at least as much improvement in the group that went from placebo to ACZ. Presumably, those that were switched to ACZ had worse underlying disease at 6 months. Both of these groups that initially took placebo had improvement in papilledema grade, more so (almost 2 times as much) in the placebo to ACZ group. This is in concert with the statistically significant effect of ACZ on lowering papilledema grade at 6 months in the IIHTT.[2]

We have reported that in the IIHTT, IIH patients' QoL at time of diagnosis is affected, even in patients with mild visual impairment.[12] This included vision-specific QoL measures.[12] In addition, we found that at 6 months the ACZ-treated participants experienced significant improvement in QoL measures, including the VFQ-25 total score and its 10-item neuro-ophthalmic supplement, as well as the SF-36 Physical Component Summary and Mental Component Summary scores.[2] In the LIIHT subjects at 12 months we found significant improvement in QoL only in the placebo group that started open-label ACZ.

TABLE 5. Quality-of-Life Measures Showing Visual Function Questionnaire-25 Scores by Group at 6 and 12 Months

Group	VFQ-25 Score[a]	SD[a]	VFQ Improvement	*P* Value
ACZ to open-label ACZ	91.95	8.75		
	91.64	6.03	−0.31	.78
PLB to open-label ACZ	86.05	12.27		
	88.64	10.7	2.59	.01
ACZ tapered off ACZ	93.13	8.60		
	93.69	7.78	0.56	.82
PLB to no ACZ	92.36	6.21		
	94.27	2.20	1.92	.2

ACZ = acetazolamide; PLB = placebo; VFQ = Visual Function Questionnaire.

[a]The first VFQ-25 score (and standard deviation) is at 6 months and the second is at 12 months.

TABLE 6. Visual Function Questionairre-25 10-Item Supplement Total Scores by Group at 6 and 12 Months

Group	VFQ-10 Score[a]	SD[a]	VFQ Improvement	*P* Value
ACZ to open-label ACZ	85.06	11.36		
	85.13	8.89	0.07	.97
PLB to open-label ACZ	79.51	12.59		
	82.91	12.24	3.4	.05
ACZ tapered off ACZ	86.03	13.49		
	87.13	12.10	1.09	.75
PLB to no ACZ	84.73	9.90		
	85.36	8.25	0.64	.72

ACZ = acetazolamide; PLB = placebo; VFQ = Visual Function Questionnaire.

[a]The first VFQ-10 score (and standard deviation) is at 6 months and the second is at 12 months.

TABLE 7. Headache Impact Test Total Scores by Group at 6 and 12 Months

Group	HIT-6 Score[a]	SD[a]	HIT-6 Improvement	*P* Value
ACZ to open-label ACZ	51.70	8.52		
	50.80	9.26	−0.90	.63
PLB to open-label ACZ	53.26	9.31		
	49.56	9.40	−3.70	.01
ACZ tapered off ACZ	46.63	7.80		
	45.06	10.62	−1.56	.56
PLB to no ACZ	47.82	7.37		
	48.45	6.33	0.64	.74

ACZ = acetazolamide; HIT-6 = Headache Impact Test; PLB = placebo.

[a]The first HIT-6 score (and standard deviation) is at 6 months and the second is at 12 months.

TABLE 8. Subject Change in Weight by Group From 6 to 12 Months

Group	Weight[a]	SD[a]	Weight Change	*P* Value
ACZ to open-label ACZ	205.96	40.74		
	205.23	40.17	−0.73	.71
PLB to open-label ACZ	220.40	53.33		
	214.60	54.87	−5.80	.02
ACZ tapered off ACZ	259.24	73.17		
	266.58	75.86	7.34	.03
PLB to no ACZ	226.30	64.84		
	221.15	62.77	−5.16	.15

ACZ = acetazolamide; PLB = placebo.

[a]The first weight value (and standard deviation) is at 6 months and the second is at 12 months.

On the contrary, the placebo group that did not receive ACZ had mild worsening in the SF-36 mental components scores, but this change did not reach statistical significance. These findings add to the evidence that ACZ treatment for IIH improves QoL despite having a variety of side effects.

At the month 6 primary outcome time point, both treatment groups had improvement in headache disability but no effect of ACZ was appreciated. At month 12, after the ACZ exchange, the only significant improvement in headache disability scores was in the placebo-plus diet group that started ACZ. Therefore it appears that ACZ may have a beneficial effect on headache in this subgroup. This may be mediated by the lowering of CSF pressure that accompanies ACZ treatment in IIH.[2,13]

The IIHTT was designed primarily to determine benefits of ACZ over the first 6 months of treatment. The LIIHT was conducted to address other questions. Although protocols were followed for the first 3 months of the LIIHT, in many respects this follow-up cohort should be considered an observational study. A study weakness is that by year 1 only 58% of subjects remained, although participants in the study compared with those that dropped out were similar with regard to baseline IIHTT demographic, neuro-ophthalmologic, and vision- and general health–related QoL characteristics and we expect the impact of excluding those that dropped out to be minimal. In addition, reasons for dropping out were similar in the groups. Another weakness is the placebo-plus diet subjects were not randomized during the LIIHT, so there is no true control group. Therefore, it is possible that some of the effects represent the natural history of IIH, with some subjects improving spontaneously rather than from an effect of weight loss or ACZ. Though all outcomes were preplanned and were the same as the primary study outcomes at month 6, we did evaluate multiple outcomes and multiple groups

within each outcome. Therefore, our primary outcome of change in MD should be considered stronger than the significant findings in the secondary outcomes, which should be considered suggestive, possibly meriting further research.

In conclusion, the 12-month results support the 6-month conclusions. ACZ again significantly reduced papilledema grade and it significantly improved QoL measures when added to subjects originally in the placebo group. A new finding is the significant positive effect on headache disability in the group that transitioned from placebo to ACZ. Visual field function as measured by perimetric mean deviation continued to improve in all groups and improved most in the placebo group, whose IIH symptoms and signs had resolved at 6 months. We conclude that ACZ has a beneficial effect on a variety of IIH outcomes.

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The composition of the NORDIC Idiopathic Intracranial Hypertension Study Group is detailed in the Co-investigator Appendix (Supplemental Material available at AJO.com).

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