The Idiopathic Intracranial Hypertension Treatment Trial: A Long-Time Coming but Worth the Wait

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Randomized clinical trials have served as the foundation for much of the knowledge that we have gained in the last 50 years with regard to efficacy and safety of treatments of various medical conditions. In neuro-ophthalmology, there have been 3 major randomized trials funded by the National Eye Institute. From the Optic Neuritis Treatment Trial (ONTT), we learned about the role of corticosteroids in the treatment of acute optic neuritis (1). From the Ischemic Optic Neuropathy Decompression Trial, we learned about the role of optic nerve sheath decompression as a treatment for anterior ischemic optic neuropathy (2). And now, most recently, from the Idiopathic Intracranial Hypertension Treatment Trial (IIHTT), we have learned about the effect of acetazolamide on visual function in idiopathic intracranial hypertension (IIH) (3). All 3 trials should be considered landmark studies for neuro-ophthalmology.

The IIHTT was a long-time coming. A pilot study funded by the National Eye Institute was conducted between 1989 and 1992 by James Goodwin, James Corbett, and Michael Wall, and there has been a need for a definitive randomized trial since then. With the formation of the Neuro-ophthalmology Research Disease Investigator Consortium (NORDIC), the framework was in place for the conduct of a major randomized trial, which began in 2010 and published the primary results in JAMA in 2014 (4).

The IIHTT enrolled 165 individuals into a placebo-controlled trial at 38 NORDIC sites to answer the question of whether acetazolamide plus a low-sodium weight-reduction diet has a beneficial effect on vision for IIH and mild visual loss compared with diet alone. Eligibility was limited to mild visual loss because of concern about treating patients with more advanced visual loss with a placebo. The trial had a rigorous design and was well conducted with the exception of a higher than desirable dropout rate. However, it seems unlikely that this produced appreciable bias. Overall, there was a modest benefit of acetazolamide seen in the visual field mean deviation, which was the primary outcome. Although the magnitude of the treatment group difference seems small, there was a meaningful treatment group difference found on the quality of life questionnaires favoring the acetazolamide group despite the fact that the treated group, as expected, had substantially more side effects than the placebo group. This suggests that the study participants realized a benefit in their vision that outweighed the negative effect of side effects.

Beyond these overall results, what is important in the interpretation of the IIHTT results and application to clinical practice is that there was a strong statistical interaction ($P < 0.001$) between the degree of baseline papilledema and treatment. The beneficial effect of acetazolamide treatment on visual field was seen solely in participants whose worse eye had Grade 3–5 papilledema at baseline (treatment group difference in mean deviation = 2.27 dB directionally favoring the acetazolamide group) and not present in those with Grade 1–2 papilledema (difference in mean deviation = −0.67 directionally favoring the control group). Epidemiologic dogma would say that in the face of such strong interaction, the overall analysis is not relevant and in fact is misleading because it consists of an overall average effect that does not apply to any patient—for patients with high-grade papilledema, the treatment effect is greater than the overall effect and, for patients with mild papilledema, the treatment effect is less and there may not be visual field benefit at all. This subgroup analysis result has biologic plausibility in the

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direction that would have been hypothesized before the trial. Thus, although one must be cautious in the interpretation of subgroup analyses, there is a strong probability that the interaction is real. Therefore, my view on the results is that acetazolamide has a beneficial effect of clinically meaningful magnitude on visual field when Grade 3–5 papilledema is present but when papilledema is milder, the IIHTT results do not support prescribing acetazolamide in a typical case if the goal of treatment is to provide a beneficial effect on visual field. However, there might be other reasons to prescribe acetazolamide for IIH with Grade 1–2 papilledema such as to treat headaches or if the papilledema appears to be worsening or is associated with any degree of optic disc pallor. It would be useful to examine the quality of life results stratified by baseline degree of papilledema to see if they are concordant with the stratified visual field results.

In a large randomized trial, we generally learn a great deal more than just information about the effect of treatment. From the ONTT clinical trial and subsequent longitudinal data, more than 30 articles were published in addition to the primary treatment group comparison covering a wide range of topics, including the natural history of vision following optic neuritis (from the control group), the relationship of optic neuritis to multiple sclerosis, systemic side effects of corticosteroids in a systemically healthy cohort of patients, characteristics of optic neuritis visual field defects, and visual function changes in the fellow eye. The IIHTT already has published 8 articles covering a variety of topics, including the quality of life of patients with IIH (5), characteristics of patients with IIH (6), visual field findings with IIH (7), relationship of baseline optical coherence tomography (OCT) to clinical features (8), OCT methodology (9), papilledema outcomes assessed with OCT (10), factors associated with acetazolamide response (11), and factors associated with a poor visual outcome from IIH (12).

In this issue of the Journal, the IIHTT adds 2 more articles to the literature, providing further information about visual field testing in IIH and about side effects occurring with acetazolamide. The main objective of the visual field article by Cello et al (13) was to determine how frequently abnormal visual fields in IIH are due to true worsening of disease as opposed to what the authors term a "performance failure." Performance failures were defined as either (1) visual field results met treatment failure criteria on 1 field that were not confirmed on a second field, or (2) deterioration was confirmed on the retest but the adjudication committee concluded that true worsening due to IIH was unlikely. The article by Cello et al presents data showing that only 4% of participants had a treatment failure, whereas 21% had at least 1 abnormal visual field considered to be a performance failure. The point to take away in caring for patients with IIH is that a visual field with a worsened mean deviation is more likely to be related to the patient's performance than to a true worsening of the condition and as such should be repeated before concluding that any worsening is real. Furthermore, the study showed that 87% of the perimetry results classified as a performance failure had "reliability criteria" calculated by the perimeter software within normal limits. Therefore, the perimeter's reliability criteria are not useful for judging whether a visual field change is real and it is only through repeat testing that this determination can be made.

The report by ten Hove et al (14) shows one of the benefits of having a placebo group in a randomized trial. With a placebo group for comparison, an assessment can be made about the side effects occurring with a treatment. Although side effects as expected were greater with acetazolamide than placebo, the proportion of participants reporting side effects with placebo was not trivial. For instance, 22% of the placebo group reported gastrointestinal adverse effects. The acetazolamide results need to be interpreted in the context of the dose used in the trial of up to 4 grams per day of acetazolamide, a dose higher than some prescribe in usual practice. Only 44% of the acetazolamide-treated patients were able to tolerate 4 g per day but most tolerated 1 gram per day for the 6-month period of the trial. Therefore, the clinical points to take home are that although 6 months of acetazolamide produces more side effects than placebo, it is generally safe and as shown in the primary article, side effects did not seem to overly influence the participants' quality of life assessment. It is reasonable to strive to achieve the dose of 4 grams per day prescribed in the IIHTT but a lower dose may be effective; therefore, the maximum tolerated dose should be the goal. It is unknown whether a dose of 4 grams per day is better, if tolerated, than a lower dose, and it is not possible to discern this from the IIHTT data, because an analysis based on the dose used in the trial potentially would be biased because the willingness to tolerate a higher dose might be related to perceived benefit on the part of the participant.

The IIHTT is an important trial for neuro-ophthalmology. The trial leadership, investigators, coordinators, and the NORDIC organization are to be congratulated for conducting an excellent clinical trial that has furthered knowledge for how to treat patients with IIH and mild visual field loss, and, like other large randomized trials, the IIHTT has contributed to knowledge about IIH in many other important ways.

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