Landmark Studies in Neuro-Ophthalmology

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ABSTRACT

High-quality clinical evidence, derived from well-designed and implemented clinical trials, serves to advance clinical care and to allow physicians to provide the most effective treatments to their patients. The field of ophthalmology, including the subspecialty of neuro-ophthalmology, abounds with such high-quality clinical trials that provide Level 1 clinical evidence. This review article summarizes the research design, key findings, and clinical relevance of select monumental clinical studies in neuro-ophthalmology with the primary goal of providing the readers with the rationale for current standard of care of various neuro-ophthalmic diseases. This includes the Optic Neuritis Treatment Trial, Ischemic Optic Neuropathy Decompression Trial, Idiopathic Intracranial Hypertension Treatment Trial, Rescue of Hereditary Optic Disease Outpatient Study, and Controlled High-Risk Avonex® Multiple Sclerosis Study.

Keywords: Optic Neuritis Treatment Trial, Ischemic Optic Neuropathy Decompression Trial, Idiopathic Intracranial Hypertension Treatment Trial, Rescue of Hereditary Optic Disease Outpatient Study, and Controlled High-Risk Avonex® Multiple Sclerosis Study

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High-quality clinical evidence, derived from well-designed and implemented clinical trials, serves to advance clinical care and to allow physicians to provide the most effective treatments to their patients. A properly designed and executed randomized clinical trial remains the best method in most circumstances to evaluate the efficacy of a medical or surgical intervention for a given disease process, and such evidence has been assigned a Level 1 rating by the Oxford Centre for Evidence Based Medicine.[1] The field of ophthalmology abounds with such high-quality clinical trials, the results of which serve as guides to clinicians around the world. Some of the most widely cited and highly regarded trials in the different subspecialties include the Herpetic Eye Disease Study, the Age-Related Eye Disease Study, and the Collaborative Initial Glaucoma Treatment Study. Although relatively a small subspecialty, neuro-ophthalmology is not lacking with its share of clinical studies that offer Level 1 clinical evidence. The purpose of this review article is to summarize the key findings of select monumental clinical studies in neuro-ophthalmology. This includes the Optic Neuritis Treatment Trial, Ischemic Optic Neuropathy Decompression Trial, Idiopathic Intracranial Hypertension Treatment Trial, Rescue of Hereditary Optic Disease Outpatient Study, and Controlled High-Risk Avonex® Multiple Sclerosis Study. This review article hopes to provide the readers with the rationale for current standard of care of various neuro-ophthalmic diseases.

The Optic Neuritis Treatment Trial

The Optic Neuritis Treatment Trial (ONTT) is, by far, the most well-known randomized, placebo-controlled, clinical trial in the field of neuro-ophthalmology.[2] Supported by the National Institutes of Health (NIH), it was conducted at 15 centers in the United States (US). The primary objective of the study was to determine if administration of either oral or intravenous corticosteroids improved visual outcomes as determined by visual field testing and contrast sensitivity assessment. Secondary outcomes included final visual acuity (VA) and color vision as well as the effect of treatment on the speed of visual recovery and likelihood of recurrent or new optic neuritis. Treatment-related complications also were investigated. Four hundred fifty-seven (457) patients between the ages of 18 and 46 years with acute, unilateral demyelinating optic neuritis were enrolled in the study from 1988 to 1991. Subjects were randomized to 1 of 3 treatment groups: intravenous methylprednisolone (IVMP) (n=150), oral prednisone (n=151), or oral placebo (n=156). Patients in the first group received IVMP at a dose of 250 mg every 6 hours for 3 days followed by oral prednisone at a dose of 1 mg/kg/day for 11 days, with a short tapering dose of 20 mg on day 15, then 10 mg on days 16 and 18. The oral prednisone group was treated with oral prednisone at 1 mg/kg/day for 14 days followed by the same taper, while the placebo group received oral placebo following the same schedule as the oral prednisone group. Additionally, all patients underwent magnetic resonance imaging (MRI) of the brain and had a complete neurological examination and chest X-ray in addition to blood tests for serum glucose, antinuclear antibody (ANA), and fluorescent treponemal antibody absorption (FTA-ABS). At baseline, patients with worse than 20/200 vision were more likely to have an abnormal brain MRI, and those with retrobulbar optic neuritis rather than papillitis were more likely to have been given a diagnosis of multiple sclerosis (MS) based on the study examination.

The initial study findings showed that the IVMP group had a faster rate of visual recovery compared to the placebo group.[2] Differences in VA, contrast sensitivity, and visual field scores were greatest on days 4 and 15 and were mostly maintained up to month 6 except for VA. By month 6, VA between the 2 groups was similar. On the other hand, when the oral prednisone and placebo groups were compared, there were no significant differences in the rates of recovery across all 4 visual parameters.

One unexpected finding in the ONTT was the significantly higher rate of a new attack of optic neuritis observed in the oral prednisone group between months 6 and 24 (27, 13 and 15% in the oral prednisone, IVMP and placebo groups, respectively) . This finding led investigators of the study to conclude that oral prednisone given at 1 mg/kg/day has no role in the treatment of optic neuritis of presumed demyelinating in origin.

Since its initial publication, the ONTT study group has published several other papers to report upon the longitudinal data collected on follow-up of the study cohort. Another monumental finding of the ONTT was the predictive value of baseline cranial MRI on the development of MS among patients who initially presented with optic neuritis. These patients were followed over a 15-year period with interim results published at 5 and 10 years.[3,4] Results at 5-, 10-,

and 15- year follow-up were consistent: presence of white matter lesions greater than 3 mm in diameter on non-contrast brain MRI at the time of optic neuritis attack was associated with increased risk of MS. For the sake of brevity, only the 15-year data are mentioned here.[5] The final report published in 2008 showed that the 15-year risk for developing MS was 25% when brain MRI lesions are absent and 72% when lesions are present. The aggregate cumulative risk for developing MS 15 years after an episode of optic neuritis regardless of brain MRI findings was 50%. This risk for MS was also independent of the original treatment group assignments. Additionally, patients with a normal MRI at baseline were very unlikely to progress to MS if they had not done so at the 5-year timepoint. Moreover, characteristics that were negatively predictive of MS among patients who presented with clinically-isolated optic neuritis were absence of eye pain, baseline VA of no light perception, and presence of severe disc swelling, disc or peripapillary hemorrhages, or macular exudates on ophthalmoscopy. Males who presented with anterior optic neuritis were also less likely to develop MS.

The discovery of serum glial autoantibodies such as the aquaporin-4-antibody (AQP4- IgG) and the myelin oligodendrocyte glycoprotein antibody (MOG-IgG) in the past decade have allowed for further classification and prognostication in a subset of optic neuritis patients. AQP4- IgG is a biomarker for neuromyelitis optica (NMO), while presence of MOG-IgG is a hallmark of MOG-associated diseases, a neurologic entity distinct from NMO and MS. In the study by Chen and colleagues, serum samples from 177 subjects from the original ONTT were analyzed for the presence of AQP4 and MOG IgGs.[6] None of the samples tested positive for AQP4-IgG while MOG-IgG was found in 3 subjects (1.7%). All 3 had anterior optic neuritis and negative brain MRI on presentation; none developed MS at 15-year follow-up. The authors concluded that AQP4-IgG and MOG-IgG were infrequent in isolated unilateral optic neuritis.

COMMENT: Following its publication, the results of the ONTT have guided ophthalmologists and neurologists around the world in managing optic neuritis. A 3-day course of IVMP or no treatment, in lieu of placebo for patients presenting with VA better than 20/40 in the affected eye, has been preferred over oral prednisone. However, administration of IVMP in many parts of the world would require hospitalization, adding to the cost of treatment. In 2012, a Cochrane review on oral vs intravenous steroids for treatment of acute relapses, including optic neuritis, in MS demonstrated that either treatment resulted in similar clinical and radiological outcomes.[7] However, more rigorous study design to investigate equivalence between the 2 routes of administration was recommended. In 2015, the COPOUSEP study demonstrated no difference in outcomes in a series of 199 patients with MS relapses who were randomized to oral or intravenous methylprednisolone therapy.[8] A recent single-masked, single-center, randomized clinical trial investigated the non-inferiority of a bioequivalent dose of oral prednisone given at 1250 mg daily against standard IVMP regimen in patients with optic neuritis.[9] Fifty-five (55) patients were enrolled in the study: 23 in the IVMP group and 22 in the oral high-dose prednisone group. Results showed that VA, contrast sensitivity, and P100 latency on visual evoked potential were similar in both groups at 6 months. Of note, at least 1 adverse event was reported in 25 (45%) of the enrolled subjects. These included gastrointestinal disturbance, insomnia, and fatigue. However, the number of adverse events in both groups was not significantly different. Despite the long experience in the MS community with use of high dose oral corticosteroids, caution should still be exercised in an outpatient setting.

The Ischemic Optic Neuropathy Decompression Trial

The Ischemic Optic Neuropathy Decompression Trial (IONDT), a randomized, multicenter, clinical trial in the United States, began subject recruitment in October 1992.[10] In 1994, even before the calculated sample size could be reached, the trial was terminated early due to safety concerns from interim analysis.

The IONDT included 244 subjects aged 50 years and older with non-arteritic ischemic optic neuropathy (NAION) of recent onset (defined as less than 14 days from onset of visual symptoms to patient enrollment) and best-corrected visual acuity (BCVA) of 20/64 or worse in the study eye. Subjects were randomized to 1 of 2 groups: optic nerve decompression surgery (ONDS) or "careful follow-up" (control group). ONDS involved creation of at least 2 slits or a window on the optic nerve sheath of the study eye by an experienced orbital surgeon. The rationale of ONDS was to relieve compartment syndrome in NAION.

The primary outcome measure of the study was

BCVA at 6 months. Efficacy of ONDS was assessed by the proportion of eyes that had BCVA improvement of at least 3 lines at 6 months, while the proportion of eyes that had worsening of BCVA by at least 3 lines at 6 months was used as a primary measure of safety. Other outcome measures included visual field score, quality of life score, number of intraoperative complications, and morbidity and mortality related to ONDS. Patients were followed-up for 1 year with outcome measures collected at 3, 6, and 12 months.

Of the 244 patients enrolled in the study, 237 patients were included in the final analysis: 122 in the careful follow-up (control) group and 115 in the ONSD group. Patient characteristics at baseline were similar between the 2 groups, except for a significantly greater proportion of diabetic patients in the control group.

Results of the study revealed that at 6 months, 43% of the control group experienced visual improvement of at least 3 lines, 45% had little or no change in BCVA, while 12% lost 3 lines or more of BCVA. On the other hand, the corresponding numbers in the surgical intervention group were 33%, 44%, and 24%, respectively. Relative risk ratios suggested that ONDS was associated with lesser likelihood of visual improvement than careful follow-up and may be more hazardous.

In terms of changes in visual field scores, the differences were not significant between the 2 groups. There were also no statistical differences in the medical morbidity and mortality between the 2 groups at 12 months. Complications in the ONDS group included intraoperative central retinal artery occlusion (n=1), loss of light perception immediately following surgery (n=2), postoperative pain, and transient diplopia.

Five years after the initial report, a 24-month update on the IONDT was published in Archives of Ophthalmology.[11] This included 85 subjects in the ONDS group and 89 subjects in the control group. This follow-up report confirmed previous findings that ONDS has no benefit over conservative management in terms of BCVA improvement. At 24 months, proportions of eyes belonging to the control group that experienced improvement, little or no change, and loss in BCVA were 31%, 47%, and 22%, respectively versus 30%, 50%, and 20% in the surgical intervention group.

A final report was published in 2002 in which occurrence of fellow eye (subsequent) NAION was evaluated.[12] Over a median follow-up of 5.1 years, 48 of 326 (14.7%) patients had experienced fellow eye NAION. This analysis excluded the 80 patients who at entry into the study had previously experienced NAION in the nonstudy eye and 12 additional patients who had optic nerve pallor without a compelling history to support NAION. Calculation of proportional hazards ratios showed that diabetes and presenting visual acuity of 20/200 in the first affected (study) eye were significant risk factors for second eye NAION.

COMMENT: While ONDS fell out of favor for the treatment of NAION, the IONDT provides us with important information on the natural history of NAION. Specifically, even without active intervention, either surgical or medical, spontaneous improvement of vision occurs in 43% at 6 months. Additionally, 12% stand to lose more vision (>3 lines) in the same time period. This data is particularly useful in interpreting findings from present and future research studies on treatment modalities for NAION.

The Idiopathic Intracranial Hypertension Treatment Trial

The Idiopathic Intracranial Hypertension Treatment Trial (IIHTT) assessed the efficacy and safety of acetazolamide vs placebo in the treatment of mild visual impairment in patients with idiopathic intracranial hypertension (IIH).[13] This was a double-masked, randomized, placebo-controlled clinical trial conducted at 38 centers in North America from 2010 to 2012. Patients aged 18 to 60 years with IIH satisfying the modified Dandy criteria and mild visual loss (defined as perimetric mean deviation [PMD] between -2 and -7 dB) were enrolled in the study and randomized to receive either dose-escalating oral acetazolamide or placebo. All were enrolled in a weight-reduction, low-sodium dietary program. The main outcome measure was change in the PMD at 6 months in the eye with more severe visual loss at baseline (study eye). Secondary outcome variables included change in PMD in the fellow eye, BCVA, papilledema grade, quality of life scores, cerebrospinal fluid (CSF) pressure, headache, and adverse events. The study included 165 patients with IIH: 86 in the acetazolamide+diet group and 79 in the control (oral placebo+diet) group. Results of the study showed that changes in PMD from baseline to 6 months in both the study and fellow eye, albeit modest in both groups, were significantly greater in the acetazolamide+diet

group compared to the control group (1.43 and 0.87 dB vs 0.71 and 0.42 dB, respectively). Moreover, treatment effect was greater among eyes with baseline Frisen papilledema grade of 3-5 compared to those with grade 1-2. Additionally, the acetazolamide+diet group had significantly greater improvements in quality of life scores and CSF pressures. Although patients in the acetazolamide+diet group also had significantly greater weight loss at 6 months, mediation analysis showed that the treatment effect was still largely due to acetazolamide rather than the additional weight loss. In terms of safety profile, the adverse effects that occurred significantly more often among patients treated with acetazolamide were not unexpected and did not result in permanent morbidity. These adverse effects included dysgeusia, diarrhea, fatigue, nausea, vomiting, hypocarbia, paresthesia, and tinnitus. Despite the significant findings that favored treatment with acetazolamide, the investigators recognized the only modest effect of acetazolamide plus dietary modification on visual outcome and were forthright with yet-to-be-determined functional significance of these improvements.

COMMENT: IIHTT is the biggest interventional randomized clinical trial in IIH to date. It provides Level 1 evidence on the efficacy and safety of acetazolamide + diet modification in the management of IIH with mild visual loss. Changes in secondary outcomes measures indicate that acetazolamide treatment in patients with more severe papilledema may be particularly useful.

Rescue of Hereditary Optic Disease Outpatient Study

The Rescue of Hereditary Optic Disease Outpatient Study (RHODOS) was a randomized, double-blind, placebo-controlled, multicenter clinical trial conducted in Germany, England, and Canada.[14] It was an interventional study for the treatment of vision loss due to Leber hereditary optic neuropathy (LHON), a relatively rare bilateral optic nerve disease which typically affects otherwise healthy young patients and may cause severe loss of visual acuity. In RHODOS, 85 subjects aged 14 to 64 years old with vision loss due to genetically confirmed LHON (G11778A, T14484C, or G3460A mutations) within the preceding 5 years were included in the study. They were randomized in a 2:1 ratio to receive either idebenone (Catena®, 150 mg, Santhera Pharmaceuticals, Liestal, Switzerland) 900 mg daily (n=55) or oral placebo (n=30). The primary outcome measure was best recovery (or least worsening) of vision, defined as the most number of logMAR lines gained in one eye (or least number of logMAR lines lost, in the absence of any visual gain in both eyes), from baseline to 24 weeks. Secondary outcome measures included changes in best VA, VA in best eye at baseline, and VA of all eyes. Results of the study showed no significant differences between the treatment and control groups in best recovery, best VA, and VA in best eye at baseline. Significant difference between the idebenone and placebo groups was only detected when VA of all eyes were combined and analyzed (change in logMAR: -0.054 in idebenone vs +0.496 in placebo, p=0.026). A post-hoc analysis including only eyes with discordant VA (pre-defined as interocular difference in VA>0.2 logMAR) at baseline (n=30) disclosed statistically significant differences across all 4 outcome measures between patients who received idebenone vs placebo. Specifically, the idebenone-treated patients who had discordant VA at baseline had better best recovery, best VA, and final VA at 24 weeks compared to patients who received the placebo. Another notable finding in the study is the significantly higher proportion of eyes in which VA converted from "off-chart" at baseline to "on-chart" at 24 weeks in the idebenone group (20% vs 0% in the placebo group). Lastly, idebenone demonstrated a good safety and tolerability profile.

COMMENT: Following the publication of RHODOS, idebenone received approval from the European Medicines Agency in 2015 for the treatment of LHON. In 2017, an international consensus on the clinical and therapeutic management of LHON was released by a panel of experts from Europe and North America.[15] On this basis, idebenone may be considered a standard treatment for patients with LHON with disease onset <1 year. The recommended dose is 900 mg daily for 1 year. A phase IV open-label clinical trial on the safety and efficacy of idebenone recently concluded in several centers in the US and Europe (NCT02774005).

Controlled High-Risk Avonex® Multiple Sclerosis Study

CHAMPS or Controlled High-Risk Avonex® (intermuscular interferon beta-1a [IFNß1a]) Multiple Sclerosis Study was a randomized, double-masked, placebo-controlled, multicenter clinical trial performed in the late 1990s in the US and Canada.[16] The objective of the study was to assess the efficacy of weekly intramuscular IFNß1a in preventing the development of clinically-definite MS (CDMS) after a

first episode of acute demyelinating event in patients with characteristic demyelinating lesions on baseline MRI. Acute demyelinating event referred to any of the following: unilateral optic neuritis, incomplete transverse myelitis, or brainstem or cerebellar syndrome. Three hundred eighty-three (383) subjects were enrolled in the trial: 193 to the IFNß1a group and 190 to the placebo group. Study duration was 3 years. Patients in the IFNß1a group received weekly 30 ug intramuscular injection of Avonex® (Biogen), while the control group received placebo injections. Primary study endpoint was the development of CDMS. Secondary study endpoints were brain MRI findings at 6, 12, and 18 months.

Study findings revealed that initiation of IFNß1a after the first of episode of an acute demyelinating event resulted in a lower risk of developing CDMS compared to placebo. During the 3-year study period, 35% of patients in the treatment group developed CDMS vs 50% in the control group. In addition, demyelinating brain MRI lesions were fewer in the treatment group compared to the control at all time-points, and the likelihood of development of new lesions for IFNß1a patients was less than ½ that seen in control patients. Because of the beneficial effect of IFNß1a seen at an interim analysis, this study was halted early and all patients were transitioned to IFNß1a therapy. Ultimately, the investigators concluded that presence of subclinical demyelinating brain MRI lesions at the time of the first demyelinating attack is a risk for developing CDMS. The data support the idea that commencement of IFNß1a after the first episode of acute demyelinating event is beneficial for patients with brain MRI lesions at baseline.

COMMENT: Although not a clinical trial exclusive to neuro-ophthalmology, the results of CHAMPS are pivotal in the management of demyelinating optic neuritis. Individuals who present with typical optic neuritis require a baseline brain MRI to check for presence of demyelinating lesions. Additionally, those that do have demyelinating brain lesions should be immediately referred to a neurologist for possible disease modifying therapy, which now includes a host of both injectable and oral agents.

CONCLUSION

Neuro-ophthalmology has been at the forefront of evidence-based medicine, with several randomized clinical trials having been conducted to assess the efficacy of medical and surgical interventions for neuro-ophthalmic disease. A number of trials are still in progress at the time of this writing (gene therapy for LHON, surgical treatment of IIH, possible treatments for NAION) that may serve to change and guide our management of patients with these optic neuropathies and vision loss.

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