Using Acute Optic Neuritis Trials to Assess Neuroprotective and Remyelinating Therapies in Multiple Sclerosis

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Abstract

This cohort study comprehensively assesses key biological and methodologic aspects of trials of acute optic neuritis for testing neuroprotection and remyelination in multiple sclerosis.

Importance Neuroprotective and remyelinating therapies are required for multiple sclerosis (MS), and acute optic neuritis (AON) is a potential condition to evaluate such treatments. Objective To comprehensively assess key biological and methodological aspects of AON trials for testing neuroprotection and remyelination in MS. Design, Setting, and Participants The AON-VisualPath prospective cohort study was conducted from February 2011 to November 2018 at the Hospital Clinic of University of Barcelona, Barcelona, Spain. Consecutive patients with AON were prospectively enrolled in the cohort and followed up for 18 months. Data analyses occurred from November 2018 to February 2019. Exposures Participants were followed up for 18 months using optical coherence tomography, visual acuity tests, and in a subset of 25 participants, multifocal visual evoked potentials. Main Outcomes and Measures Dynamic models of retinal changes and nerve conduction and their associations with visual end points; and eligibility criteria, stratification, and sample-size estimation for future trials. Results A total of 60 patients (50 women [83%]; median age, 34 years) with AON were included. The

patients studied displayed early and intense inner retinal thinning, with a thinning rate of approximately 2.38 mu m per week in the ganglion cell plus inner plexiform layer (GCIPL) during the first 4 weeks. Eyes with AON displayed a 6-month change in latency of about 20 milliseconds, while the expected change in the eyes of healthy participants by random variability was 0.13 (95% CI, -0.80 to 1.06) milliseconds. The strongest associations with visual end points were for the 6-month intereye difference in 2.5% low-contrast letter acuity, which was correlated with the peripapillary retinal nerve fiber layer thinning (adjusted R-2, 0.57), GCIPL thinning (adjusted R-2, 0.50), and changes in mfVEP latency (adjusted R-2, 0.26). A 5-letter increment in high-contrast visual acuity at presentation (but not sex or age) was associated with 6-month retinal thinning (1.41 [95% CI, 0.60-2.23] mu m less peripapillary retinal nerve fiber layer thinning thinning; P = .001; adjusted R-2, 0.20; 0.86 [95% CI, 0.35-1.37] mu m less GCIPL thinning; P = .001; adjusted R-2, 0.19) but not any change in multifocal visual evoked potential latency. To demonstrate 50% efficacy in GCIPL thinning or change in multifocal visual evoked potential latency, a 6-month, 2-arm, parallel-group trial would need 37 or 50 participants per group to test a neuroprotective or remyelinating drug, respectively (power, 80%; alpha, .05). Conclusions and Relevance Acute optic neuritis is a suitable condition to test neuroprotective and remyelinating therapies after acute inflammation, providing sensitive markers to assess the effects on both processes and prospective visual recovery within a manageable timeframe and with a relatively small sample size.

Question May acute optic neuritis help to assess neuroprotection and remyelination? Findings This cohort study found that trials testing neuroprotection using optical coherence tomography as an outcome should include 37 to 50 participants per arm within 15 days after onset to reveal a 50% reduction in 6-month peripapillary retinal nerve fiber layer or ganglion cell plus inner plexiform layer thinning; stratified randomization by sex and high-contrast visual acuity is highly recommended. Larger sample sizes may be needed for trials testing remyelination using 6-month latency changes in multifocal visual evoked potentials; the correlation of optical coherence tomographic measures with low-contrast letter acuity was stronger than with multifocal visual evoked potentials, although cohorts were not identical. Meaning Acute optic neuritis appears to be an appropriate condition to test neuroprotective and remyelinating therapies after acute inflammation.

Palabras clave

KeyWords Plus:NERVE-FIBER LAYER; PHASE-2; VISION; OPICINUMAB; PHENYTOIN

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