Neurodegeneration and inflammation in MS

The eye teaches us about the storm

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In multiple sclerosis (MS), neurodegeneration contributes to axon loss and irreversible disability, but the degree to which neurodegeneration is a consequence of inflammatory mechanisms is unknown. Urgent need exists in all forms of MS, but especially in progressive MS, for therapies that preserve the integrity and function of CNS tissue in the face of a partially controlled chronic disease. It is likely that agents envisioned to fulfill that role (primary neuroprotective therapies) will act via a mechanism outside immune modulation. In analogous terms, the CNS could be likened to a home that we aim to protect from storm damage. Immune-modulating therapies are the equivalent of a weather machine that prevents the storm from ever brewing, and in that way provide indirect neuroprotection. Primary neuroprotection would be achieved by another mechanism, something akin to installing storm shutters or reinforcing the structure of a home to help it weather the years. The concern in MS is that ongoing neurodegeneration may occur even in the absence of detectable active inflammation, compelling a need for primary neuroprotective therapies that utilize novel mechanisms of action.

For clinical trials evaluating primary neuroprotective therapies, our traditional outcome measures of relapses and inflammatory (enhancing or new T2) MRI lesions will not be of use. Instead, we envision clinical trial designs that rely on clinical disability measures and imaging measures of neuronal degeneration. One of those proposed measures, optical coherence tomography (OCT), is relatively new but holds promise as a highly reproducible, accessible outcome measure. OCT utilizes near-infrared light to generate cross-sectional images of the retina, yielding quantitative anatomic data.[1] Cross-sectional and longitudinal studies have demonstrated thinning of the retinal nerve fiber layer (RNFL) that is most dramatic in the months following optic neuritis (ON), but also occurs throughout the natural history of MS in the absence of clinical ON.[2] Newer-generation spectral-domain OCT allows for reliable segmentation of both axonal and neuronal elements of the retina. The peripapillary RNFL is comprised mainly of unmyelinated axons projecting from the retinal ganglion cells prior to their coalescence as the optic nerve. The ganglion cell layer of the macula contains a high density of first-order sensory neurons, and its thickness can be measured as the ganglion cell layer plus inner plexiform layer (GCIP) (figure in Ratchford et al.[3]).

In this issue of *Neurology*®, Ratchford et al.[3] report a multicenter prospective longitudinal registry of 164 patients (75% with relapsing-remitting MS and 25% with a progressive form of MS) undergoing twice-yearly OCT for approximately 2 years.[3] This is one of the largest reports to date that combines longitudinal spectral-domain OCT with MRI and clinical measures. Rates of GCIP thinning were estimated from mixed-effects regression models based on select disease characteristics, controlling for age and sex. The key finding is that macular GCIP thinning (but not peripapillary RNFL thinning) occurs at higher rates in patients with earlier and more active disease. New gadolinium-enhancing brain lesions conferred a 54% faster rate of GCIP thinning over the 2-year follow-up interval, while relapses and new T2 brain lesions also increased the rate. Patients with disease duration of less than 5 years and those with disability progression during the study also experienced faster GCIP thinning. The calculated rate estimates for GCIP thinning are compelling. For patients with disease duration <5 years and new T2 and gadolinium-enhancing brain lesions, GCIP loss is estimated at >1 μM per year (vs 0.33 μM for those with MS <5 years without either lesion type).

These findings require replication, but at face value provide some interesting data that may help to optimize the future design of clinical trials using OCT as an outcome measure. Clinical trials enriched for patients with ongoing relapses or active lesions may have improved power to detect neuroprotective effects using OCT. Testing neuroprotection in the setting of ongoing active inflammation, however, has 2 hazards: visible

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new lesions and relapses are less common in progressive MS, where the need for neuroprotective therapies is greatest; and in the setting of active inflammation, separating primary neuroprotection from immune modulation or secondary neuroprotection becomes difficult. One practical way to enrich clinical trials utilizing OCT in progressive MS based on these data would be to require evidence of active progression and shorter disease duration as inclusion criteria for study entry. Alternately, trials in long-standing, slowly progressive MS in the absence of inflammatory disease activity may be more difficult to power sufficiently for OCT outcomes. Another implication for trial design and outcome specification is that the inclusion of macular GCIP analysis will likely become important in future trials as a marker of neurodegeneration. Another factor making GCIP an attractive outcome measure is that it seems not to be affected by edema, unlike RFNL and measures of whole-brain atrophy.[4]

The results presented here also provide indirect evidence that active inflammation (even if subclinical or occurring in a different functional system) is connected with greater rates of retinal neurodegeneration. One postulated reason for this is that subclinical episodes of ON occur as a manifestation of uncontrolled active inflammation and contribute to retinal thinning over time in MS, though other possibilities exist (in situ retinal inflammation, global neurodegenerative processes).

A similar relationship has been identified between gadolinium-enhancing lesions and whole-brain atrophy.[5] Though that relationship may become less apparent in later stages of MS, pathologic evidence suggests that at least to some extent inflammation and neurodegeneration remain linked.[6]

Ongoing inflammation in MS, even if subclinical in the form of gadolinium-enhancing or new T2 lesions, places patients at risk for ongoing neurodegeneration. Immune-modulating therapies therefore likely provide an element of secondary neuroprotection. But as even our most aggressive immune-modulating therapies fail to completely normalize brain atrophy rates, it becomes apparent that other mechanisms of neurodegeneration likely exist. As therapeutics are developed to address those mechanisms, ganglion cell analysis by OCT may play a key role in measuring their efficacy. The message for patients: primary neuroprotection is in the forecast.

DISCLOSURE

R. Bermel has served as a consultant or advisory board member for Biogen Idec, Teva, Novartis, and Astellas. M. Inglese reports no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

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